CHAPTER 2

Drugs Affecting the Autonomic Nervous System

Questions

DIRECTIONS (Questions 75 through 107): 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.

75. You are treating a patient with bronchial asthma with an inhaled beta-adrenergic agonist. The patient calls your office complaining that the inhaler is not working. On questioning, it appears this person has an elevated heart rate. The most appropriate course of action is to
(A) add an inhaled glucocorticoid to the regimen
(B) administer a systemic glucocorticoid
(C) immediately stop the use of the inhaled agonist
(D) substitute an inhaled glucocorticoid for the beta-agonist
(E) switch to a different inhaled agonist

76. The tachycardia associated with the use of alpha-adrenergic-blocking agents is most likely due to
(A) blockade of the alpha2-adrenergic receptors
(B) elimination of beta-adrenergic receptor activity
(C) inhibition of the cholinergic nervous innervation
(D) reflex activation in a recumbent patient
(E) the release of epinephrine from the adrenal gland

77. The most likely reason for selecting a beta-adrenergic agonist with intrinsic sympathomimetic activity is
(A) agents without intrinsic sympathomimetic activity are subject to first pass metabolism
(B) the need for an agent that has a prolonged duration of action
(C) these types of agonists are very long acting due to the covalent bond they form with the receptor
(D) the potential to have less depressant effect on the heart
(E) to prevent reflex tachycardia

78. The use of beta-adrenergic agonists in bronchial asthma is mainly designed to
(A) compete with alpha-adrenergic agonists the beta-agonist
(B) inhibit the airway inflammatory response
(C) stimulate airway secretion
(D) manage acute contraction of airway
(E) prevent awakening during the night

79. A major clinically important advantage of noncatecholamines over catecholamines is
(A) noncatecholamines have a lower potential to cause central nervous system stimulation
(B) their duration of action is longer
(C) they are more effective in treating acute allergic reactions
(D) they are not naturally occurring
(E) they have a structure that permits parenteral administration

80. The effectiveness of beta-adrenergic blocking agents in treating essential hypertension is most likely due to
(A) a combination of inhibition of cardiac output and renin release
(B) inhibition of calcium entry into blood vessels
(C) stimulation of vagal nerves, leading to increased circulating levels of acetylcholine
(D) the direct blockade of angiotensin receptor
(E) the production of nitric oxide

81. Low concentrations of which of the following agents administered on a background of low adrenergic nervous system activation can be expected to increase blood flow to the kidney?
(A) cocaine
(B) dopamine
(C) epinephrine
(D) phenylephrine
(E) tyramine

82. Which of the following agents causes increased peripheral resistance due to the inhibition of reuptake at noradrenergic synapses?
(A) cocaine
(B) dopamine
(C) epinephrine
(D) phenylephrine
(E) tyramine

83. Administration of which of the following will lead to an increase in peripheral resistance without cardiac stimulation?
(A) cocaine
(B) dopamine
(C) epinephrine
(D) phenylephrine
(E) tyramine
84. Alpha-adrenergic blocking agents will convert which of the following vasoconstrictors to a vasodilator?
(A) cocaine
(B) dopamine
(C) epinephrine
(D) phenylephrine
(E) tyramine

85. When it is desirable to administer an agent that will lower peripheral resistance but does not cause an increase in catecholamine release from the adrenergic nerve ending, prazosin is selected as the agent. Its mechanism of action is
(A) activation of beta1 receptors
(B) elimination of the effects of beta2 receptor activation
(C) nonequilibrium alpha-adrenergic receptor blockade
(D) selective blockade of alpha1 receptors
(E) specific activation of alpha2 receptors

86. In choosing a noncatecholamine versus a catecholamine, which of the following factors is important?
(A) Noncatecholamines have a shorter duration of action.
(B) Catecholamines are effective only if administered orally.
(C) Noncatecholamines are metabolized at a more rapid rate.
(D) Catecholamines are considered indirect-acting agents since they must enter the nerve ending and release norepinephrine.
(E) Noncatecholamines tend to have greater action on the central nervous system(CNS).

87. The administration of an adrenergic amine to a patient taking a tricyclic antidepressant may result in an unexpected elevation of blood pressure. The mechanism responsible for this effect is most likely
(A) increased sensitivity of the tissue to norepinephrine
(B) increased activity of catechol-O-methyl-transferase (COMT)
(C) interference with uptake of the amine into adrenergic nerve endings
(D) increased activity of monoamine oxidase(MAO)
(E) decreased destruction of the amine by metabolic enzymes

88. Increasing cardiac output with a selective beta$_1$-adrenergic agonist causes less tachycardia than increasing cardiac output with a nonselective beta agonist because
(A) the vasodilator action at beta$_2$ receptors is absent
(B) beta$_1$-receptor agonists cause upregulation of receptors
(C) nonselective agents are less potent
(D) selective agents are very specific for the heart and do not block other sites
(E) alpha receptors are inactivated by beta$_1$ selective agents
89. Which of the following is an accepted therapeutic use of epinephrine?
(A) treatment of pheochromocytoma
(B) combination with local anesthetics in 1:10,000 concentrations
(C) intravenous (IV) infusion for hemorrhagic shock
(D) treatment of acute hypersensitivity reaction to drugs
(E) cardiogenic shock

90. In the treatment of glaucoma, timolol would be preferred over propranolol because
(A) propranolol has a longer duration of action
(B) propranolol is nonselective
(C) propranolol will depress the heart
(D) timolol does not have local anesthetic activity
(E) timolol has intrinsic sympathomimetic activity

91. A gardener has been concerned about insects eating the vegetables he worked diligently to cultivate. He decides to use an insecticide to prevent any damage to his crop. His wife finds him in the gardening shed with signs of intoxication.
Cholinesterase inhibitors
(A) cannot be reactivated until the enzyme inhibitor has “aged”
(B) do not affect skeletal muscle nicotinic receptors
(C) like edrophonium have duration of action lasting hours
(D) of the neostigmine type are effective in reversing the central effects of atropine intoxication
(E) are used to treat myasthenia gravis and may cause excessive salivation

92. The vasodilator activity of acetylcholine is due to
(A) an influx of calcium ion following calcium channel activation
(B) blockade of the release of norepinephrine
(C) release of endothelial relaxing factor (EDRF)
(D) stimulation of muscarinic receptors
(E) stimulation of nicotinic receptor

93. Studies conducted on patients who have survived myocardial infarctions show a reduction in mortality if they are maintained on
(A) dobutamine
(B) metaproterenol
(C) nitroglycerin
(D) phentolamine
(E) timolol

94. In the treatment of diseases of the eye, which of the following choices would be appropriate?
(A) placing eyedrops containing pilocarpine to relax the ciliary muscle
(B) the administration of an adrenergic amine to produce mydriasis and cycloplegia
(C) the use of diuretics to stimulate the kidney and reduce systemic fluids
(D) the use of beta-adrenergic blocking agents to reduce the formation of aqueous humor in glaucoma
(E) none of the above

95. Activation of which of the following results in inhibition of cardiac muscle contraction?
   (A) alpha\_1 receptors
   (B) beta\_1 receptors
   (C) beta\_2 receptors
   (D) dopamine D\_1 receptors
   (E) muscarinic M\_2 receptors

96. Activation of which of the following results in contraction of vascular smooth muscle?
   (A) alpha\_1 receptors
   (B) beta\_1 receptors
   (C) beta\_2 receptors
   (D) dopamine D\_1 receptors
   (E) muscarinic M\_2 receptors

97. Which of the following neuromuscular blocking agents has the most rapid onset of action?
   (A) atracurium
   (B) metocurine
   (C) pancuronium
   (D) rapacuronium
   (E) tubocurarine

98. Which of the following neuromuscular blocking agents has the shortest duration of action when a single dose is administered?
   (A) pancuronium
   (B) pipecuronium
   (C) rocuronium
   (D) succinylcholine
   (E) vecuronium

99. Which of the following neuromuscular-blocking agents is broken down spontaneously in the body to form laudanosine and a related quaternary acid?
   (A) atracurium
   (B) metocurine
   (C) pancuronium
100. Which of the following is the most accurate description of tubocurarine?
(A) ganglionic-blocking agent
(B) muscarinic agonist
(C) nicotinic agonist
(D) noncompetitive neuromuscular-blocking agent
(E) nondepolarizing neuromuscular-blocking agent

101. Which of the following drugs is accurately classified as a depolarization type of neuromuscular blocking agent?
(A) atracurium
(B) metocurine
(C) succinylcholine
(D) tubocurarine
(E) vecuronium

102. Which of the following terms most accurately characterizes the phase II neuromuscular blockade produced by succinylcholine?
(A) depolarizing block
(B) desensitizing block
(C) flexible block
(D) rigid block
(E) tetanus-producing block

103. Which of the following types of neuromuscular blockade respond(s) to tetanus-producing nerve stimulations by manifesting a diminished, but constant amplitude of contractile responses?
(A) nondepolarizing blockade
(B) phase I depolarizing blockade
(C) phase II depolarizing blockade
(D) all of the above
(E) none of the above

104. Which of the following neuromuscular blocking agents produces transient muscle fasciculations during its onset of action?
(A) atracurium
(B) rapacuronium
(C) succinylcholine
(D) tubocurarine
(E) vecuronium
105. Which of the following neuromuscular blocking agents produces a moderate block of cardiac muscarinic receptors, but no effect on autonomic ganglia and no tendency to cause release of histamine?
(A) atracurium
(B) metocurine
(C) pancuronium
(D) succinylcholine
(E) tubocurarine

106. Which of the following drugs produces the most pronounced cardiovascular effects?
(A) pipecuronium
(B) rapacuronium
(C) rocuronium
(D) tubocurarine

107. Which of the following drugs produces a neuromuscular blockade that is least likely to be reversed by neostigmine?
(A) atracurium
(B) metocurine
(C) succinylcholine
(D) tubocurarine
(E) vecuronium

DIRECTIONS (Questions 108 through 156): Each group of questions in this section consists of groups of lettered headings followed by lists of numbered words or phrases. For each numbered word or phrase, select the ONE lettered heading that is most closely associated with it. Each lettered heading may be selected once, more than once, or not at all.

Questions 108 through 110

Beta-adrenergic blocking agents can be utilized based on several properties listed below. For each condition listed, select the proper choice of an agent.
(A) cardioselectivity
(B) beta₂ selectivity
(C) duration of action
(D) intrinsic sympathomimetic activity
(E) nonequilibrium blockade

108. There is concern about a patient who may forget to take a dose of the drug due to memory impairment.
109. A patient with a history of bronchial asthma develops atrial arrhythmias, and it is deemed appropriate to place the individual on a beta-adrenergic blocking agent.

110. In the operating room, a patient develops an arrhythmia and the choice of esmolol as the most desirable agent is most likely based on _____.

Questions 111 through 114
Match the appropriate drug to its action. Match the appropriate drug with its use.
(A) butoxamine
(B) carvedilol
(C) phenoxybenzamine
(D) prazosin
(E) salmeterol
(F) tramsulosin

111. Selective action on the alpha_{1A}-adrenergic receptor
112. Blocks beta2-adrenergic receptors
113. Used in hypertension and congestive heart failure because it decreases peripheral resistance and protects the heart from abnormal cardiac rhythms
114. Forms ethyleneimonium ions

Questions 115 through 120
Match the result of activation of the following receptors with a physiologic response.
(A) alpha1
(B) alpha2
(C) beta1
(D) beta2
(E) muscarinic
(F) nicotinic

115. Bradycardia
116. Bronchodilation
117. Vasoconstriction
118. Dilation of skeletal muscle vascular beds
119. Release of adrenal catecholamines
120. Inhibition of norepinephrine release

Questions 121 through 123
Match the appropriate drug with its use.
(A) acetycholine
(B) carbachol
(C) bethanechol
(D) methacholine
(E) choline
121. Predominantly used for its cardiovascular effects
122. Primarily used to increase tone of the urinary retention and not hydrolyzed by cholinesterases
123. Not employed therapeutically because of its rapid hydrolysis and lack of specificity

Questions 124 through 126
Match the appropriate agent with each statement below.
(A) muscarinic agonists
(B) anticholinergic agents
(C) ganglionic-blocking drugs
(D) nicotinic agonists
(E) nicotinic antagonists
124. Contraindications include asthma, coronary insufficiency, and peptic ulcer.
125. Signs of toxicity may include hot, dry skin and delirium.
126. Stimulates both skeletal muscle and ganglionic sites.

Questions 127 through 130
Match the appropriate agent with the actions below.
(A) atropine
(B) botulirium toxin
(C) hemicholinium
(D) synaptobrevin
(E) vesamicol
127. Inhibits the release of acetylcholine from cholinergic
128. A cellular protein that promotes fusion of the vesicular membrane
129. Blocks the reuptake of choline into cholinergic fibers

Questions 131 through 134
Match the appropriate agent with its action below.
(A) bretylium
(B) glucocorticoids
(C) metyrosine
(D) reserpine
(E) tricyclic antidepressants
131. Inhibits the rate-limiting enzyme responsible for norepinephrine synthesis
132. Inhibits the uptake of norepinephrine into extraneuronal sites
133. Leads to loss of granular storage of norepinephrine
134. Inhibits norepinephrine release from adrenergic nerve endings

Questions 135 through 138
Match the appropriate enzyme with the correct statement below.
(A) COMT
(B) dopamine beta hydroxylase
(C) MAO
(D) phenylethanolamine N-methyltransferase (PNMT)
(E) thyroid hormone (TH)

135. Found in the effluent following adrenergic nerve stimulation
136. Inhibition leads to dangerous increases in blood pressure when fermented food
are ingested
137. Responsible for synthesis of epinephrine
138. Leads to the production of normetanephrine

Questions 139 through 142
In all of the traces provided, assume that blood pressure was recorded from the carotid
artery and drugs administered through an indwilling catheter in the femoral vein.
Animal were anesthetized with 30 mg/kg of pentobarbital sodium. (See Fig. 2.1 on
page 24)
(A) atropine
(B) neostigmine
(C) phentolamine
(D) pralidoxime
(E) propranolol
139. Drug A
140. Drug B
141. Drug C
142. Drug D

Questions 143 through 146 (See Fig. 2.2 on page 24)
(A) epinephrine
(B) isoproterenol
(C) metaproterenol
(D) norepinephrine
(E) phenylephrine
143. Drug A
144. Drug B
145. Drug C
146. Drug D

Questions 147 through 150
Using Figure 2.3 on page 25, answer the following questions. The letters in the
diagram refer to processes occurring in the adrenergic nerve ending.
147. Bretylium inhibits this process.
148. Activation of this site will result in effector activation.
149. Indirect-acting amines release norepinephrine from this site.
150. Stimulation of this site will inhibit norepinephrine release.
Questions 151 through 156

Match the reaction with the appropriate receptor.

(A) alpha1 receptors
(B) alpha2 receptors
(C) beta1 receptors
(D) beta2 receptors
(E) beta3 receptors
(F) dopamine D1 receptors
(G) dopamine D2 receptors
(H) dopamine D3 receptors
(I) muscarinic M1 receptors
(J) muscarinic M2 receptors
(K) nicotinic N_M receptors
(L) nicotinic N_N receptors

151. Skeletal muscle contraction
152. Activation of the phosphoinositide pathway in CNS neurons and sympathetic postganglionic neurons
153. Renal vasodilation
154. Smooth muscle relaxation
155. Ganglionic stimulation
156. Primary location is on lipocytes

Answers and Explanations

75. (C) The administration of inhaled glucocorticoids is for maintenance therapy, and simply adding this agent may cause upregulation of beta receptors, worsening the situation. The use of systemic glucocorticoids is reserved for management of airway
reactivity, and the problem here appears to be the accelerated heart rate. Substituting an inhaled glucocorticoid for the beta agonist may be useful but probably not the most immediate course of action. Adding a different inhaled agonist would not be expected to improve the problem of receptor downregulation. Even though this point is arguable, the cautious approach is to discontinue the agonist.

76. (A) The most obvious answer is the inhibition of alpha2-shutdown of norepinephrine release. Neither beta receptors nor muscarinic receptors are altered, and epinephrine release would be expected only in someone who is standing. Standing reflexes are not present in a recumbent patient.

77. (D) Since compounds of this type have partial agonist activity, they depress the heart less (beta2 > beta1 activity). The metabolism, duration of action, and covalent bonding are not relevant issues. These agents would not be any more effective in preventing reflex tachycardia than any other beta blockers.

78. (D) Beta-adrenergic agonists are used to relax airway smooth muscle acutely by increasing cyclic adenosine monophosphate (cAMP) levels. This is a beta2-adrenergic receptor effect.

79. (B) The major reason for selecting these agents is that they have oral effectiveness, are longer acting, or penetrate into the CNS. Some of them (e.g., ephedrine) are naturally occurring; they are less effective than catecholamines in treating acute allergic reactions, and their structure does not offer a solubility advantage.

80. (A) The major reasons beta-adrenergic blocking agents lower blood pressure are due to these two effects. These agents are not classes of calcium channel blockers, vagal nerve stimulants, or activators of nitric oxide. (Katzung, p. 145)

81. (B) At low doses the activation of D1 receptors in the renal beds may lead to vasodilation and increased blood flow. As the dose of dopamine increases, beta1-adrenergic receptors in the heart are activated. With even higher doses, alpha1-adrenergic receptors in the skin vascular beds are activated leading to a progressive increase in peripheral resistance.

82. (A) Cocaine, a local anesthetic, blocks the reuptake of norepinephrine, which results in a major increase in peripheral resistance. In the CNS, cocaine inhibits the reuptake of dopamine, leading to sensations that are intensely pleasurable.
83. (D) Phenylephrine is one of a group of drugs that will cause an increase in peripheral resistance due to its selective activation of alpha1-adrenergic receptors in skin vascular beds.

84. (C) This is the classic “epinephrine reversal response”. Because epinephrine nonselectively activates both alpha- (alpha1 and alpha2) and beta- (beta1 and beta2) adrenergic receptors, the response following alpha blockade (vasoconstriction) results in beta2 receptor-induced vasodilation due to relaxation of blood vessels in skeletal muscle vascular beds.

85. (D) Prazosin is an antihypertensive agent that reduces blood pressure by selectively blocking receptors on blood vessels. This results in a decrease in peripheral resistance. Even though tachycardia may occur due to reflex effects, there is no blockade of the process that inhibits norepinephrine release from adrenergic nerve endings.

86. (E) Noncatecholamines are resistant to enzymatic inactivation by MAO and COMT. This fact means they have a longer duration of action, are orally effective, and are indirect acting (release norepinephrine from the adrenergic nerve ending). These compounds (e.g., dextroamphetamine) tend to penetrate to the CNS.

87. (C) Tricyclic antidepressants along with cocaine block the transport system in the axonal membrane of the adrenergic nerve terminal. This is the major pathway for termination of the response, and inhibiting this process results in a greater amount of the adrenergic amine in the vicinity of the receptor.

88. (A) Nonselective agents will activate beta2 receptors in skeletal muscle vascular beds, leading to a reflex tachycardia. Isoproterenol (nonselective) causes greater increases in heart rate than does dobutamine (selective).

89. (D) Epinephrine, 1:1,000, is a time-honored drug used to treat acute hypersensitivity reactions to drugs and other allergens. It is also widely used with local anesthetics to delay absorption and prolong anesthesia; however, concentrations of 1:200,000 to 1:100,000 are employed for this purpose.

90. (D) When treating glaucoma, it is important that local anesthesia does not occur since lack of sensation in the eye could easily result in damage to the cornea. Timolol does not have intrinsic sympathomimetic activity, local anesthetic activity, or selectivity. Its duration of action is standard, approximately 4 hours.

91. (E) Myasthenia gravis is often treated with cholinesterase inhibitors, such as neostigmine, that do not cross the blood-brain barrier. Edrophonium, a short-acting agent, is useful in diagnosing myasthenia gravis. These agents cause signs of excessive muscarinic receptor activation, including excessive salivation. Atropine will
antagonize these effects without suppressing the effect on nicotinic skeletal muscle sites.

92. (C) The most correct answer is the release of EDRF (nitric oxide). A Nobel prize was awarded for the discovery that intact (in vivo) blood vessels released nitric oxide, which increased cyclic guanosine monophosphate and thus caused relaxation of blood vessels. Vessels with the endothelium removed contract in response to acetylcholine.

93. (E) The Norwegian multicenter study of timolol after acute myocardial infarction demonstrated a reduction in mortality with 6-year follow-up. Propranolol and metoprolol also prolong survival.

94. (D) Timolol is a beta-adrenergic blocking agent that reduces the secretion of aqueous humor from the ciliary epithelium.

95. (E) The activation of cardiac muscarinic M2 receptors results in opening of potassium channels, and inhibition of adenylyl cyclase leading to a decrease in contractile force development.

96. (A) The major control of peripheral resistance is through activation of alpha1-adrenergic receptors. This is a consequence of activation of the phosphoinositide cascade and increased levels of IP3 levels.

97. (D) Rapacuronium has the most rapid onset of action of the nondepolarizing neuromuscular blocking agents, and it has a duration of action of about 10 to 20 minutes. It is useful for procedures requiring a rapid induction of neuromuscular blockade and a short duration of action such as endotracheal intubation.

98. (D) Succinylcholine has a relatively brief duration of action of less than 8 minutes mainly due to its rapid hydrolysis by plasma cholinesterase.

99. (A) Laudanosine has little or no neuromuscular-blocking activity, but it has a relatively long elimination half-life and can cause seizures if it reaches high concentrations in the blood.

100. (E) Tubocurarine blocks the neuromuscular junction by surmountable blockade of postjunctional nicotinic receptors.

101. (C) Succinycholine is the only depolarizing neuromuscular-blocking agent presently in use in the United States. It blocks the neuromuscular junction by combining with nicotinic receptors to cause depolarization of the motor end plate and adjacent membranes.
102. (B) After prolonged exposure to succinylcholine, the postjunctional membrane becomes repolarized, but it is resistant to depolarization by acetylcholine. The exact mechanism for this desensitizing blockade is unclear.

103. (B) Whereas the amplitude of the contractile responses to a tetanus-producing train of nerve stimuli is constant with a phase I depolarizing blockade, it fades with time with phase II depolarizing blockade and nondepolarizing blockade.

104. (C) The transient muscle fasciculations, which are most prominent over the chest and abdomen, are probably associated with the depolarization caused by succinylcholine during its onset of action.

105. (C) Pancuronium produces a moderate blockade of cardiac muscarinic receptors, which is the main mechanism responsible for the moderate increase in heart rate caused by this drug.

106. (D) Tubocurarine produces hypotension, which is principally caused by its release of histamine and, in larger doses, to its ganglionic-blocking action.

107. (C) The neuromuscular blockade produced by nondepolarizing agents is reversed by neostigmine and other cholinesterase inhibitors because the accumulation of acetylcholine at the neuromuscular junction tends to reverse the surmountable blockade produced by the nondepolarizing agents. Accumulation of acetylcholine at the neuromuscular junction does not reverse the phase I depolarizing blockade produced by succinylcholine. In addition, neostigmine inhibits the enzyme (plasma cholinesterase) responsible for the inactivation of succinylcholine.

108. (D) The agents that have intrinsic sympathomimetic activity (ISA) or partial agonist activity (FAA) are characterized as preferred agents in this case since they may be less prone to cause rebound hypertension if a patient misses a dose of the drug. The overall clinical significance of this effect is unclear.

109. (A) Beta-adrenergic blocking agents that are selective for the heart (beta1) would be preferred. These types of agents, when used in the lower dosage range, have selective actions on the heart without adversely affecting airway smooth muscle. This property would be particularly important in patients with asthma.

110. (C) Esmolol can be administered intravenously in the operating room to suppress arrhythmias. It has a short (10 mm) duration of action, making it a relatively safe agent for reversing the arrhythmia. The short duration of action is due to the fact that it is an ester that is rapidly hydrolyzed by plasma esterases.

111. (F) Tramsulosin is a competitive alpha1 blocking agent with selectivity for alpha1A receptors over alpha1B receptors. The efficacy of tramsulosin in benign prostatic
hypertrophy (BPH) suggests that the alpha$_{1A}$ receptor is important in mediating prostate smooth-muscle contraction.

112. (A) There is currently no clinical use for butoxamine, but it is employed in experimental studies to define receptor types.

113. (B) Carvedilol is a nonselective beta-adrenergic blocking agent with alphal selective blocking activity. Thus, this agent would protect the heart from catecholamine-induced arrhythmias and lower peripheral resistance to effectively increase cardiac output while reducing the energy required. The drug also appears to inhibit mitogenesis of vascular smooth muscle.

114. (C) Phenoxybenzamine, a nonequilibrium alpha-adrenergic blocking agent, forms an ethyleneimonium ion when placed in solution. This occurs as a result of the ethylene side chain “cyclizing” with the nitrogen. The charge exists on the nitrogen but transfers to the carbon, making a highly reactive carbonium ion. This ion has a short half-life and it binds covalently to the receptor, effectively permanently removing the receptor’s function. These agents are modeled after the nitrogen mustards (war gases).

115. (E) Stimulation of muscarinic receptors in the heart will lead to slowing of the heart rate. These are M2 receptors, which act by opening potassium channels and inhibiting adenylyl cyclase.

116. (D) Airway smooth muscle relaxes when beta2-adrenergic receptors are stimulated. This receptor activation results from stimulating adenyl cyclase, resulting in an increase in cAMP.

117. (A) The predominance of alpha1 receptors on vascular smooth muscle in skin beds leads to an increase in peripheral resistance when these receptors are stimulated.

118. (D) Activation of beta2 receptors in skeletal muscle vascular beds delivers increased blood flow to these tissues.

119. (F) Catecholamine release from the adrenal gland is mediated by nicotinic receptors. The adrenal gland is similar to a large ganglion, and stimulation results in an increase in circulating epinephrine.

120. (B) Vascular smooth muscle contains alpha2 receptors, which, when stimulated, provide a negative feedback on norepinephrine release from adrenergic nerve endings.

121. (D) Methacholine has selectivity for muscarinic versus nicotinic receptors and is hydrolyzed at a slower rate by acetylcholine esterase than acetylcholine. It is resistant to nonspecific cholinesterase.
122. (C) The primary action of bethanechol is to increase urinary bladder tone and to increase tone of the lower esophageal sphincter in patients with reflux esophagitis. It is not hydrolyzed by cholinesterases.

123. (A) Because acetylcholine is so rapidly hydrolyzed, it has virtually no therapeutic use. Derivatives that have resistance to enzymatic degradation have been synthesized to provide longer duration of action and some selectivity at organ sites.

124. (A) Agents that activate the muscarinic receptor may produce untoward effects in patients with underlying conditions. In asthmatics they cause bronchial smooth-muscle contraction. In patients with angina pectoris, the danger is a hypotensive response that may reduce coronary blood flow. In patients with gastric ulcer, the stimulation of gastric acid secretion would be undesirable.

125. (B) Intoxication with atropine or plants containing anticholinergic agents may include a rapid/weak pulse, flushed skin (scarlet color), widely dilated pupils, and ataxia. The old adage is used to describe anticholinergic intoxication: dry as a bone, blind as a bat, red as a beet, and mad as a hatter. This alkaloid produces both peripheral cholinergic blockade and central nervous system effects.

126. (D) Ganglionic stimulants such as nicotine do not show specificity for nicotine receptors. The effects observed are unpredictable, since nicotine has low selectivity at nicotinic sites and it first stimulates then blocks receptors. The major interest in nicotine is related to its acute and chronic toxicity. However, the use of nicotine patches has led to a renewed interest in this compound in other disease states.

127. (B) Botulinum toxin inhibits vesicular release of acetylcholine by enzymatic removal of two amino acids from fusion proteins.

128. (D) Calcium ion destabilizes the acetylcholine-containing vesicles by interacting with vesicular membrane association proteins (synaptotagmin and synaptobrevin) and terminal membrane proteins (SNAP-25).

129. (E) The antiporter that removes protons an allows storage of acetylcholine in the vesicle can be inhibited by vesamicol.

130. (C) A group of compounds called hemicholiniums block a sodium-dependent membrane carrier, which recovers the cholin from hydrolyzed acetylcholine.

131. (C) The tyrosine analog metyrosine inhibits tyrosine hydroxylase, the rate-limiting enzyme in norepinephrine biosynthesis.
132. (B) Extraneuronal uptake, referred to as up take, is inhibited by glucocorticoids. These agents also stimulate the synthesis of epinephrine in the adrenal gland.

(D) The high-affinity carrier for catecholamines, which is responsible for concentrating catecholamines in the storage granule is inhibited by reserpine alkaloids. These agents deplete several biogenic amines both in the periphery and in the CNS.

134. (A) Bretylium is a local anesthetic sodium channel blocker that concentrates in adrenergic nerve endings and paralyzes the release mechanism for norepinephrine.

135. (B) When dopamine enters the granula vesicle, its beta carbon is hydroxylated to norepinephrine. With nerve stimulation, the contents of the granule, including dopamine hydroxylase, are released.

136. (C) Ingestion of indirect-acting amines found in fermented foods (beer, cheese, wine) can result in the release of large amounts of norepinephrine that has accumulated in adrenergic nerve endings when monoamine oxidase inhibitors (MAOIs) are administered as antidepressants.

137. (D) In the adrenal gland, norepinephrine is converted to epinephrine by the addition of a methyl group on the nitrogen. This process is catalyzed by PNMT.

138. (A) COMT O-methylates the hydroxy group on the ring structure of catecholamines, thus rendering them inactive. Norepinephrine is converted to normetanephrine, and epinephrine is converted to metanephrine. These metabolites can then be oxidatively deaminated by MAO to 3-methoxy-4-hydroxy mandelic acid (VMA).

139. (B) Neostigmine in this example potentiates the muscarinic effects of acetylcholine.

140. (A) The exogenous administration of acetylcholine is competitively inhibited by atropine so that muscarinic responses do not occur with the large acetylcholine dose. The presence of neostigmine allows acetylcholine to penetrate to the adrenal gland, resulting in epinephrine release and the stimulation of ganglia, resulting in the release of norepinephrine (active at adrenergic sites) and acetylcholine (blocked by atropine).

141. (C) Phentolamine will eliminate the alpha1 induced vasoconstriction, leaving the combined beta1 and beta2 activity (classic epinephrine reversal).

142. (E) After the administration of phentolamine, only the beta-adrenergic response remains. Administration of a nonselective blocking agent will eliminate both the beta1 and beta2-adrenergic responses, that is, cardiac stimulation and skeletal muscle vasodilation, respectively.
143. (A) The stimulation of alpha1, alpha2, beta1, and beta2 will give this classic epinephrine response.

144. (D) The stimulation of alpha1, alpha2, and beta1 will give this classic norepinephrine response. Vasodilation in skeletal muscle beds is not present with norepinephrine.

145. (B) Isoproterenol, the classic nonselective beta-adrenergic agonist will stimulate both beta1 (heart) and beta2 (skeletal muscle vascular beds) to give this classic response.

146. (E) The stimulation of alpha1-adrenergic receptors by this agent, which is not inactivated by the usual processes, will result in a prolonged increase in blood pressure.

147. (D) Bretylium has local anesthetic activity. It concentrates in adrenergic nerve endings and inactivates the transport of norepinephrine out of the nerve.

148. (E) Simulation of the receptor on the effector will initiate a cascade of biochemical events, resulting in an action determined by the tissue cells (e.g., contraction of vascular smooth-muscle cells).

149. (G) Indirect-acting adrenergic amines, the prototype being tyramine, enter the nerve ending and release norepinephrine from a “cytoplasmic storage” area. This “pool” is readily depleted and tachyphylaxis occurs.

150. (F) Auto receptors of the alpha2 type activate a negative feedback mechanism that inhibits norepinephrine release from the adrenergic nerve endings.

151. (K) The activation of nicotinic N_M receptors located on skeletal muscle neuromuscular endplates results in opening of sodium and potassium channels and depolarization.

152. (I) Formation of inositol 1,4,5-triphosphate(IP3) and diacylglycerol (DAG) result in increased intracellular calcium. A similar process occurs in postsynaptic effector cells through alpha1 receptor activation.

153. (F) In the renal vascular bed, the admirdstration of low-dose dopamine will selectively vasodilate and result in increased renal perfusion as a consequence of adenylyl cyclase activation.

154. (D) The activation of adenylyl cyclase in bronchial and vascular smooth muscle as a consequence of stimulating beta2 receptors results in relaxation.
155. (L) The primary ganglionic receptor eliciting an excitatory postsynaptic potential (EPSP) in ganglia of the sympathetic or parasympathetic divisions of the autonomic nervous system occurs as a consequence of activation $N_N$ receptors and the opening of sodium and potassium channels on the postganglionic neuron.

156. (E) Stimulation of postsynaptic beta receptors on lipocytes results in an activation of adenylyl cyclase and increased cAMP.