

Mastering the subject of pharmacology taxes painful amounts of time and sweat. This booklet provides a concise content of pharmacology that will help the medical students to pass their USMLE step #1 test.

Choe's Choices of Pharmacology (Quick Cut to the USMLE #1)

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**CHOE'S CHOICES OF
PHARMACOLOGY**

(Quick Cuts to the USMLE Step #1)

By

Jae Y. Choe, Ph.D.

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The author has taken efforts to describe generally accepted views of selected drugs, and to ascertain the accuracy of the information presented. However, considering the constant influx of new drug information, the reader is asked to check the package insert of each drug for any change in indications, mechanisms of action, side effects or special warnings. The author or the publisher is not responsible for errors of omission or for any consequences resulting from utilization of the information in this book.

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He published the books Choe Notes (A Handbook of Pharmacology), the first and second editions; and Choe's Medical Pharmacology, the 3rd edition.

Preface

The expanse of pharmacology is vast, and mastering the subject taxes a painful amount of time and sweat. The agony is acute with medical students who are preparing for their USMLE (United States Medical Licensing Examination) step #1 on pharmacology. What they currently have as a textbook as general are too cumbersome to digest in a short period of time. Here comes the urgency of this booklet aimed at providing an enough yet concise content of pharmacology that will lighten their burden and assist them to pass the test.

To save time of the readers, only focal points in each topic are presented; each drug is presented with major indication(s), mechanism of action(s) if well established, and salient side effect(s) and metabolic fate(s) if worthy to note.

The use of trade names (brand names or product names) of drugs, which are created more for commerce purpose than for science, is avoided in favor of the officially recognized generic names, which are used in medical schools, teaching hospitals, and on the USMLE.

The table of contents this booklet runs in parallel to that of my earlier book entitled Choe's Medical Pharmacology@ 3rd edition Published in 2002 by Wm. Caxton, Ltd.

I am indebted to my two young daughters: Carol Choe for setting up the figures and proof-readings, and Christina Choe, M.D. for reviewing the texts. I hope that this new booklet will serve well in assisting the readers to pass their USMLE on pharmacology.

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March 1, 2007

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I. General Aspects of Pharmacology

1. Introduction

- 1) Pharmacokinetics deals with drug's absorption, distribution, metabolism, and excretion.
- 2) Pharmacodynamics deals with drug's mechanism of action, and dose-response relationship.

2. Drug & Receptors

- 1) Power (or efficacy) of a drug represents the maximal (or ceiling) effect (on Y-axis for bio-response) generated by a pharmacologic agonist.
- 2) Potency compares the amounts of two drugs (on X-axis) which are required to obtain an identical level of pharmacologic effect such as ED_{50} of a standard drug. The drug requiring a smaller dose to do so is the more potent one; and the drug requiring a larger dose, less potent.
- 3) More potent drug does not necessarily mean a more powerful drug.
- 4) ED_{50} is the dose required to produce 50% of the maximal bio-response (in a graded dose-response curve), or the dose that generates a response in 50% of a population (in a quantal-dose response).
- 5) LD_{50} is the dose required to kill 50% of a population.

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6) Therapeutic index (TI) is the ratio of toxic dose over therapeutic dose (LD_{50} / ED_{50}); the higher the TI value, the safer the compound.

7) Spare receptors, if present, influence the sensitivity of the receptors to an agonist but do not affect maximal efficacy of the agonist.

8) A competitive antagonist competes with an agonist for binding to the same receptor. It thereby shifts the log-dose response curve to the right (a greater shift occurs with greater amounts of antagonist). However, there is no depression of the ceiling (or maximal) effect (refer to figure 2-1). This competitive antagonism can be overcome by sufficient amounts of the agonist.

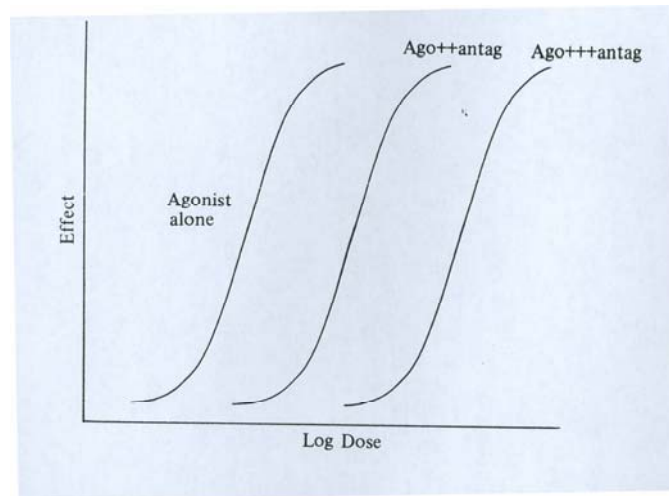


Figure 2-1

9) A noncompetitive antagonist does not compete with an agonist for the same receptor. Instead, it binds close to the active site and blocks the access of the agonist to the receptor. The log dose-response curve is shifted to the right with a depressed ceiling (or depressed maximal)

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effect. The greater the amount of antagonist present, the greater the depression of the ceiling (refer to figure 2-2).

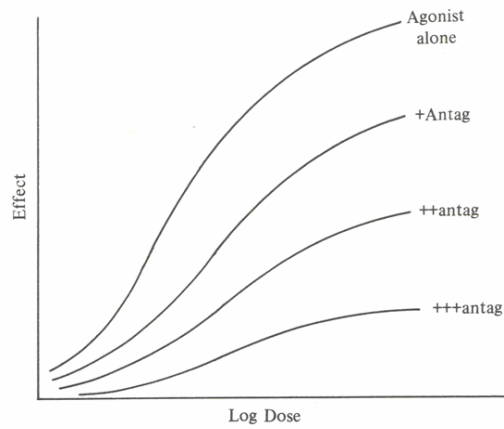


Figure 2-2

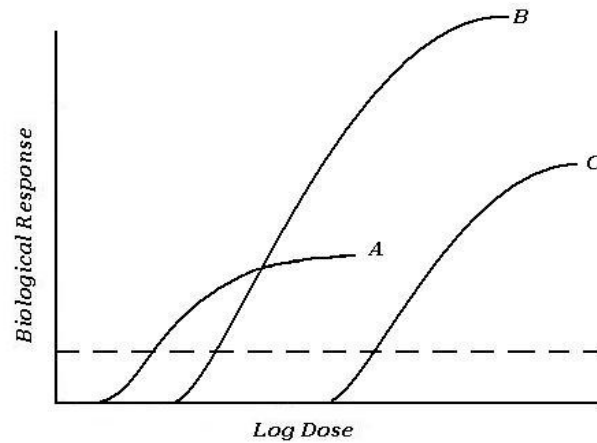


Figure 2-3

10) Among the three drugs shown in figure 2-3, drug B is the most powerful (or most efficacious since it hits the highest ceiling), while drug A is the most potent (since it requires the smallest dose to provide an identical level of response shown by the dotted line).

3. Pharmacokinetics

1) Urinary excretion of Phenobarbital (an acidic drug) will be increased by making the urine alkaline by administration of an alkalinizing agent such as Sodium Bicarbonate (baking soda). This is so because the acidic drug will be more ionized in alkaline urine than in acidic urine, and the ionized drug cannot back-diffuse into the circulation and is excreted in the urine.

2) A drug with a higher affinity for binding to plasma proteins, such as Phenylbutazone, Aspirin or other salicylates, and sulfonamides can

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displace from the protein-binding sites an already-bound drug with lower affinity, such as Tolbutamide (oral hypoglycemic agent) or Warfarin (oral anticoagulant). The displaced drug (now being active unlike the bound one) can generate serious side effects such as hypoglycemia and bleeding respectively.

3) The Apparent Volume of Distribution (Vd) of a drug is the theoretical volume required to contain the total amount of the drug available in the body to produce the same concentration as that present in plasma. Calculation: since concentration by definition is amount/volume, then Volume (Vd) = total amount of the drug/blood concentration of the drug. Example: (refer to figure 3-1) assume 1.2g of a drug was i.v. injected into a patient. The plasma concentration of the drug at time zero is estimated at 100 $\mu\text{g}/\text{mL}$ (or 0.1 mg/mL). Then $V_d = 1.2\text{g}$ (or 1200mg)/0.1mg = 12,000 mL = 12 liters.

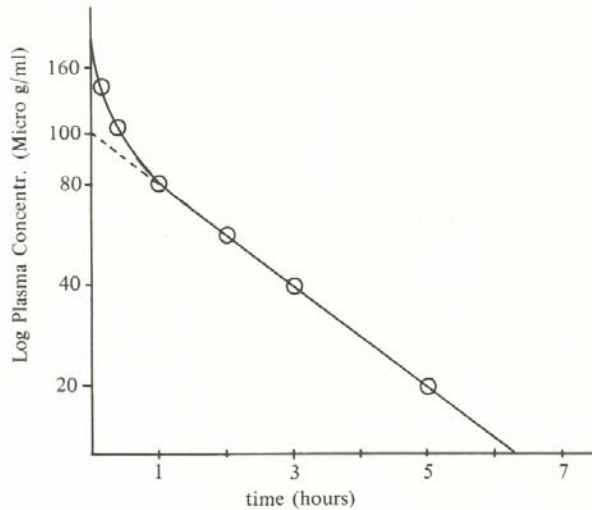


Fig 3-1

4) The elimination half-life here (refer to figure 3-1) is about 2 hours because the drug concentration at 3 hours was 40 units and then was

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reduced to half (20 units) 2 hours later.

Theoretically,

$T_{1/2} = 0.693V_d/Cl$ (where V_d is volume of distribution, and Cl is total body clearance of the drug).

Therefore, the greater the V_d or the smaller the Cl , the longer the elimination half-life.

5) Loading dose (LD) is calculated by this equation; since Concentration by definition is Amount/Volume, then its rearrangement leads to; Amount = Volume x Concentration.

This amount is the loading dose if a drug is given by intravenous injection. If the drug is given by the oral route, we have to factor in bioavailability of the drug (fraction of the amount of drug that gets into the circulation; for instance; $f = 0.8$ meaning 80% entry into the circulation). To compensate for the fraction lost, the adjusted equation is;

$LD \times \text{bioavailability of the drug (f)} = V_d \times \text{desired plasma Concentration of the drug.}$

6) Elimination of most drugs (which includes not only excretion through the kidney, liver, lung, sweat glands and so on, but also metabolism to other products in the liver or other tissues) follows first-order kinetics. That is, a relatively constant fraction (not a constant amount) of an existing amount of drug is eliminated per unit time. In first-order kinetics, it takes 4 half-lives to get about 94% of a drug eliminated. Ethanol, on the other hand, is unusual in that it follows zero-order kinetics, where a relatively constant amount (not constant fraction) per unit time is eliminated regardless of how much is present in the body.

7) Aspirin, at doses below 2 grams a day, follows first-order kinetics, but if its dose exceeds 5 grams a day it will follow zero-order kinetics for its elimination.

8) Therapeutic concentration of Phenytoin is 10-20 $\mu\text{g/mL}$ of blood

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and follows first-order kinetics for elimination. If its concentration exceeds this level, it could follow zero-order kinetics.

9) If a drug is infused continuously the drug will accumulate. If the drug follows first-order kinetics, its accumulation will have a mirror image of its elimination curve; that is, one half-life later it will reach 50% of maximal (or steady state) level, and 2 half-lives later, 75% of the maximum [because half of the remainder (50%) is 25% and will be added to the previous level of 50% full]. At 3 half-lives, half of the remainder (25%), or 12.5%, will be further added to attain at 87.5% of maximum, and so forth.

A sample question below:

A patient requires infusion of an anti-arrhythmic drug, whose half-life is 3 hours. The infusion was started at 11 A.M. and at 5 P.M. the same day a blood sample was taken. The drug concentration was found to be 3 mg/L. What is the probable steady state concentration of this drug at 24 hours of infusion?

- A) 1 mg/L B) 2 mg/L C) 3 mg/L
D) 4 mg/L E) 5 mg/L

Answer is D) because the 6 hours (infusion from 11 AM to 5 P.M.) equals 2 half-lives for drug accumulation. At the 2nd $T_{1/2}$, the drug will have accumulated to reach 75% of the maximum level (or $\frac{3}{4}$ of the steady state level). Since 3 mg/L at the 2nd half-life represents $\frac{3}{4}$ full, then 4 mg/L will be the plateau steady-state level.

10) The total amount of a drug present at its steady state (when the drug rate-in equals drug rate-out) is estimated by $1.5D \times T_{1/2} / I$ (where "D" is the amount of drug administered by each intravenous injection, and "I" represents its dosing interval). Therefore, if 20mg of a drug (with $T_{1/2} = 3$ hours) is injected every 3 hours, the half-life and the "I" cancel each other out, and then the accumulated amount at steady state is $20 \times 1.5 = 30$ mg.

4. Biotransformation of Drugs

- 1) Drugs are metabolized by nonsynthetic (or phase-1) reactions (such as oxidation, reduction, and hydrolysis) or by synthetic (or phase-2) reactions (conjugation with glucuronic acid, glycine, sulfate, a methyl group, or an acetyl group).
- 2) Microsomal enzyme inducers include Phenobarbital, Griseofulvin, Rifampin, and Chloralhydrate.
- 3) Microsomal enzyme inhibitors include Phenylbutazone, Chloramphenicol, Cimetidine, and Erythromycin.
- 4) Use of a barbiturate is contraindicated in patients with porphyria because it also induces mitochondrial enzyme δ -aminolevulinic acid synthase which promotes formation of porphobilinogen (a heme precursor) to cause acute intermittent porphyria.
- 5) Rapid elimination of the neurotoxic bilirubin requires conjugation with glucuronic acid. Therefore, deficiency of glucuronyltransferase in the liver causes accumulation of bilirubin, which is then bound to albumin to float in circulation and to make the skin yellowish in color. Salicylates (such as Aspirin), Phenylbutazone, or other drugs that have a higher affinity than bilirubin for binding to the proteins will displace bilirubin, which as a free unbound form will enter the brain of infants to damage it (kernicterus).
- 6) Deficiency of the enzyme glucose-6-phosphatase leads to hypoglycemia and excessive accumulation of glycogen in the liver and kidney (Glycogen Storage Disease or Von Gierke's Disease).
- 7) Glucose-6-phosphate dehydrogenase is involved in the formation of NADH (reduced form of nicotinamide adenine dinucleotide), which is important for reduction of methemoglobin back to normal hemoglobin, as well as to convert oxidized glutathione back to the biologically active reduced form of glutathione. Therefore, this

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enzyme deficiency will bring about methemoglobinemia and ruptured RBC (red blood cell) membrane with hemolysis.

5. Drug Effectiveness versus Genetic Factors

- 1) Tachyphylaxis is a rapid (within minutes or hours)-developing tolerance.
- 2) Chemical antagonism: effects of Heparin (organic acid) can be antagonized by chemical neutralization by Protamine (organic base).
- 3) Physiological antagonism: effect of Histamine (bronchoconstriction) can be antagonized by Epinephrine (bronchodilation).
- 4) Pharmacological antagonism: effects of Pilocarpine (an agonist on the muscarinic receptors) can be antagonized by Atropine (a blocker at the muscarinic receptors).
- 5) Rate of acetylation of Isoniazid (antituberculous drug) varies genetically. Most Eskimos and Asians are more rapid-acetylators than are most African and Caucasians. Rapid-acetylators are more prone to suffer hepatitis as a side effect, while slow-acetylators are more prone to suffer peripheral neuritis.
- 6) Primaquine, an antimalarial drug, generates an oxidant metabolite that can deplete NADPH, whose regeneration requires the enzyme glucose-6-phosphate dehydrogenase. Hence, patients having a deficiency of this enzyme are vulnerable to methemoglobinemia and hemolytic anemia.
- 7) Succinylcholine (a neuromuscular blocker) is rapidly inactivated by plasma cholinesterase. In persons with a genetic abnormality of

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this enzyme, Succinylcholine cannot be quickly inactivated and will cause a prolonged apnea. Dibucaine Number refers to percent inhibition of the plasma cholinesterase in the presence of Dibucaine. A normal enzyme has its value around 80, but an atypical enzyme has a value around 20 or only slightly higher.

6. Variables Affecting Pharmacokinetic Parameters

- 1) In geriatric patients, concentration of blood albumin is lower than in young adults. Hence a lesser amount of Phenylbutazone binds to albumin and provides a greater free drug concentration, causing a greater incidence of adverse effects of the drug.
- 2) In neonates the microsomal enzyme glucuronyltransferase is not yet fully developed and Chloramphenicol (antibiotic) cannot be quickly eliminated via the enzyme, causing the so-called “Gray-Baby Syndrome”.
- 3) Tetracycline taken by a nursing mother can be excreted into the milk to affect suckling infants. Tetracycline can cause permanent discoloration of the teeth of the baby.
- 4) Lithium Carbonate (antimanic drug) is also excreted into the milk and may cause convulsions in the baby.
- 5) Ethanol ingestion for a week or so can induce microsomal enzymes to promote oxidation of Acetaminophen to generate a free radical metabolite (N-acetylbenzoquinoneimine), whose detoxification need the presence of the reduced form of glutathione. If availability of the reduced form of glutathione is insufficient, the free radical causes necrotic damage to the liver and the kidney. Overdoses of Acetaminophen also cause accumulation of the toxic metabolite. Toxicity of the drug can be prevented by administration of

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Acetylcystein (0.1g/kg within 12 hours of the overdosing), which promotes formation of the reduced form of glutathione.

6) During starvation, urine becomes more acidic and water-soluble basic drugs such as Amphetamine will be eliminated more quickly in the urine.

7) In achlorhydria, the gastrointestinal absorption of Ketoconazole (antifungal drug) is inhibited.

II. Drugs Acting on the Autonomic Nervous System & Autacoids

7. Neuropharmacology

- 1) Acetylcholine has nicotinic receptors (N_n : at the autonomic ganglia; and N_m : at the end plate of skeletal muscle), and muscarinic receptors (M_1 at the autonomic ganglia; M_2 at the SA node and the AV nodes of the heart; and M_3 at the blood vessels, bronchial smooth muscle, intestinal smooth muscle, urinary tract, and exocrine glands).
- 2) Activation of N_n receptors causes increased impulse transmission at the autonomic ganglia, and since the adrenal medulla behaves like a modified ganglion, activation of the N_n receptors there causes increased secretions of catecholamine from the medulla.
- 3) Activation of N_m receptors at neuromuscular junctions opens sodium channels, which in turn triggers the opening of calcium channels. An influx of calcium ions triggers the contraction of skeletal muscles. However, prolonged stimulation by a nicotinic agonist produces a "depolarizing blockade." That is, the continued presence of a nicotinic agonist on the N_m receptor causes the neuron to stop firing and results in flaccid paralysis of the muscle.
- 4) Activation of M_1 receptors at the autonomic ganglia facilitates impulse transmission. Pirenzepine is a specific M_1 receptor blocker that can reduce gastric acid secretions.
- 5) Activation of M_2 receptors at the SA-node increases K^+ permeability of the cell (or decreases c-AMP) to hyperpolarize the node to reduce heart rate; and activation of M_2 receptors at the AV

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node likewise reduces cardiac conduction speed there.

6) The M_3 receptors have a wide distribution on smooth muscles. Vasodilation through M_3 receptors causes reflex activation of sympathetic system, which in turn increases the heart rates to overshadow the direct M_2 effect (reduced heart rate), but if the subject is pretreated with a ganglionic blocker such as Hexamethonium or Mecamylamine, the reflex activity disappears to show the direct effect which is the reduced heart rate.

7) Epinephrine or Norepinephrine has adrenergic α_1 , α_2 receptors, and β_1 , and β_2 receptors. Activation of adrenergic α_1 receptors causes contractions of smooth muscles such as vasoconstriction, mydriasis (eccentric contraction of iris muscles), contraction of ileocecal sphincter, and contraction of sphincter of urinary bladder, all through the formation of Inositol-1, 4, 5-triphosphate (IP_3).

8) Activation of adrenergic α_2 receptors (presynaptic autoreceptors) causes inhibited release of norepinephrine from adrenergic nerve terminals (through inhibited formation of c-AMP), inhibited release of insulin from the pancreas, and inhibited release of free fatty acids from the fat-cells.

9) Activation of adrenergic β_1 receptors causes increased cardiac output (with increased cardiac contractility and increased heart rate) and increased release of kidney enzyme renin.

10) Activation of adrenergic β_2 receptors causes relaxations of smooth muscles such as bronchodilation, vasodilation, and relaxation of uterine muscle; and it causes glycogenolysis and increased gluconeogenesis to elevate blood levels of glucose.

11) Norepinephrine (NE) acts on the adrenergic β_1 receptors to increase heart rate (its direct effect), but vasoconstriction caused by Norepinephrine (NE) via its activation of adrenergic α -receptors triggers a reflex activation of the parasympathetic system to lower the

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heart rate by overpowering its direct effect. However, pre-treatment of the subject with a ganglionic blocker such as Hexamethonium or Mecamylamine can abolish the indirect reflex effect to show its direct effect of increased heart rate. A α_1 blocker or a muscarinic antagonist also can abolish this indirect effect.

12) Metyrosine is a drug that can inhibit tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of NE, and is used to diminish formation of NE in pheochromocytoma.

13) Alpha-methyldopa is converted to alpha-methyl norepinephrine which activates the presynaptic α_2 receptors to reduce the release of NE and thereby reduces vascular resistance in hypertensive patients.

14) Both epinephrine and norepinephrine are metabolized by MAO (monoamine oxidase) and COMT (catechol-O-methyltransferase) to become a common inactive metabolite VMA (vanillyl mandelic acid).

15) Glycine is an inhibitory neurotransmitter at spinal motoneurons. It opens chloride channels to promote influx of the chloride ions to cause hyperpolarization of the motoneurons (hence inexcitable), and Strychnine competitively blocks this action of glycine to cause convulsions.

16) GABA (gamma-aminobutyrate) is another inhibitory neurotransmitter in many different areas of the brain. It has postsynaptic GABA-A receptors to open chloride channels and this effect is blocked by Bicuculline, and it has presynaptic GABA-B receptor which by promoting potassium efflux causes hyperpolarization to inhibit the release of excitable neurotransmitters such as acetylcholine that can cause skeletal muscle spasticity. This receptor is activated by Baclofen which is used to relieve muscle spasticity.

17) Botulinum toxin (exotoxin from *Clostridium botulinum*) inhibits the release of Ach, whereas Latrotoxin (venom of black widow

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spider) can cause excessive release of Ach. Tetanus toxin (from *Clostridium tetani*) inhibits the release of both glycine and GABA to cause lock-jaw (trismus).

8. Cholinomimetic Drugs

1) Activation of M₃ receptors is causative of vasodilation (through the release of nitric oxide that induces synthesis of c-GMP in vascular smooth muscle cells), bronchoconstriction, increased peristaltic activity of intestine, and contraction of detrusor muscle of the urinary bladder to cause urine voiding (this last three effects may be through formation of Inositol-1, 4, 5-triphosphate [IP₃] that causes the release of calcium ions from the endoplasmic reticulum).

2) Pilocarpine is a drug of choice (DOC) to lower intraocular pressure.

3) Bethanechol is a DOC in the treatment of postoperative urinary retention and abdominal distention.

4) Neostigmine is a reversible inhibitor of acetylcholinesterase (hence, an indirect-acting drug), but it also has a direct agonistic effect on the nicotinic receptors at neuromuscular junctions. Neostigmine is therefore useful to relieve urinary retention and to treat myasthenia gravis.

5) Pyridostigmine is another reversible inhibitor of acetylcholinesterase and is a DOC in the maintenance treatment of myasthenia gravis.

6) Edrophonium chloride is another indirect-acting cholinergic drug like Neostigmine, but Edrophonium is more rapid-acting and shorter-acting than Neostigmine. Edrophonium is a DOC to rapidly reverse

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muscle paralysis caused by curare poison, and it is a DOC to differentiate between myasthenia gravis and cholinergic crisis.

7) As Edrophonium works only by blocking inactivation of acetylcholine released from intact cholinergic fibers, it by itself cannot lower blood pressure because vascular smooth muscle has muscarinic receptors (M_3) but has no cholinergic fiber from which acetylcholine can be released to cause vasodilation with its consequent hypotension.

8) Physostigmine is another reversible inhibitor of acetylcholinesterase. Unlike Neostigmine, Physostigmine can easily get into the brain to cause accumulation of central acetylcholine. Hence, Physostigmine can counteract CNS toxicity of muscarinic blocking drugs such as Atropine.

9) Donepezil, Galantamine, Rivastigmine, and Tacrine are drugs used to treat Alzheimer's disease. All of them are reversible inhibitors of acetylcholinesterase that destroys acetylcholine in the brain.

10) Memantine is also used to limit dementia in Alzheimer's disease, but its effects are independent of acetylcholine and acetylcholinesterase. Memantine noncompetitively blocks the N-methyl-D-aspartate (NMDA) receptors and thereby opposes the effects of glutamate on the receptors.

11) Pralidoxime can reactivate acetylcholinesterase or other pseudoacetylcholinesterase that is inactivated by organophosphates such as soman (a nerve gas), tabun (a liquid warfare agent), malathion (an insecticide), parathion (an insecticide), and sarin (a nerve gas).

9. Belladonna Alkaloids & Other Antimuscarinic Drugs

- 1) Belladonna alkaloids (Atropine and Scopolamine) are natural antimuscarinic agents. Atropine is a nonspecific muscarinic antagonist (as it blocks all types of muscarinic receptors; M₁, M₂, and M₃).
- 2) Antimuscarinic drugs produce mydriasis and cycloplegia. They can also prevent such muscarinic effects as reduced heart rate, slowed AV conduction speed, reduced cardiac contractility, vasodilation and lowered blood pressure, and bronchoconstriction.
- 3) Atropine, an antimuscarinic drug, causes a slight fall of the heart rate initially and then slight rise (80-90/min) later.
- 4) The diameter of arteries and arterioles is not controlled by cholinergic fibers as there is no cholinergic innervation there. However, the vessels have muscarinic receptors, activation of which cause vasodilation and consequent fall of blood pressure.
- 5) Blockade of the vascular muscarinic receptors by an antimuscarinic drug can prevent the fall of blood pressure caused by a muscarinic agonist, but that drug has little effect in a normotensive person to cause postural hypotension.
- 6) Antimuscarinic drugs reduce intestinal motility, reduce secretions of gastric acid, and inhibit exocrine secretions such as tearing, salivation, lacrimation, and sweating. Atropine can cause hyperthermia as an important side effect especially in children.
- 7) Antimuscarinic drugs can cause urinary retention and is useful in treatment of enuresis in children. Oxybutynin, Solifenacin, and Darifenacin may be used to treat overactive bladder. They block M₃ receptors. Trospium and Tolterodine are other drugs useful to treat

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overactive bladder, but both are nonspecific muscarinic receptor blockers.

8) Glycopyrrolate is an antimuscarinic agent useful in the treatment of duodenal ulcer and to decrease pulmonary secretions occurring during general anesthesia.

9) In Parkinson patients, the level of dopamine in their brain is subnormal, making cholinergic input the predominance tone impacting their CNS function. Hence, an antimuscarinic drug that can enter the brain is useful to treat Parkinson disease. Such drugs include the belladonna alkaloids (Atropine and Scopolamine), and synthetic antimuscarinic agents such as Benztropine, Orphenadrine, Diphenhydramine, and Trihexyphenidyl. Another approach to treat Parkinsonism is to raise the brain levels of dopamine. Since dopamine itself is poorly absorbed and cannot get into the brain, its precursor L-dopa is used. However, since L-dopa itself can be quickly converted by dopa decarboxylase to dopamine before entering into the brain, Carbidopa that inhibits this enzyme must be used together. Since L-dopa can also be converted by another enzyme COMT (catechol-o-methyltransferase) to 3-methyl dopa, which can interfere by competition with the entry of L-dopa into the brain, an inhibitor of COMT, such as Tolcapone, or Entacapone is recommended to use together. Once in the brain, L-dopa is converted by intracellular dopa decarboxylase to dopamine to raise its brain levels.

10) Some dopamine agonists that directly activate the brain dopamine receptors are used for treatment of Parkinsonism. They include Pergolide, Piribedil, Ropinirole, and Pramipexole.

11) Bromocriptine also has an agonistic effect on the brain dopamine (D-2) receptors and is useful in the treatment of Parkinsonism. The dopamine agonist can enhance release of gonadotropins such as FSH (follicle stimulating hormone) and LH (luteinizing hormone) while inhibiting the release of prolactin and GH (growth hormone). So Bromocriptine is also used to restore fertility, to treat breast

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engorgement, and to treat acromegaly. Side effects of Bromocriptine include erythromelalgia (red and painful toes and fingers) and postural hypotension.

12) Since dopamine in the brain is inactivated by MAO-B, Selegiline that selectively inhibits this enzyme is also useful to treat Parkinsonism.

13) Some drugs release dopamine in the brain and are useful to treat Parkinson disease. They include Amantadine.

10. Ganglionic & Neuromuscular Blocking Drugs

1) Hexamethonium is regarded as a ganglionic blocker. All the indirect autonomic reflex effects of a drug disappear in the presence of a ganglionic blocker to reveal its direct effects.

2) Norepinephrine (NE) has its agonistic effect on the cardiac β_1 receptors to increase heart rate (HR) as a direct effect, but clinically NE causes reduction of heart rate instead. This is so because vasoconstriction caused by NE via its α_1 receptors triggers a reflex activation of the parasympathetic system to activate M_2 receptors on the SA node and to reduce the heart rate. This indirect effect overshadows the direct effect of NE. However, if a subject is pretreated with a ganglionic blocker, this indirect effect of Norepinephrine disappears to show its direct effect, which is the increased HR.

3) The indirect effect of lowered heart rate by NE also disappears in the presence of α_1 receptor-blocker (hence no vasoconstriction to trigger the reflex), or in the presence of a muscarinic receptor-blocker (hence, no mediation of the reduced heart rate).

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- 4) The dominant tone to the cardiovascular system is that of the sympathetic input to support blood pressure and to lower the heart rate; ganglionic blockade causes a drop in blood pressure and increased heart rate.
- 5) Acetylcholine (ACh) has an M_2 agonistic effect on the SA node to lower HR (a direct effect). Acetylcholine also acts on the vascular M_3 receptors to induce vasodilation, which triggers a reflex activation of the sympathetic system to increase HR (an indirect effect) to overpower its direct effect. This indirect effect of increased HR by ACh disappears when the subject is pretreated with a ganglionic blocker to reveal its direct effect (lowering of the HR).
- 6) Mecamylamine is an orally effective ganglionic blocker used to lower blood pressure. It can enter the brain to cause mental confusion and choreiform movement.
- 7) Mydriasis and cycloplegia occur in the presence of a ganglionic blocker because the usually predominant parasympathetic tone to the ocular tissue (causing miosis and convex lens) is blocked to reveal sympathetic influence on the eyes.
- 8) D-tubocurarine (a curare ingredient) competes with acetylcholine for binding to nicotinic receptors at neuromuscular junctions (hence, a competitive blocker) to cause skeletal muscle paralysis. A drug that can accumulate acetylcholine by blocking its destruction, such as Neostigmine, or Acetylcholine itself can overcome this blockade.
- 9) Synthetic competitive nondepolarizing blockers include Pancuronium, Atracurium, Mivacurium, Vecuronium, and Rocuronium.
- 10) Atracurium, a synthetic competitive nondepolarizing blocker, is inactivated spontaneously to form laudanosine, which enters the brain to cause seizures.

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11) Succinylcholine is a depolarizing blocker. Unlike acetylcholine, Succinylcholine causes a nonsynchronized, aberrant, and persistent depolarization that does not cause effective muscle contractions, but creates a prolonged refractoriness (the so-called phase-1 block by this drug). Eventually repolarization takes place, but as long as the drug is bound to the nicotinic receptors the muscle paralysis is continuous (phase-2 block by Succinylcholine). The phase-1 block (fasciculation, during which muscle injury may cause myoglobin excretion in the urine, is followed by paralysis of muscle) can be aggravated by acetylcholine or a drug that accumulates acetylcholine by blocking its metabolizing enzyme. This phase-1 block can be reversed by a curare-like drug. The phase-2 block, on the other hand, is aggravated by a curare-like drug but can be reversed by acetylcholine or a drug that can accumulate acetylcholine by blocking its inactivation.

12) Succinylcholine releases histamine and can cause malignant hyperthermia as a side effect. An early sign of malignant hyperthermia is trismus (contraction of jaw muscle). Acidosis may occur as a consequence of malignant hyperthermia.

13) Dantrolene is used to produce muscle relaxation. Dantrolene opposes the release of calcium ions from sarcoplasmic reticulum onto the contractile units of skeletal muscle.

14) Methocarbamol, Cyclobenzaprine, Metaxalone, and Chlorzoxazone are all centrally acting skeletal muscle relaxants.

11. Sympathomimetic Drugs

1) Norepinephrine (NE) has a strong α_1 -agonistic effect to cause vasoconstriction, with consequent elevation of both systolic and diastolic blood pressures.

2) The released NE from the adrenergic nerve terminals is taken back

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into the neurons to activate presynaptic α_2 - receptors to inhibit any further release of NE.

3) Norepinephrine (NE) has a mild β_1 -agonistic effect to increase heart rate (HR), but this direct effect is overshadowed by its indirect reflex effect; in other words, the strong vasoconstriction by NE triggers reflex activation of the parasympathetic system to lower the HR. This indirect effect of the lowered HR disappears if the subject is pretreated with a ganglionic blocker, with an alpha-blocker, or with a muscarinic blocker to reveal its direct effect of increased HR.

4) Epinephrine (EPI) has a strong β_1 -effect on the heart to increase both cardiac contractility and heart rate. The effect of EPI on the blood vessels is dose-dependent; at low physiological doses, EPI has a strong β_2 -agonistic effect to cause vasodilation, but at high pharmacologic doses, EPI generates a strong α_1 -agonistic effect to cause vasoconstriction so that both systolic and diastolic blood pressures elevated. The pulse pressure (difference between systolic and diastolic pressure) is not much altered at high doses of EPI, but the pulse pressure is increased at its low doses because EPI elevates systolic blood pressure (because of the heart contraction), while lowering diastolic pressure (during the heart relaxation).

5) Even though EPI at low doses has a strong vasodilating β_2 -agonistic effect, the blood vessels of the skin, intestine, uterus, and kidney are constricted because their blood vessels are equipped mainly or solely with α_1 receptors, mediating the vasoconstriction instead.

6) Adrenergic α_1 receptor agonists cause vasoconstriction to support blood pressure, or to obtain nasal vasoconstriction to relieve nasal congestion. Those α_1 receptor agonists include Methoxamine, Phenylephrine, and Ephedrine.

7) Adrenergic β_1 -agonists used to increase cardiac output include Dopamine, and Dobutamine. They increase formation of c-AMP

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through activation of adenylate cyclase. The c-AMP in turn activates protein kinase-A to phosphorylate calcium channels, which leads to increased influx of calcium ions to cause the increased cardiac output.

8) Adrenergic selective β_2 -agonists useful to obtain bronchodilation for asthma include Albuterol, Terbutaline, and Metaproterenol. All of them increase c-AMP to mediate the bronchodilation. Their side effects include muscle tremor.

9) Tyramine is an ingredient of some foods and drink (such as cheese, red wine, and chicken' liver) that can release excessive amount of norepinephrine to cause hypertensive crisis. Normally, tyramine is inactivated by intestinal MAO-A (monoamine oxidase), but if tyramine is taken with any drug that can inhibit this MAO, it causes this crisis (the so-called Cheese Reactions).

10) Dopamine at low infusion rates of 2-5 μ g/kg/minute can generate β_1 -agonistic effect to increase cardiac output. Dopamine at this dose range is also useful to increase glomerular filtration rate and to promote urinary excretion of sodium, because Dopamine has its own D-1 (dopamine) receptors at the renal vessels, whose activation causes renal vasodilation. However, if the infusion rate of Dopamine is greater than 10 μ g/kg/min, it activates adrenergic α_1 -receptors on blood vessels to cause wide-spread vasoconstriction, including that of the renal vessels, overpowering the renal vasodilation caused by its low doses. NE and EPI, unlike Dopamine, cannot increase renal blood flow because renal vessels are not equipped with β_2 -receptors to mediate vasodilation, but have α -receptors to cause renal vasoconstriction instead.

11) Dobutamine is a selective adrenergic β_1 -agonist that can increase both blood pressure and heart rate.

12) Ritodrine and Terbutaline are β_2 -agonists acting on the uterus to cause relaxation. They may be used to prevent premature labor.

13) Phenylpropanolamine has α_1 .agonistic effects to cause nasal

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vasoconstriction, which is useful to relieve nasal congestion. Phenylpropanolamine is also used as an anorexiant (agent that cuts down food appetite).

14) Methamphetamine, Dextroamphetamine, Amphetamine, or Methylphenidate may be used to treat narcolepsy, attention deficit disorder, or to obtain anorexic effect. Benzphetamine is also used to reduce body weight.

15) Atomoxetine is used to treat mental depression. It is a selective norepinephrine reuptake inhibitor and hence it increases the brain levels of norepinephrine.

16) Brimonidine is a selective α_2 agonist that blocks the release of norepinephrine. Brimonidine is used to lower intraocular pressure, as it diminishes formation of aqueous humor.

12. Adrenergic Blocking & Adrenergic Neuronal Blocking Drugs

1) Epinephrine-Reversal: Epinephrine has both α_1 -agonistic effects (vasoconstriction) and β_2 -agonistic effects (vasodilation). At low doses (10 $\mu\text{g}/\text{kg}$ body weight or less) vasodilation dominates to lower blood pressure, but at high doses (above 200 $\mu\text{g}/\text{kg}$ body weight) vasoconstriction dominates to elevate blood pressure. This pressure-elevating effect of Epinephrine can be reversed to a blood pressure-lowering effect (the so-called Epinephrine-Reversal), provided that the subject was pretreated with an adrenergic α -blocker. In the absence of the α -agonistic effect that supports blood pressure, the unmasked β_2 -agonistic effect (vasodilation) causes a profound hypotension. Phenylephrine or Norepinephrine, on the other hand, has only vasoconstricting α -agonistic effects with no vasodilating β_2 effects. Hence, blood pressure elevation by these drugs can be

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abolished by an α -blocker, but the blood pressure cannot be reversed to hypotension.

2) Phentolamine is a competitive α -blocker, whereas Phenoxybenzamine is a noncompetitive (or irreversible) blocker. Hence, Phentolamine causes parallel shifting of a dose-response curve of α -agonist without depression of its maximal response (so only affinity for binding to receptors affected), whereas Phenoxybenzamine causes not only shifting to the right but depressions of maximal responses as well (so both affinity and efficacy affected).

3) Adrenergic β -blockers cause negative inotropic effect (reduced cardiac contractility), negative chronotropic effect (reduced heart rate), and lowering of blood pressure.

4) AMEBA (Atenolol, Metoprolol, Esmolol, Betaxolol, and Acebutolol) are cardioselective (or β_1 -selective) blockers and have little significant blocking effect on the bronchodilating β_2 -receptors. Hence, asthma patients should prefer these β_1 -selective blockers.

5) CAPP (Carteolol, Acebutolol, Pindolol and Penbutolol) have some ISA (intrinsic sympathomimetic activity) such as some vasodilation for patients with cold hands or feet. They cause a less dramatic reduction of cardiac contractility and heart rate.

6) TMBL (Timolol, Metipranolol, Betaxolol, and Levobunolol) are approved to lower intraocular pressure for glaucoma patients.

7) Side effects of β -blockers include bronchoconstriction by nonselective beta-blockers, and delayed recovery from hypoglycemia caused by hypoglycemic agents such as insulin.

8) Reserpine depletes norepinephrine, serotonin, dopamine, and GABA (gamma-aminobutyrate) in the brain, causing many side effects.

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9) Guanethidine and Guanadrel have reserpine-like NE-depleting effects, but Guanadrel has a much quicker onset and much shorter duration of action than Guanethidine. Side effects of Guanethidine include retrograde ejaculation and postural hypotension. They both can initially release norepinephrine to elevate blood pressure and their use therefore is contraindicated in patients with pheochromocytoma.

10) Alfuzosin and Tamsulosin are used to treat benign prostatic hyperplasia. They are α_1 -blockers and relax the neck muscles in the prostate and bladder to allow easier flow of the urine.

13. Antihypertensive Drugs

1) Antihypertensive drugs have different modes of action. Some activate central adrenergic α_2 receptors to depress sympathetic outflow from the vasopressor area of the vasomotor center. This results in lowering of blood pressure. Those drugs include Clonidine, Guanfacine, Guanabenz, and Methyldopa. All except Methyldopa can cause rebound hypertension if withdrawn abruptly. All including Methyldopa produce drowsiness and dizziness as side effects, and Methyldopa produces additional side effects of hemolytic anemia, gynecomastia, and inappropriate lactation.

2) Some antihypertensive drugs block impulse transmission at the sympathetic ganglia to lower blood pressure. Such drugs include Hexamethonium and Mecamylamine, but since they can also block transmissions at numerous parasympathetic ganglia and generate a wide variety of adverse effects, they are not routinely used to lower blood pressure.

3) Nonselective α -blockers such as Phentolamine and Phenoxybenzamine are not routinely used to lower blood pressure because their blockade on presynaptic α_2 -receptors causes increased

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release of norepinephrine whose β -agonistic effect on the heart causes palpitation. Therefore, α_1 -selective blockers that do not cause NE release (hence little palpitation) are preferred. Those α_1 -selective blockers include Prazosin, Terazosin, and Doxazosin. Their side effects include the so-called “first-dose phenomenon” of postural hypotension and syncope.

4) Almost all of the currently available β -blockers are used to lower blood pressure. They include Propranolol, Nadolol, Atenolol, Acebutolol, and Pindolol. They decrease cardiac output and decrease release of Renin (a kidney enzyme which is involved in the formation of angiotensin, a powerful vasoconstrictor and releaser of aldosterone, a hormone that causes sodium and water retention). Side effects of β -blockers include elevation of blood levels of triglyceride.

5) Some antihypertensive drugs work by inhibition of the enzyme ACE (angiotensin converting enzyme) involved in the formation of angiotensin-II from angiotensin-I. Such drugs include Captopril, Enalapril, Lisinopril, Benazepril, Fosinopril, Quinapril, and Ramipril. Side effects include nephrotoxicity (proteinuria); elevation of blood K^+ with altered sense of food taste; and bronchoconstriction with dry cough (this is so because the ACE is also the enzyme that inactivates kinins which are bronchoconstrictive peptides; hence, ACE inhibitors accumulate the bronchoconstrictive kinins).

6) Some antihypertensive drugs work by blocking the angiotensin receptors. They include Losartan, Valsartan, Candesartan, Olmesartan, Irbesartan, Rosuvastartan, and Valsartan. Since they do not inhibit the enzyme ACE (angiotensin converting enzyme), they are less likely to accumulate kinins to cause bronchoconstriction.

7) Some antihypertensive drugs cause direct-vasodilation of the resistance vessels. They include Diazoxide, Minoxidil, Sodium Nitroprusside, and Hydralazine.

8) Both Diazoxide and Minoxidil increase membrane permeability to

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potassium ions to cause hyperpolarization of vascular smooth muscle and hence vasodilation. Diazoxide is a drug of choice to treat hypertensive encephalopathy. One side effect of diazoxide is hyperglycemia because it opposes the release of insulin from the pancreas. Minoxidil is usually taken orally. Since its vasodilation can trigger sympathetic activation (and cause a coronary attack) it is usually taken together with a β -blocker. Side effects of minoxidil include pericardial effusion as well as hirsutism (hairiness) and hypertrichosis (overgrowth of hair).

9) Sodium Nitroprusside releases nitric oxide from its own molecule, whereas Hydralazine releases nitric oxide from the vascular endothelium. The released nitric oxide activates guanylate cyclase to raise cyclic-GMP, which in turn causes vasodilation. Sodium Nitroprusside causes a rapid vasodilation of both arterioles and venules and hence is a drug of choice to rapidly control blood pressure in patients with left ventricular failure. Hydralazine is used more often by oral route than by injection. Since its vasodilation can trigger sympathetic activation to cause coronary attack it is usually taken together with a β -blocker to avoid such mishap. Side effects of Hydralazine include systemic lupus-erythematosus-like symptoms (skin rash, swelling and tenderness of wrist and knees).

10) Calcium channel blockers such as Verapamil, Diltiazem, Amlodipine, and Nifedipine are useful to lower blood pressure. Side effects of them include constipation, and headache.

11) Eplerenone is used to obtain diuresis or to lower blood pressure. It blocks aldosterone receptor.

14. Histamine

- 1) Both Epinephrine and Theophylline can increase intracellular levels of c-AMP; the former by activation of adenylate cyclase to increase the formation of c-AMP, and the latter by inhibition of phosphodiesterase, the enzyme that destroys c-AMP. The c-AMP inhibits the release of histamine and induces bronchodilation.
- 2) Cromolyn Sodium has nothing to do with c-AMP but it opposes the release of histamine by blocking transmembrane influx of calcium ions. Its inhalation can help prevent but not treat asthma attack.
- 3) Histamine activates nitric oxide synthase to increase formation of nitric oxide (NO), which in turn activates guanylate cyclase to increase c-GMP that causes rapid vasodilation. Histamine also increases c-AMP at the parietal cells of the stomach and activates the H^+/K^+ -ATPase pump to increase gastric acid secretion.

15. Antihistamines

- 1) Antihistamines are compounds that block H-1 receptors located at bronchial smooth muscle and at intestinal smooth muscle. Bronchoconstriction or intestinal contractility caused by histamine can be prevented by antihistamine. Commonly used antihistamines include Chlorpheniramine, Brompheniramine, Hydroxyzine, Cyclizine, and Azelastine.
- 2) Most antihistamines generate anticholinergic side effects such as sedation/drowsiness, but few are exceptions to this rule. Those antihistamines without such sedation and drowsiness include Fexofenadine, Cetirizine, Loratadine, and Desloratadine.
- 3) Antihistamines are used to treat allergic rhinitis (runny nose),

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conjunctivitis, and angioedema but not asthma nor anaphylaxis, where a physiological antagonist such as Epinephrine or Isoproterenol is a drug of choice.

4) Sedation generated by some antihistamines is so great that they are used to promote sleep. Those drugs include Diphenhydramine, Promethazine, Pyrilamine, and Doxylamine.

5) Olopatadine is used to treat “red eye”. Olopatadine inhibits the release of histamine.

6) H-2 receptors are found on parietal cells of the stomach, whose stimulation leads to increased c-AMP and activation of the H^+/K^+ -ATPase pump to increase secretions of gastric acid. Therefore, H-2 antagonists, which decrease c-AMP, are used to stop secretions of gastric acid for peptic ulcer patients. The H-2 antagonists include Cimetidine, Ranitidine, Famotidine, and Nizatidine. Cimetidine unlike others can generate such side effects as reduced hepatic blood flow, inhibited activity of hepatic microsomal enzymes, increased release of prolactin (hence, inappropriate lactation in females, and gynecomastia in men), and antiandrogenic effects such as atrophy of seminiferous tubules and seminal vesicles.

16. Serotonin & Related Compounds

1) Serotonin or 5-HT (short for 5-hydroxytryptamine) has many different receptors. Important ones include the 5-HT-1a receptor whose activation by Buspirone increases neuronal permeability to potassium ions, causing hyperpolarization of the central neurons and thereby resulting in a mild antianxiety effect. The 5-HT-1d receptors can be activated by Sumatriptan which causes cerebral vasoconstriction; it is used as a DOC to treat acute attack of migraine headache. Side effects (SE) of Sumatriptan include chest discomfort; its use is contraindicated in patients with variant angina. Activation

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of brain 5-HT-2 receptor causes increased formation of inositol-1,4,5-triphosphate and can cause CNS excitation and hallucination; activation of peripheral 5-HT-2 receptor, on the other hand, causes smooth muscle contraction such as bronchoconstriction, intestinal hypermotility, and vasoconstriction.

2) Activation of 5-HT-3 receptor causes nausea and vomiting.

3) Activation of 5-HT-4 receptor increases intestinal motility, and increases secretions from the alimentary tract. Tegaserod is a partial agonist of the receptor and is used to improve bowel movement in IBS (irritable bowel syndrome) associated with constipation.

4) Sertraline is a SSRI (selective serotonin reuptake inhibitors) used to treat premenstrual dysphoric mood.

5) Ondansetron, Alosetron, Palonosetron, and Dolasetron are 5-HT-3 receptor antagonists. They are used to prevent vomiting caused by anticancer drugs such as Cisplatin.

6) Ergotamine is a drug choice for treatment of acute attack of migraine headache. It has a very strong vasoconstricting and uterine-contracting effects. Hence, Ergotamine should not be used to induce labor.

7) Ergonovine is used mainly to stop postpartum uterine bleeding. It has a strong uterine vasoconstricting effect. Side effects of Ergonovine include elevation of blood pressure.

8) Methysergide has some anti-serotonin effect. Methysergide is used to prevent migraine headache. Its important side effects include retroperitoneal fibrosis to cause obstruction of urinary tract. It was withdrawn from market due to this effect but can be available from its manufacturer.

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9) Cyproheptadine has antagonistic effects against both histamine receptors and serotonin receptors. Its antihistaminic effect is beneficial for skin pruritus, and its antiserotonin effect is for intestinal hypermotility in carcinoid patients.

17. Kinins, Prostaglandins & Eicosanoids

1) Kinins are algescic (or pain-producing) peptides that have powerful vasodilating and bronchoconstricting abilities. They are destroyed by ACE (angiotensin converting enzyme) and therefore ACE inhibitors such as Captopril cause accumulation of kinins to help reduce blood pressure.

2) Kallikrein, an enzyme, is involved in the formation of kinins. Aspirin or glucocorticoids can inhibit conversion of prekallikrein (inactive precursor) to active kallikrein and hence they oppose formation of algescic kinins.

3) Aprotinin is an inhibitor of the enzyme kallikrein involved in the synthesis of kinins (vasodilator), and also is an inhibitor of plasmin, the enzyme that dissolves fibrin-clot. Therefore, Aprotinin is used to stop blood loss during coronary bypass operations.

4) Prostaglandins are organic acidic substances. PG-E causes vasodilation and bronchodilation probably through c-AMP, whereas PG-F causes vasoconstriction and bronchoconstriction probably through IP₃ (inositol-1, 4, 5 - triphosphate) that causes release of calcium ions from sarcoplasmic reticulum.

5) Both PG-E and PG-F cause uterine contractions to be useful as abortifacient. Prostaglandin preparations must not be used during the period of pregnancy. Their common side effects include diarrhea.

6) PG-E and prostacyclin (PG-I₂) are beneficial to the gastric mucosal

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cells. They promote secretions of protective gastric mucus and bicarbonate ions, and inhibit secretions of gastric acid (they activate G_i protein to block the formation of c-AMP that by activation of the H^+/K^+ -ATPase pump enhances secretions of gastric acid).

7) Thromboxane ($TX-A_2$), not a prostaglandin but an eicosanoid, can cause vasoconstriction, bronchoconstriction, and aggregation of platelets. It is formed inside platelets. Prostacyclin ($PG-I_2$), on the other hand, is synthesized in vascular endothelia and has an opposite effect. It causes vasodilation, bronchodilation, and prevents platelet aggregation.

8) Small doses (less than 100 mg a day) of Aspirin can block the enzyme cyclooxygenase (COX or prostaglandin synthetase) in platelets to inhibit synthesis of thromboxane. However, it does not inhibit synthesis of prostacyclin in the vascular endothelia; hence its use is recommended to prevent heart attack in vulnerable patients.

9) There are two sets of COX enzymes: COX-1 is ubiquitously available, whereas COX-2 is induced only in the inflammatory cells. NSAIDS (nonsteroidal antiinflammatory drugs) are nonselective COX inhibitors. Therefore, they not only suppress inflammation by blocking the COX-2-mediated synthesis of PG-E at inflammatory sites but produce their side effects of gastric ulcer as they block the COX-1-mediated synthesis of cytoprotective PG-E as well. Therefore, COX-2 selective inhibitors are developed to suppress inflammation such as in rheumatoid arthritis without suppressing production of the protective PG-E at the stomach. The selective COX-2 inhibitors include Celecoxib, and Rofecoxib, but the latter was recently withdrawn from the market because of a cardiotoxicity.

10) Aspirin, unlike other NSAIDS (nonsteroidal antiinflammatory drugs), can acetylate COX-1 and COX-2 enzymes to inactivate them irreversibly, whereas other NSAIDS work by competitive inhibition of the enzymes.

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11) Glucocorticoids can inhibit the release of arachidonic acid and thereby block the formation of prostaglandins via the COX, and block the formation of leukotrienes including SRS-A (slow reacting substance of anaphylaxis) via 5-lipoxygenase.

12) Prostaglandin preparations medically used include Carboprost Tromethamine (a methyl analog of PG F-2 α), and Dinoprostone (PG E-2), both of which are used to obtain abortion. Dinoprostone is also used to ripen the uterine cervix before initiation of labor. Misoprostol, a PG-E derivative, is used to promote gastric mucus secretion, and to decrease gastric acid secretion. Alprostadil, a PG-E analog, is used to maintain patency of ductus arteriosus; Latanoprost, an analog of PG-F₂, is used to improve outflow of aqueous humor to lower intraocular pressure for glaucoma patients. Other PG preparations used to lower IOP include Bimatoprost and Travoprost.

13) Epoprostenol (PG I₂ or prostacyclin) is used to treat pulmonary hypertension.

14) Sildenafil or Vardenafil or Tadalafil is used orally to treat erectile dysfunction. They are not a PG member but each causes penile erection. Sexual stimulation causes the release of nitric oxide to activate guanylate cyclase that in turn elevates intracellular c-GMP. They inhibit phosphodiesterase, the enzyme that destroys c-GMP, and the accumulated c-GMP induces a rapid vasodilation to improve blood flow into the penile corpus cavernosum. Side effects include diminished visual acuity and loss of some color perception (blue-green discrimination difficulty). Alprostadil, a PG member, also can cause penile erection but is used by injection only.

15) Treprostinil is used to treat pulmonary hypertension.

III. Psychopharmacology

18. Antipsychotic & Antianxiety Drugs

1) Chlorpromazine is a classic drug for the treatment of psychosis. Chlorpromazine appears to work by blocking the D-2 receptors in mesolimbic system in the brain. This drug is also indicated for treatment of acute mania, Phencyclidine-intoxication, Tourette's symptoms, skin pruritus, and intractable hiccough.

2) Chlorpromazine also has an antiemetic effect, which may arise from blockade of D-2 receptors in chemoreceptor trigger zone. Side effects of Chlorpromazine include extrapyramidal symptoms such as acute dystonia and akathisia that may be due to its blockade of the D-2 receptors in nigrostriatal pathway in the brain. These dystonic effects may be treated with anticholinergic drugs such as Benztropine and Diphenhydramine.

3) Chlorpromazine and other phenothiazines such as Fluphenazine, Haloperidol, and Thioridazine can generate anticholinergic side effects such as dry mouth, cycloplegia, urinary retention, and constipation. Chronic administration of Chlorpromazine for more than four months may develop tardive dyskinesia, a side effect difficult to treat. Risperidone is more effective in treating negative psychotic symptoms, and generates fewer extrapyramidal side effects or tardive dyskinesia than does Haloperidol or Chlorpromazine.

4) Dopamine in the brain promotes the release of gonadotropins while inhibiting the release of prolactin. Therefore, blockade of dopamine receptors by Chlorpromazine can inhibit the release of gonadotropins to cause amenorrhea and atrophy of sex organs. It can also increase the release of Prolactin to cause galactorrhea as a side effect.

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5) Clozapine is an unusual (or atypical) antipsychotic drug since it seldom produces extrapyramidal side effects, but side effects of Clozapine include agranulocytosis and seizures. Other atypical antipsychotic drugs that generate little or no incidence of extrapyramidal side effects include Olanzapine, Quetiapine, and Ziprasidone. They may block not only dopamine-2 receptors but 5-HT-2 receptors in the brain as well. They may cause weight gain as a side effect. Olanzapine is also used to treat anxiety and mental depression.

6) Aripiprazole is another atypical antipsychotic drug that blocks 5HT-2A receptors, but it is a partial agonist at 5HT-1A receptors, and D-2 (dopamine) receptors.

7) Benzodiazepine antianxiety drugs such as Diazepam, Chlordiazepoxide, and Alprazolam increase frequency of chloride channel opening by enhancing the binding of GABA to its receptors. They have some anticonvulsant effect as well. All benzodiazepine antianxiety drugs except Oxazepam, Lorazepam, and Temazepam require hepatic activation. Side effects of benzodiazepines include drowsiness and physical dependency.

8) Some antianxiety drugs do not belong in the benzodiazepine group. Such drugs include Meprobamate, Buspirone, and Hydroxyzine.

9) Lithium Carbonate is a choice drug to treat manic phase of manic-depressive disorder. Side effects of Lithium Carbonate include acne, confusion, aphasia, and polyuria. Urinary excretion of lithium cannot be increased by a powerful diuretic agent such as a loop diuretic or by any thiazide diuretic, but by an isotonic saline solution.

19. Antidepressants & Psychotomimetic Agents

1) Tranylcypromine is an antidepressant that has an MAO-inhibitory effect. Hence, it is incompatible with foods containing tyramine since hypertensive crisis can ensue if used together.

2) Tricyclic antidepressants include Imipramine, Desipramine, Protriptyline, Nortriptyline, Amitriptyline, and Doxepin. They have anticholinergic side effects such as mydriasis with blurred vision, urinary retention, constipation, erectile difficulty, mental confusion, convulsions, and coma.

3) Clomipramine, a tricyclic, is not only used for treatment of mental depression but also for obsessive-compulsive disorder as well. The drug can block serotonin reuptake.

4) Nontricyclic newer antidepressants include Amoxapine, Maprotiline, Trazodone, Nefazodone, Bupropion, and Mirtazapine.

5) Bupropion, an antidepressant, blocks reuptake of both norepinephrine and dopamine. It is also used to stop smoking cigarettes.

6) Mirtazapine is an unusual antidepressant that works by blocking central adrenergic α_2 receptors to increase the release of norepinephrine and serotonin. Its side effects include sedation and increased food appetite.

7) Fluoxetine, a most popular antidepressant, is a SSRI (selective serotonin reuptake inhibitor). It generates little anticholinergic side effects. Its typical side effects include loss of food appetite. Fluoxetine and other SSRIs are also useful in the treatment of obsessive-compulsive disorder. Other SSRIs used in treatment of mental depression include Citalopram (Escitalopram being active pure s-enantiomer of Citalopram), Fluvoxamine, Paroxetine,

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Venlafaxine, and Sertraline. Their side effects, collectively called “Serotonin Syndrome” include muscle rigidity, tremor, agitation, insomnia, and hyperthermia. Therefore, a SSRI must not be taken together with an MAOI (monoamine oxidase inhibitor) lest the serotonin syndrome may occur. All the SSRIs are inhibitory to the hepatic microsomal enzymes and interrupt inactivation of many other drugs. They may cause withdrawal symptoms if abruptly terminated.

8) Duloxetine is used to treat major depression. It inhibits reuptake of both serotonin and norepinephrine in a balanced fashion.

9) Phencyclidine (PCP), a psychotomimetic agent, generates disinhibition and confusion probably by blocking the NMDA (N-methyl D-aspartate) receptors. This agent produces symptoms mimicking schizophrenia, and it can cause hypertensive crisis. Phencyclidine (PCP) is a weak base and its excretion can be increased by acidification of urine.

10) THC (tetrahydrocannabinol) generates some β -agonistic effects such as tachycardia and conjunctival vasodilation. This compound has an excellent antiemetic effect. Dronabinol (THC) is approved to prevent vomiting caused by anticancer agents. THC can lower blood levels of testosterone to affect production of sperms. It also can cause chromosomal damage.

IV. Drugs Acting On the Central Nervous System

20. Hypnotic Drugs & Alcohol

1) Ultra-short acting barbiturates such as Thiopental are often used as an anesthetic induction agent. Ultra-short duration of action by Thiopental is due to its rapid redistribution from the brain to other peripheral tissues.

2) Thiopental causes cerebral vasoconstriction to help lower intracranial pressure.

3) Barbiturates induce hepatic microsomal enzymes and hence their use is contraindicated in patients with porphyria.

4) Barbiturates promote binding of GABA to its GABA-A receptors and thereby prolong duration of chloride channel opening, providing an anticonvulsant effect.

5) Administration of Sodium Bicarbonate can promote ionization and urinary excretion of Phenobarbital but not other barbiturates.

6) Chloralhydrate has to be reduced by alcohol dehydrogenase, a cytosol enzyme, to trichloroethanol which is the active form. If taken with ethanol, which generates NADH during its own oxidation, the reduction of Chloralhydrate is accelerated to cause the so-called "dead drunk." In the presence of excess NAD, on the other hand, Chloralhydrate is oxidized to trichloroacetic acid that has no hypnotic effect but has a high affinity for binding to plasma proteins and can displace other weakly bound drugs to enhance their effects.

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- 7) Flurazepam is a popular hypnotic drug that belongs in the benzodiazepine group. The drug must be activated in the liver.
- 8) Temazepam, Lorazepam, and Oxazepam are all benzodiazepine members that do not need activation by the liver.
- 9) Triazolam is a very potent but very short-lasting hypnotic drug that also belongs in the benzodiazepine group. Since this drug tends to cause rebound insomnia, it may be used to overcome “jet-lag”. One side effect of Triazolam is loss of memory (amnesia).
- 10) Zolpidem and Zaleplon are other hypnotic drugs that do not belong in the benzodiazepine group. They have no anticonvulsant or muscle relaxant effects. Nevertheless, their effects can be reversed by Flumazenil, the drug that reverses antianxiety effects of benzodiazepines.
- 11) Eszopiclone is used to treat insomnia. It is a non-benzodiazepine sedative.
- 12) Ramelteon is also used to promote sleep. It is a melatonin agonist.
- 13) Ethanol increases deposition of triglyceride in the liver, while it decreases glycogen storage in the liver.
- 14) Ethanol inhibits the release of ADH (antidiuretic hormone) to increase urine output, and inhibits the release of oxytocin to suppress premature uterine contractility.
- 15) Elimination of ethanol follows zero-order kinetics. Disulfiram inhibits aldehyde dehydrogenase, the enzyme that catalyzes oxidation of acetaldehyde, a metabolite of ethanol, to acetic acid. The accumulated acetaldehyde by Disulfiram causes such toxic effects as flushing, palpitation, headache, and fall of blood pressure.
- 16) Naltrexone is approved to reduce craving for ethanol drinking.

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- 17) Acamprosate is used to maintain an alcohol-free state.
- 18) Ethanol inhibits formation of platelets and generates a bleeding tendency. It also inhibits migration of white blood cells to infection sites, thereby lowering the body's immune capability.
- 19) Ethanol can cause Korsakoff–Wernicke's neurological disorders probably by inducing deficiency of vitamin B-1 (thiamine).
- 20) GHB (gamma-hydroxybutyrate) or Flunitrazepam when taken together with ethanol can lead to a profound unconsciousness and motor disturbance and hence they are used as a "rape drug". The effect of Flunitrazepam, a benzodiazepine member, can be reversed by use of Flumazenil, a benzodiazepine receptor antagonist. There is no antidote to GHB.
- 21) Methanol is oxidized by alcohol dehydrogenase to formaldehyde, a toxic substance that can cause blindness (snow storm-like vision). This conversion of methanol to formaldehyde can be blocked by administration of ethanol since it has a higher affinity for the same enzyme alcohol dehydrogenase than has methanol.
- 22) Formic acid, generated by oxidation of formaldehyde, can tip the pH balance to acidosis and promote toxicity of formaldehyde. Administration of Sodium Bicarbonate is useful to neutralize this acidosis caused by formic acid.
- 23) Fomepizole can block oxidation of methanol to formaldehyde, and can block oxidation of ethylene glycol to glycoaldehyde, which can be further oxidized to glycolic acid and then further to oxalic acid that can damage kidney tubules.

21. Central Nervous System Stimulants

- 1) Doxapram, a CNS stimulant, is indicated to stimulate respiration.
- 2) Theophylline and its derivative Aminophylline can cause bronchodilation for asthma patients. They increase cellular levels of c-AMP by blocking phosphodiesterase, the enzyme that destroys c-AMP.
- 3) Modafinil is used for improving wakefulness in patients with excessive sleepiness. The effect of Modafinil is similar to that of Caffeine.

22. Antiepileptic Drugs

- 1) Drugs effective against tonic-clonic seizures include Phenobarbital, Primidone, Phenytoin, and Carbamazepine. They appear to work by blocking sodium channels in the epileptic foci in the brain.
- 2) Side effects of Phenytoin include gingival hyperplasia, nystagmus, ataxia, hyperglycemia, loss of physical balance, and osteomalacia (the drug inhibits intestinal absorption of calcium ions).
- 3) If the blood concentration of Phenytoin exceeds 10-20 $\mu\text{gram/mL}$, its elimination is likely to follow zero-order kinetics instead of its usual first-order kinetics.
- 4) Carbamazepine is a DOC (drug of choice) for automatism (complex partial seizure) and for trigeminal neuralgia. Side effects of Carbamazepine include osteomalacia, spina bifida, and many anticholinergic side effects.

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5) Drugs effective against absence seizures include Ethosuximide and Valproic Acid. They appear to work by blocking the T-type calcium channels in thalamic and other brain epileptic regions. Side effects of both drugs include gastrointestinal distress. They seldom produce drowsiness.

6) Some antiepileptic drugs work by accumulation of GABA, an inhibitory neurotransmitter in the epileptic region of the brain. They include Tiagabine, Vigabatrin, and Valproic Acid. They are useful in treatment of partial seizures.

7) Valproic Acid also blocks the sodium channels so as to be useful in tonic-clonic seizure as well. Side effects of Valproic Acid include hepatotoxicity, gastrointestinal irritation, hemorrhagic pancreatitis, and spina bifida.

8) Clonazepam is used as a back-up drug for absence seizures, myoclonic seizures, and also to control mania. Its side effects include drowsiness.

9) Diazepam, Lorazepam, and Fosphenytoin may be used to treat status epilepticus.

10) Lamotrigine is an antiepileptic drug (partial and generalized seizures) that may also be used to treat bipolar disorder as well. Its side effects include life-threatening skin rash (Stevens-Johnson syndrome).

11) Gabapentin and Topiramate are antiepileptic drugs, but not for absence seizures.

12) Other antiepileptic drugs include Divalproex and Oxcarbazepine.

23. Narcotic Analgesic Drugs

- 1) Morphine activates postsynaptic μ -receptors which increase permeability to potassium ions and generates hyperpolarization and inexcitability of brain neurons. Morphine also activates presynaptic κ -receptors to diminish influx of calcium ions, which causes inhibited release of many neurotransmitters including NE (norepinephrine), Ach (acetylcholine), and substance P.
- 2) Morphine produces a strong analgesic effect that is accompanied by narcosis and respiratory depression.
- 3) Morphine generates vasodilation and urinary retention. A cardinal sign of Morphine intoxication is dark-resistant miosis, which can be reversed by anticholinergic drugs or by narcotic antagonists.
- 4) Tolerance develops to analgesic, euphoric, and respiratory depressant effects of Morphine, but no tolerance develops to miosis and constipation caused by Morphine.
- 5) Naloxone, a pure narcotic antagonist, can reverse respiratory depression caused by Morphine.
- 6) Naltrexone is another pure narcotic antagonist, but it is not used for reversal of respiratory depression but for maintenance of a narcotic-free state in previously detoxified patients. This drug is also approved to reduce cravings for alcohol consumption.
- 7) Codeine is a narcotic drug of choice to suppress coughing. Oxycodone, on the other hand, is not used to suppress coughing but to obtain analgesic effects whose potency is greater than Codeine but less than Morphine. Oxycodone is orally effective and is one of the most abused narcotic drugs.
- 8) Dextromethorphan is not a narcotic drug (no euphoria, no analgesic effect, nor respiratory depression) but has equipotent antitussive

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effect as Codeine.

9) Levorphanol is a synthetic narcotic drug whose analgesic potency is greater than Morphine but generates a lower incidence of constipation than with Morphine. It is often used orally to control pain in cancer patients.

10) Meperidine is a synthetic narcotic analgesic agent. It differs from Morphine in that it is orally effective and causes mydriasis rather than miosis, has little cough-suppressant effect, and little effect on the GI and uterine smooth muscles (hence, it seldom causes constipation or depression of uterine contractility). Therefore, it is a DOC for obstetric analgesia. Its side effects include respiratory depression. Chronic use of this drug can accumulate normeperidine, which inhibits reuptake of serotonin and causes convulsions.

11) Pentazocine is a synthetic orally effective pain-killer. It acts mainly on the κ -receptors in the spinal cord to generate the so-called spinal analgesia, and also activates σ -receptors to produce dysphoria. This is the reason why this drug does not develop abuse potential and it is suitable to control chronic pain. This drug also has some antagonistic effect on μ -receptors to reduce the pain-killing effect of morphine, but it does not reverse respiratory depression caused by Morphine. Other drugs that activate κ -receptors in the spinal cord but antagonize μ -receptors (hence, mixed-acting drugs) include Butorphanol and Nalbuphine.

12) Buprenorphine has a partial agonistic effect on the μ -receptors and full agonistic effect on κ -receptors to generate its analgesic effect as much as 30 times as potent as Morphine. The drug also has antagonistic effect on δ (delta)-receptors and its abuse potential is low, and generates little withdrawal symptoms. This drug may be used to treat narcotic dependency of Heroin or other narcotic agents.

24. Nonnarcotic Analgesic & Antiinflammatory Drugs

- 1) Aspirin has an analgesic effect, antipyretic effect, and antiinflammatory effect. Aspirin irreversibly acetylates COX (cyclooxygenase) enzymes to inhibit formation of prostaglandins, thromboxane (both at low doses), and prostacyclin (at high doses).
- 2) Aspirin is metabolized to salicylic acid and then conjugated with glycine by glycine-N-acylase in the mitochondria to form salicyluric acid. Elimination of aspirin and its acidic metabolites is increased by making urine alkaline such as by administration of Sodium Bicarbonate (NaHCO_3).
- 3) Acute toxicity of Aspirin includes bleeding tendency, respiratory alkalosis, metabolic acidosis, and hyperthermia (not hypothermia). Chronic mild toxicity caused by prolonged administration of high doses (salicylism) includes tinnitus, blurred vision, and dizziness.
- 4) Aspirin can displace drugs that weakly plasma protein-bound, such as Tolbutamide and Dicumarol, and thus enhance their toxicity.
- 5) Aspirin at low doses (2g or less per day) inhibits urinary excretion of uric acid and hence it is not recommended to control patients with gout.
- 6) Balsalazide and Sulfasalazine, both salicylates, are used to treat ulcerative colitis.
- 7) Acetaminophen has a similar analgesic and antipyretic potency as does Aspirin, but Acetaminophen has no significant antiinflammatory effect for arthritis, nor antithrombotic effect (it does not increase the mean bleeding time, unlike Aspirin).
- 8) Acetaminophen is not irritating to the GI tract, does not displace

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other drugs from protein binding sites, nor affects urinary excretion of uric acid.

9) A small portion of Acetaminophen (about 5%) is inactivated by microsomal oxidation to produce a toxic semiquinone metabolite, which is inactivated by the reduced form of glutathione. However, if the drug dose is excessive, the oxidation dominates to generate a greater amount of the toxic compound and can deplete the reduced form of glutathione and then the toxic free radical snatches electrons from body tissues to cause hepatic and renal necrosis. Ethanol consumption for one week, or microsomal enzyme inducers such as Rifampin, also causes Acetaminophen to be more heavily oxidized and produce a greater amount of the toxic metabolite. Acetylcysteine given shortly after overdoses of Acetaminophen can minimize its toxicity.

10) Ketorolac is a nonnarcotic yet very potent pain-killer. It inhibits synthesis of prostaglandins. Ketorolac is not used to manage chronic pain or rheumatoid arthritis because its side effects with long term use include intestinal perforation and interstitial nephritis.

11) Other NSAIDs (nonsteroidal antiinflammatory drugs) include Indomethacin, Phenylbutazone, Ibuprofen, Naproxen, Sulindac, Piroxicam, Meloxicam, Nabumetone, and Oxaprozin. All of them inhibit synthesis of prostaglandins by inhibition of the enzymes COX-1 and COX-2 without discrimination. The NSAIDs increase renal reabsorption of lithium ions.

12) Celecoxib, a useful drug for rheumatoid arthritis, selectively inhibits COX-2 enzymes with little or no effect on the COX-1, thus allowing the synthesis of protective PG-E at the gastric mucosa via COX-1 to reduce incidences of gastrointestinal ulcer and bleeding.

13) DMARDs (disease-modifying antirheumatic drugs) include Auranofin, Methotrexate, Penicillamine, Hydroxychloroquine, Etanercept, and Infliximab. The last two drugs work by binding to

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TNF (tumor necrosis factor) to inactivate this inflammatory substance. Other DMARD members include Anakinra, which is also used to treat rheumatoid arthritis. It works by blocking the actions of IL (interleukin)-1.

14) Tramadol is an unusual pain-killer in that though it is not classified as a narcotic, it may develop psychological and physical dependence.

V. Anesthetics

25. General Anesthetic Agents

- 1) The potency of general anesthetic agents is related to their lipid-solubility; the greater the lipid-solubility of an agent, the greater the potency of the agent. On the other hand, the greater the solubility in water, the slower the induction and recovery speed. If water-solubility is the same, increasing cardiac output slows induction speed, whereas more rapid respiratory rates increase induction speed.
- 2) Halothane is one of the most arrhythmogenic anesthetic agents, whereas Nitrous Oxide is the least arrhythmogenic. Halothane must not be used in patients with pheochromocytoma because catecholamines released by Halothane from the tumor may cause serious arrhythmia. Halothane also causes higher incidences of malignant hyperthermia than other anesthetic agents.
- 3) Nitrous Oxide is commonly used together with Fentanyl and Droperidol to generate the so-called neuroleptanesthesia.
- 4) Ketamine has no dramatic effects on the cardiovascular or the respiratory system, nor does it depress skeletal muscle tone. The drug induces dissociative analgesia probably by blocking the NMDA (N-methyl D-aspartate) receptors.
- 5) Enflurane may cause seizure-like muscle twitching if used at high doses coupled with hypocapnia (subnormal PCO_2).
- 6) Isoflurane has little depressant effect on contractility of the myocardium, but produces profound vasodilation (including coronary

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vasodilation) and respiratory depression.

7) Desflurane and Sevoflurane are the most rapid-acting general anesthetic agents.

8) Glycopyrrolate is an anticholinergic drug that is often used to prevent bronchial secretions during surgical anesthesia.

9) Propofol is used as an anesthetic induction agent. It has an antiemetic effect, and hence nausea and vomiting is unlikely during its post-anesthetic period.

26. Local Anesthetic Agents

1) Increase in concentration of calcium ions in ECF (extracellular fluid) can oppose local anesthetic effects, whereas an increase in potassium ions in the ECF can potentiate it.

2) Local anesthetic agents are maximally effective at a pH close to their own pKa values. Local anesthetic agents cannot work properly when applied to areas where an abscess, boil or skin infection exists because the pH there is too acidic. Addition of Baking Soda can help.

3) Cocaine is used as a surface anesthetic agent. Cocaine is unusual in that it blocks uptake of norepinephrine, dopamine, and serotonin. Because of accumulated NE, Cocaine causes mydriasis, nasal vasoconstriction, and elevation of blood pressure. Pyrexia is a typical sign of Cocaine poisoning.

4) Procaine is used only for injection anesthesia. Its toxicity is reduced and its duration of action is increased if used in combination with an adrenergic α -agonist such as Epinephrine and Phenylephrine.

5) Sulfonamides, to generate their chemotherapeutic effect, compete

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with PABA (p-aminobenzoic acid) for the enzyme dihydropteroate synthase to block formation of dihydrofolate (which is dihydropteroate linked up with glutamic acid), the precursor of tetrahydrofolate required to synthesize bacterial DNA. Procaine releases PABA by hydrolysis and thereby undercuts chemotherapeutic effectiveness of sulfonamides.

6) Tetracaine is a choice drug for spinal anesthesia.

7) Lidocaine is the reference drug for local anesthesia. It is both for surface anesthesia and for injection anesthesia. Lidocaine is DOC for epidural anesthesia. Its unique side effects include sedation, drowsiness, and paresthesias.

8) Bupivacaine, an amide type local anesthetic agent, is a second-line drug for epidural and spinal anesthesia. It has a very long duration of action up to 7 hours or more. Its unique side effects include a serious ventricular arrhythmia.

VI. Drugs Used in Cardiovascular Diseases

27. Digitalis Glycosides & Related Drugs

1) Drugs that can increase cardiac contractility and output include Dopamine and Dobutamine (both increase intracellular levels of c-AMP by activation of adenylate cyclase); Inamrinone and Milrinone (both increase intracellular c-AMP by inhibition of phosphodiesterase, the enzyme that destroys c-AMP); and digitalis glycosides (they increase intracellular calcium ions by inhibition of Na^+/K^+ -dependent ATPase pumping system of the myocardial cells).

2) ACE (angiotensin converting enzyme) inhibitors such as Captopril may be used in conjunction with a diuretic to treat congestive heart failure. ACE-inhibitors not only block formation of angiotensin (a powerful vasoconstrictor) but also block inactivation of kinins (vasodilators) to reduce afterload of the heart. Diuretic agents reduce ECF volume to reduce preload of the heart.

3) Carvedilol has both adrenergic β - and α -blocking effects, and may help reduce vascular resistance to be beneficial in chronic heart failure.

4) Nesiritide is used to improve shortness of breath due to congestive heart failure. The drug relaxes blood vessels in the lungs and the heart.

5) Digitalis glycosides (Digoxin and Digitoxin) inhibit the Na^+/K^+ -dependent ATPase pumping system to accumulate sodium and calcium ions inside the myocardial cells. This calcium increases cardiac contractility. By accumulation of sodium and calcium,

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digitalis dilutes the negative charge inside the cells to increase spontaneous depolarization (a direct effect). In addition, as the pumping system is blocked, sodium is not pumped out from the cell, and potassium concentration outside the cell remains high. In this way, digitalis increases refractory period (another direct effect).

6) Digitalis also has the ability to activate vagal nuclei and generate an indirect vagal effect (by increasing potassium efflux and causing hyperpolarization, thus providing refractoriness of such tissues as the SA and AV nodes). These effects lower the heart rate and reduce the AV conduction speed respectively. However, once an action-potential is generated, the vagal effect, by increasing potassium efflux, accelerates the process of repolarization and reduces the effective refractory period of the atrial and ventricular muscles (another indirect vagal effect).

7) Side effects of digitalis glycosides include nausea/vomiting, blurred vision, and altered perception of colors. On the EKG, digitalis glycosides elongate P-R interval, shorten the Q-T interval (therefore shorten the duration of ventricular contraction), depress the T-wave, and depress the S-T segment. A digitalis glycoside may also generate bigeminy on the EKG.

8) Arrhythmogenicity of digitalis glycosides can be enhanced by a sympathomimetic catecholamine, by hypercalcemia, by hypomagnesemia, by hypokalemia, or by hypoxia.

9) Lidocaine may be used to treat digitalis-induced arrhythmia. Digoxin Immune F_{ab} that binds both Digoxin and Digitoxin may be used to reduce cardiac toxicity.

28. Antiarrhythmic Drugs

1) Most of the antiarrhythmic drugs currently in use are classified into 4 groups; Class-I (sodium-channel blockers having some anesthetic effects); Class-II (adrenergic β -blockers), Class-III (potassium-channel blockers), and Class-IV (calcium-channel blockers).

2) Sodium-channel blockers depress phase-4 slope and raise threshold of excitation, and slow the depolarization process. The class-I drugs are subdivided into three: 1) the Ia drugs slow repolarization process probably by blocking potassium channel as well. Drugs of this class include Quinidine, and Procainamide; 2) the Ib drugs quicken the repolarization process. Drugs of this class include Lidocaine, Tocainide, and Mexiletine; 3) the Ic drugs have little or no significant effect on the repolarization process. Drugs of this class include Propafenone, and Flecainide.

3) Adrenergic β -blockers used as antiarrhythmic drugs include Esmolol and Sotalol (which also has Class-III activity, and more often is used as a Class-III drug). They depress phase-4 slope elevated by catecholamines, and slow A-V conduction, but have little effect on the QRS width or Q-T interval.

4) Potassium-channel blockers include Sotalol, Bretylium, and Amiodarone. By blocking the potassium-channel they increase refractory period and thereby reduce the chance of reentry of retrograde impulses. Amiodarone also has adrenergic β -blocking and calcium-channel blocking effects, and so it is useful in almost any type of arrhythmia.

5) Calcium-channel blockers include Verapamil and Diltiazem. They depress phase-2, phase-3 and phase-4 slopes. Side effects include constipation, fall of blood pressure, and Torsade de Pointes arrhythmia, which can be relieved by magnesium ions.

6) Quinidine is orally used to control atrial arrhythmia in combination

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with a digitalis glycoside, whose vagal effect counteracts the anticholinergic side effect of Quinidine to prevent a paradoxical ventricular arrhythmia. Quinidine increases P-R interval, QRS width, and increases the Q-T interval. Quinidine depresses all kinds of muscles: skeletal muscle (hence good for nocturnal leg cramp), cardiac muscle (hence lowers blood pressure), and vascular smooth muscle (lowering blood pressure). It also has adrenergic α -blocking effects. Side effects of the drug include cinchonism (tinnitus, nausea, and blurred vision), syncope, and thrombocytopenia.

7) Procainamide is safer than quinidine for injections, has no cinchonism, no thrombocytopenia, nor α -blocking effect. Important side effects of Procainamide include systemic lupus erythematosus-like symptoms.

8) Lidocaine is not used by the oral route (but Tocainide and Mexiletine are orally effective Lidocaine-like drugs). Lidocaine is a drug of choice (DOC) for ventricular arrhythmia but has no effect on atrial arrhythmia. Lidocaine does not slow down conduction speed at the A-V node and has little anticholinergic side effect (hence no paradoxical arrhythmia). Side effects of Lidocaine include drowsiness, sedation, and paresthesias.

9) Flecainide is seldom used because of its side effects of proarrhythmia and congestive heart failure.

10) Sotalol, a β -blocker, is more often used as Class-III drug effective against ventricular arrhythmia. Esmolol, another β -blocker, is a drug of choice for rapid control (within 5 minutes) of atrial or nodal arrhythmia.

11) Amiodarone is unusual in that it has a very slow onset of action (days) and very long duration of action (weeks), and its side effects include proarrhythmia, hepatotoxicity, pulmonary fibrosis (coughing and shortness of breath etc.), thyroidal dysfunction, and Gray Man Syndrome (skin color change to bluish-gray).

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12) Adenosine is a DOC for paroxysmal supraventricular arrhythmia such as Wolff- Parkinson-White syndrome. It increases potassium permeability at the A-V node to cause hyperpolarization with increased refractoriness of the tissue, and it also suppresses c-AMP-mediated calcium influx to slow conduction speed at the A-V node. Side effects of Adenosine include flushing of the skin (burning sensation to the chest), hypotension, and bronchoconstriction (shortness of breath in asthmatic patients).

29. Antianginal Drugs

1) Nitroglycerin is a drug of choice (DOC) to abort acute attack of angina pectoris. Nitroglycerin is converted to nitric oxide, which in turn activates guanylate cyclase to increase formation of c-GMP. The c-GMP causes rapid venodilation to reduce venous return and lower the preload of the heart; this accounts for the antianginal effect of Nitroglycerin. This drug also causes coronary vasodilation to help treat myocardial infarction, and arterial dilation to relieve congestive heart failure. Nitroglycerin provides skin vasodilation to help treat Raynaud's disease as well.

2) Isosorbide Dinitrate and its active metabolite Isosorbide Mononitrate are useful as other antianginal agents.

3) Adrenergic β -blockers such as Propranolol, Metoprolol, Nadolol, and Atenolol are used orally to prevent an anginal attack. They are not recommended for variant angina (Prinzmetal angina). Adrenergic β -blockers with some intrinsic sympathomimetic activity such as CAPP (Carteolol, Acebutolol, Pindolol, and Penbutolol) are not recommended for any type of angina.

4) Calcium-channel blockers such as Verapamil, Diltiazem, Nifedipine, and Amlodipine are used as a choice drug for variant

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angina. Their side effects include constipation.

5) To treat unstable angina (crescendo angina), antiplatelet agents are preferred. Abciximab, Eptifibatide, and Tirofiban all block glycoprotein IIb/IIIa receptors expressed on the platelet's surface. These receptors are needed for binding of fibrinogen, a bridge molecule for platelet aggregation.

30. Anticoagulants

1) Ticlopidine and Clopidogrel are antiplatelet agents used to reduce incidence of myocardial infarction and stroke. They irreversibly block the ADP-receptors on the surface of platelets so as that no glycoprotein IIb/IIIa receptors can be expressed, without which fibrinogen binding cannot take place to cause platelet aggregation. Ticlopidine may be used in treatment of TIA (transient ischemic attacks). Side effects of Ticlopidine and Clopidogrel include neutropenia.

2) If no free calcium ions are available, no coagulation can take place. EDTA (ethylenediamine tetraacetic acid), citrate, and oxalate remove calcium ions and can prevent blood coagulation.

3) Urokinase, Streptokinase, Anistreplase, Alteplase (a tissue plasminogen activator), and Reteplase can dissolve already-formed blood clots.

4) ϵ -Aminocaproic Acid and Tranexamic Acid can inhibit activity of Urokinase and other plasminogen activators. They are used to reduce hemorrhage during surgery.

5) Heparin is not effective by the oral route and hence is used mostly by intravenous infusion. Heparin binds antithrombin-III in the circulation. The complex then binds to and inactivates thrombin.

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Heparin also inhibits the blood clotting factor-X to a lesser degree. Its anticoagulant effect is immediate and effective wherever blood is present whether in vivo or in vitro. Side effects of heparin include thrombocytopenia and bleeding. To avoid its side effects of excessive bleeding, its activity is monitored by partial thromboplastin time. Activity of Heparin Sodium can be neutralized by Protamine Sulfate.

6) Low molecular weight heparin such as Enoxaparin and Dalteparin bind to and inactivate coagulation factor-X more than thrombin. They are used mostly by subcutaneous injection, and provide a longer duration of anticoagulant effect than does Heparin. They produce little or no incidence of thrombocytopenia.

7) Dicumarol and Warfarin are orally effective anticoagulants. They inhibit the enzyme vitamin K epoxide reductase that converts oxidized (and inactive) vitamin K back to the active reduced form of vitamin K, which is required for activation of coagulation factors 2, 7, 9, and 10 by γ -carboxylation of their glutamic acid residues. To prevent the side effects of excessive and prolonged bleeding, their anticoagulant effects are monitored by the prothrombin time.

8) If the dose of Warfarin is excessive, it can induce deficiency of protein C (an endogenous anticoagulant) to cause a paradoxical hypercoagulability.

9) Inactivation of coumarins (Warfarin and Dicumarol) is by hepatic microsomal enzymes; enzymes inducers such as barbiturates and Carbamazepine speed up their inactivation, whereas enzyme inhibitors such as Phenylbutazone and Chloramphenicol oppose their inactivation and lead to their toxicity. Thyroid hormones quicken inactivation of blood clotting factors and can enhance anticoagulant effect of coumarins.

10) Argatroban is used as an anticoagulant. It inhibits the action of thrombin.

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11) Bivalirudin is a thrombin-specific anticoagulant used with aspirin to treat unstable angina.

12) Tinzaparin is used to treat deep vein thrombosis.

31. Diuretic Drugs

1) Mannitol is an osmotic diuretic. It is also used for measurement of glomerular filtration rate.

2) Acetazolamide inhibits the enzyme carbonic anhydrase mainly at the renal proximal tubules. Carbonic anhydrase catalyzes $\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^-$. As the enzyme is inhibited, hydrogen ions (H^+) are not available to be secreted into the tubular fluid, and bicarbonate ions (HCO_3^-) filtered from the glomeruli cannot interact with the hydrogen to form carbonic acid (H_2CO_3). The net result is that bicarbonate ions cannot be reabsorbed as usual but are eliminated in the urine together with sodium (hence, diuresis), while chloride ions that cannot be excreted with Na^+ are reabsorbed and result in hyperchloremic acidosis (a metabolic acidosis). Therefore, this drug is useful for diuresis in alkalotic, edematous patients.

3) As Acetazolamide turns the urine alkaline because of the loss of chloride ions, the solubility of calcium gets poorer to cause urocalcinosis as a side effect of the drug. The metabolic acidosis caused by this drug in turn causes such CNS side effects as drowsiness, paresthesias, and some anticonvulsant effect. Acetazolamide, in fact, may cause coma in patients with liver cirrhosis.

4) Acetazolamide is also used to lower intraocular pressure as it reduces formation of aqueous humor; and to prevent or treat acute mountain sickness (where hypoxia at high altitudes causes respiratory

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stimulation and respiratory alkalosis) which can be countered by the metabolic acidosis created by Acetazolamide.

5) Dorzolamide, another inhibitor of the enzyme carbonic anhydrase, is used to treat glaucoma. It also decreases secretions of aqueous humor.

6) Chlorothiazide or Hydrochlorothiazide inhibits the sodium/chloride cotransporter at the early part of the renal distal tubules to increase urine output. They, however, can reduce the urine volume in nephrogenic diabetes insipidus by a different mechanism. Thiazide diuretics do not increase urinary excretion of lithium ions, nor do they increase urinary excretion of calcium ions but rather increase reabsorption of calcium at the distal tubule (a unique feature). Side effects of thiazide diuretics include hypokalemia and hyperglycemia.

7) Loop diuretics work at the thick ascending limbs of loop of Henle by blocking the $\text{Na}^+\text{K}^+\text{Cl}_2^-$ cotransporter system. The loop diuretics include Furosemide, Bumetanide, and Ethacrynic Acid. They have greatest potency and the soonest onset of action (within minutes after i.v. injection), and have a short duration of action (a few hours). They increase urinary excretions of calcium, sodium, chloride, magnesium, and potassium but not lithium ions. Side effects of them include hypokalemia, hyperuricemia, and ototoxicity especially by Ethacrynic acid.

8) Some diuretics have a weak diuretic potency but can save potassium. Such drugs include Spironolactone (aldosterone antagonist), Triamterene, and Amiloride. Their side effects include hyperkalemia.

9) SIADH (syndrome of inappropriate secretion of antidiuretic hormone) involves excessive water-retention to cause hyponatremia, which is associated with swelling of the brain. Both Demeclocycline and Lithium Carbonate can block the action of ADH (antidiuretic hormone), and thereby increase urinary output to reverse

hyponatremia.

32. Drugs used in hyperlipidemia

1) Type I hyperlipidemia is caused by deficiency of lipoprotein lipase. The major lipid in this type is dietary triglyceride (not an endogenous lipoprotein). It may cause pancreatitis but not a heart attack.

2) Type IIa hyperlipidemia has a prominent β -band (low-density lipoproteins), which is rich in LDL, the so-called “bad cholesterol”, but not triglyceride; Type IIb consists of not only cholesterol but triglyceride as well.

3) Type III (with intermediate-density lipoprotein, dys- β band) shows both cholesterol and triglyceride.

4) Type IV (with very-low-density lipoprotein, pre- β band) is rich in endogenous triglyceride.

5) Type-V is rich in both endogenous triglyceride and dietary triglyceride.

6) High-density lipoprotein (α -band) is rich in the so-called “good cholesterol”. Physical exercise, Ethanol, and estrogen all increase this band. Niacin can best increase this “good cholesterol”.

7) Gemfibrozil can lower blood levels of triglyceride by increasing both the activity of lipoprotein lipase and the oxidation of free fatty acids to form ketone bodies, thereby reducing the incorporation of free fatty acids into glycerol to form triglyceride. Side effects of Gemfibrozil include cholecystitis, cholelithiasis, and muscle rigidity and muscle ache. Gemfibrozil can displace other drugs from their protein binding sites.

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8) Fenofibrate is also used to lower blood levels of triglyceride.

9) Niacin is best to lower blood levels of both cholesterol and triglyceride, and to elevate blood levels of HDL (good cholesterol-carrier). Niacin (or Nicotinic Acid) decreases the release of free fatty acids from fat cells, and thus reduces fatty acid availability for the liver to form triglyceride. Since free fatty acid is the source from which cholesterol can be formed, it can reduce the formation of cholesterol as well. Side effects of Niacin include skin pruritus and hepatitis.

10) Cholestyramine and Colestipol are anionic exchange resins that adsorb cholic acid from bile juice in exchange for chloride released from them. As the amount of cholic acid is reduced in the bile juice, more cholesterol is converted to cholic acid to make up for the loss. As the intrahepatic cholesterol level is reduced, more blood cholesterol is taken up into the liver cells, lowering the blood levels of cholesterol. However, Cholestyramine can increase blood levels of triglyceride. Side effects of Cholestyramine and Colestipol include hyperchloremic acidosis, and interference with intestinal absorption of fat-soluble vitamins such as vitamin A, D, E, and K.

11) Dextrothyroxine can enhance conversion of cholesterol to cholic acid, and can induce LDL-cholesterol receptors to increase uptake of cholesterol into tissues from the blood. Side effects of dextrothyroxine include nervousness and increased incidences of anginal attack.

12) Lovastatin and Atorvastatin inhibit the enzyme HMG CoA (3-hydroxy-3-methylglutaryl coenzyme-A) reductase, and thereby oppose production of cholesterol in the liver. Other drugs that work in the same way include Simvastatin and Fluvastatin. They also tend to lower blood levels of triglyceride and increase HDL (good cholesterol) levels. Side effects of them include hepatitis and rhabdomyolysis. Since there is some evidence of teratogenic effect, use of "STATIN" drugs is contraindicated in pregnant patients.

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13) Intestinal absorption of dietary cholesterol is selectively inhibited by Ezetimibe. A more profound lowering of cholesterol may be seen when used in conjunction with “Statin” drugs. On the other hand, grapefruit juice contains an ingredient that inhibits hepatic cytochrome oxidase and blocks inactivation of the “statin” drugs; hence the juice and the drugs should not be taken in combination.

14) Probucol lowers blood levels of both LDL (bad cholesterol) and HDL (good cholesterol) with little effect on triglyceride levels. The drug may increase tissue uptake of cholesterol. Side effects of Probucol include Q-T elongation to generate ventricular arrhythmia.

15) Orlistat is used to treat obesity. It inhibits intestinal lipase to oppose intestinal absorption of dietary fats.

VII. Drugs Acting on the Respiratory & GI Tracts

33. Drugs Acting on the Respiratory Tract

1) Ipratropium, unlike Atropine, does not enter the brain to produce CNS effects, but does produce bronchodilation (it blocks airway muscarinic receptors) and is used as a DOC for treatment of non-asthmatic bronchospasm associated with COPD (chronic obstructive pulmonary disease). Tiotropium is another similar drug used in COPD.

2) Selective adrenergic β_2 agonists are often used for the treatment of bronchial asthma. They include Albuterol, Bitolterol, and Terbutaline. Salmeterol is another selective adrenergic β_2 agonist but its onset of action is slower and duration of action longer than other selective adrenergic β_2 agonists mentioned above, and it is used only to prevent an asthmatic attack.

3) Glucocorticoids inhibit the release of arachidonic acid from the membrane phospholipids by inhibition of the enzyme phosphodiesterase A_2 . Since arachidonic acid is the source from which bronchoconstrictive leukotrienes are formed, they are useful in the treatment of asthma. Glucocorticoids so used include Dexamethasone, Beclomethasone, Mometasone, Triamcinolone, Flunisolide, and Fluticasone. Methylprednisolone is useful for emergency treatment of life-threatening acute attacks of asthma and for status asthmaticus.

4) Budesonide is another glucocorticoid used to treat the symptoms of seasonal and perennial allergic rhinitis (hay fever).

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5) Arachidonic acid is converted by 5-lipoxygenase to 5-HPETE (hydroperoxy eicosatetraenoic acid), the precursor from which many different bronchoconstrictive leukotrienes are formed. Zileuton is an inhibitor of the enzyme and may be used to prevent asthma attack. Zafirlukast and Montelukast block leukotriene receptors and are useful for prevention of an asthma attack.

6) Acetylcysteine and Guaifenesin are used as mucolytic expectorants.

34. Drugs Acting on the Gastrointestinal Tract

1) Aluminum Hydroxide is a mild antacid. It can also oppose intestinal absorption of dietary phosphate. Its side effects include constipation.

2) Magnesium Hydroxide is a powerful antacid that may have a cathartic effect. Since it can be absorbed to a significant degree, it should not be used in patients with renal insufficiency.

3) Magnesium Sulfate and Sodium Sulfate are not absorbed, but retain water to induce a cathartic effect. These saline cathartics are useful in the treatment of food poisoning.

4) Docusate Sodium is an anionic surfactant that works as wetting agent. It allows penetration of water into a hardened fecal mass to soften it.

5) Methyl Cellulose and Psyllium are hydrophilic compounds that absorb water to swell and distend the colonic wall to induce a defecation reflex.

6) Emodin released from Senna, Aloe, and from Cascara has an irritant cathartic effect via activation of the Auerbach plexus.

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- 7) Ricinoleic acid released from castor oil has a laxative effect. Phenolphthalein and Bisacodyl are used as other laxatives.
- 8) Diphenoxylate and Loperamide are used as antidiarrheal agents.
- 9) Omeprazole, Pantoprazole, Esomeprazole, and Lansoprazole bind and directly inhibit $H^+K^+-ATPase$ pumping system at the parietal cells of the stomach and thereby block secretions of gastric acid. They are used as DOC in treatment of Zollinger-Ellison syndrome.
- 10) Sucralfate is used to protect erosion of gastrointestinal tract from organic acids and enzymes such as pepsin. In acidic conditions, Sucralfate becomes a viscous gel that adheres to and protects an ulcerous site.
- 11) Metoclopramide is used to prevent vomiting in cancer chemotherapy.
- 12) Lactulose has a laxative effect; it releases both lactic acid and acetic acid, and the lowered pH suppresses intestinal bacteria that release ammonia. Hence, Lactulose can lower the concentration of ammonia in the blood.
- 13) Infliximab is used to treat Crohn's disease. It works by binding to TNF (tumor necrosis factor).
- 14) Bismuth Subsalicylate is unique in that it kills *Helicobacter pylori*, the germ that is causative of peptic ulcer. The drug in acidic environment forms a coagulant to protect stomach ulcers.
- 15) Sulfasalazine releases sulfapyridine in the colon to be useful in the treatment of ulcerative colitis, and Crohn's disease.
- 16) Gallstones may be dissolved by oral use of Chenodeoxycholic Acid.

VIII. Drugs Affecting Endocrine Functions

35. Pancreatic Hormones & Oral hypoglycemic Agents

1) Glucagon promotes both gluconeogenesis and glycogenolysis to increase blood levels of glucose (in the presence of hepatic glucose-6-phosphatase), and Glucagon has lipolytic effects to increase blood levels of FFA (free fatty acids) as well. Oxidation of the FFA will lead to ketoacidosis. Glucagon can increase cardiac contractility independent from activation of adrenergic beta-receptors.

2) Insulin lowers blood levels of glucose by the following mechanisms: Insulin increases uptake of glucose into tissues, increases glycogenesis while reducing glycogenolysis, increases oxidation of glucose, and reduces gluconeogenesis. Insulin has an anabolic effect by facilitating uptake of amino acids to increase synthesis of proteins, and a lipogenic effect by increasing uptake of free fatty acids to form triglyceride. In the absence of insulin, blood levels of glucose rise; free fatty acids are released from triglyceride and oxidized to form ketone bodies (if pH falls below 6.9, it causes diabetic coma); and amino acids are released from proteins and are converted to glucose to be lost in the urine.

3) Insulin Injection is only insulin preparation that is allowed to be given by intravenous route.

4) Insulin Lispro is unique in that its onset of action after subcutaneous injection is quickest (15-30 minutes) and its duration of action (about 3 hours) is only about half that of an Insulin injection.

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5) Insulin Glargine is unique in provides long detectable blood levels up to 24 hours after a single subcutaneous injection (with onset about 30 minutes or less).

6) Isophane Insulin Suspension (NPH Insulin) and Insulin Zinc Suspension (Lente Insulin) are intermediate-acting insulin preparations.

7) Oral hypoglycemic agents include Tolbutamide and Chlorpropamide (both first generation sulfonylureas); and Glipizide and Glyburide (both second generation sulfonylureas, which are much more potent and longer-lasting than those of the first generation). All of them block potassium channels at the beta-cells of the Islets of Langerhans to depolarize the cells, which causes an influx of calcium ions to induce insulin secretion.

8) Repaglinide is not a member of sulfonylureas but it has the same mechanism of action and its onset of action is sooner (about 30 minutes or less), and duration of action is much shorter (about 3 hours) than sulfonylureas. Nateglinide is a Repaglinide-like rapid- and short-acting drug to increase secretions of insulin.

9) PPAR (peroxisome-proliferator activated receptor)- γ nuclear receptors can be activated by Rosiglitazone and Pioglitazone. Receptor activation leads to gene transcription to make proteins involved in carbohydrate metabolism. The drugs increase target tissue sensitivity to insulin, and so increase the uptake of glucose. Their side effects include weight gain.

10) Acarbose and Miglitol are inhibitors of alpha-glucosidase, the enzyme that converts maltose or oligosaccharide to free glucose. These drugs thereby inhibit intestinal absorption of glucose.

11) Metformin also can lower blood levels of glucose. It reduces hepatic gluconeogenesis and increases glycolysis. It lowers LDL-cholesterol and increases HDL-cholesterol.

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12) Exenatide is used to treat diabetes mellitus. Exenatide increases secretion of insulin and decreases secretion of glucagon. It is a GLP-1 (glucagon-like peptide) agonist.

13) Sitagliptin is used to treat diabetes mellitus. Sitagliptin promotes secretion of insulin and opposes secretion of glucagon. It inhibits dipeptidyl peptidase that degrades incretin hormones.

14) Pramlintide is used to treat diabetes mellitus. Pramlintide inhibits glucagon secretions.

36. Mineralocorticoids & Glucocorticoids

1) Fludrocortisone is a choice drug for replacement therapy of mineralocorticoid deficiency in Addison's disease.

2) Glucocorticoids (cortisol and corticosterone), by elevation of blood glucose, can aggravate symptoms of Diabetes Mellitus. They have antiinflammatory effects, but as they inhibit synthesis of immunoglobulins in the lymphoid tissues, the body's defense mechanism can be compromised.

3) Glucocorticoids inhibit synthesis of prostaglandin-E (which increases mucus secretion and decreases gastric acid secretion to protect the gastric cell wall) and thereby allow gastric ulcers to develop.

4) Glucocorticoids, by vasoconstriction, can increase blood pressure and can raise intraocular pressure by suppressing the outflow of aqueous humor.

5) Betamethasone accelerates lung maturation of premature infants.

6) Aminoglutethimide blocks the conversion of cholesterol to Δ^5 -

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pregnenolone and thereby inhibits the synthesis of cortisol. The drug is useful in the treatment of Cushing's disease.

7) Mifepristone can block both glucocorticoid receptors and progesterone receptors. Mifepristone is used to treat Cushing's disease, and is used to obtain abortion as well.

37. Drugs Affecting the Thyroid & Parathyroid Glands & Vitamin D

1) Levothyroxine is a DOC for routine treatment of hypothyroidism, whereas Liothyronine is a DOC for emergency treatment of myxedema coma.

2) Methimazole and Propylthiouracil are used to treat hyperthyroidism (Graves' disease). They inhibit the enzyme thyroid peroxidase to block synthesis of thyroid hormones. Their side effects include systemic lupus-like symptoms and agranulocytosis.

3) Radioisotope NaI^{131} is used to treat hyperthyroidism. It emits β -rays to destroy thyroidal tissues, thereby opposing synthesis of thyroid hormones.

4) Excessive doses of iodine (such as found in Lugol's solution) can control thyroid storm as it inhibits the release of thyroid hormone already formed; inhibits the synthesis of thyroid hormone; and inhibits the action of TSH (thyroid stimulating hormone) to reduce vascularity of the thyroid gland, making it suitable for thyroidectomy.

5) Bisphosphonate drugs such as Alendronate, Risedronate, or Pamidronate is used to prevent and treat osteoporosis and to treat Paget's disease.

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6) Calcitriol is a synthetic 1, 25-dihydroxy-vitamin D₃ useful to treat hypocalcemia. It increases intestinal absorption of calcium, and increases bone resorption. Its action does not depend on the presence of kidneys, or on parathyroid hormone secretion.

7) Teriparatide is used to treat osteoporosis in postmenopausal women. It can actually increase bone formation unlike other drugs.

8) Dihydroxycholesterol, a vitamin D₂-analog, is used to treat mild hypocalcemia. Its action is mainly due to its ability to cause bone resorption, as it has little effect on the intestinal absorption of calcium. Activity of Dihydroxycholesterol does not depend on the presence of kidneys, or on parathyroid hormone secretion.

9) Cinacalcet is used to treat hyperparathyroidism. It sensitizes receptors in the parathyroid gland and thereby decreases secretions of parathyroid hormone.

10) Doxercalciferol is a synthetic 1-OH-vitamin-D₂ that by elevation of blood levels of calcium can reduce, by a negative feedback, the secretions of parathyroid hormone.

11) Zoledronic Acid is used to treat hypercalcemia in cancer patients.

38. Vasopressin & Oxytocin

1) Release of vasopressin from the posterior pituitary gland is increased by such drugs as Morphine, Chlorpropamide, and Halothane; and decreased by Ethanol.

2) Activation of the V₁ (V for vasopressin) receptors causes arterial vasoconstriction to increase blood pressure. Side effects of Vasopressin include coronary vasoconstriction.

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3) Activation of the V_2 receptors by vasopressin increases water reabsorption at the collecting duct of the kidney. If no vasopressin is secreted, Diabetes Insipidus ensues.

4) Desmopressin is a synthetic analog of vasopressin. It has a V_2 -selective action to increase water-reabsorption and increase blood levels of coagulation factor-VIII, with little vasoconstrictive effect (V_1 R) on the coronary vessel.

5) Oxytocin provides rhythmic contractions of the uterus required for labor, and contracts myoepithelial cells surrounding the breast alveoli to provide milk ejections.

6) Oxytocic effects of Oxytocin is enhanced by estrogen, but diminished by Progesterone, Ritodrine, and Magnesium Sulfate.

39. Gonadotropins & Sex Hormones

1) LHRH (Luteinizing Hormone Releasing Hormone) is renamed GnRH (Gonadotropin Releasing Hormone), a hypothalamic hormone that increases secretion of both LH (luteinizing hormone) and FSH (follicle stimulating hormone) from the anterior pituitary gland, which in turn increases secretion of androgens and estrogens from gonads.

2) Gonadorelin is used to induce secretions of gonadotropins from the pituitary gland to obtain ovulation, whereas Goserelin is used to suppress release of gonadotropins by desensitization of pituitary receptors for GnRH (gonadotropin releasing hormone).

3) Histrelin, Nafarelin, and Leuprolide all initially release gonadotropins, but their continuous administration for a few weeks causes desensitization of the pituitary receptors to the hypothalamic GnRH (gonadotropin releasing hormone) and eventually suppresses sex-hormone secretions. They are therefore used to suppress

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androgen-dependent prostate cancer, estrogen-dependent endometrial cancer, or to control precocious puberty.

4) Ganirelix blocks the pituitary receptors for hypothalamic GnRH and has an immediate effect (in about one hour) in suppressing LH release during the controlled stimulation of ovarian growth by use of FSH.

5) Octreotide is a synthetic truncated version of somatostatin, which is used to treat acromegaly, glucagonoma, and gastrinoma. Pegvisomant is another drug used to treat acromegaly, but it works by blocking GH (growth hormone) receptors.

6) Sermorelin is a synthetic truncated version of GHRH (Growth Hormone Releasing Hormone), which is used to test the pituitary ability to manufacture GH (Growth Hormone).

7) Menotropins has both FSH and LH activities and is used to induce ovulation. Its side effects include a multiple-pregnancy.

8) Urofollitropin or Follitropin has only FSH activity and is used to promote growth of ovarian follicles.

9) Clomiphene is an antiestrogen (it competes with endogenous estrogen for binding to hypothalamic estrogen receptors) and it thereby increases the release of GnRH from the hypothalamus, which in turn increases secretion of gonadotropins from the pituitary gland. Clomiphene is used to treat infertility. Its side effects include a multiple-pregnancy, and ovarian cancer.

10) Raloxifene is a member of SERM (selective estrogen receptor modulators). It has an agonistic effect on the bone to be useful to prevent osteoporosis, but it has some antagonistic effect on breast estrogen receptors. Another SERM member is Tamoxifen, which has a strong antagonistic effect on breast estrogen receptors and so is used to treat estrogen-dependent breast cancer, but it has some agonistic

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effect on the uterine receptors to increase chances of uterine cancer.

11) Both Anastrozole and Letrozole inhibit the enzyme aromatase that converts androstenedione to estrone and hence are useful in the treatment of estrogen-dependent breast cancer in postmenopausal women.

12) Oral contraceptive pills often contain both estrogens and progestogens. Estrogens include Ethinyl Estradiol and Mestranol, whereas progestogens often used include Norethindrone, Norgestrel, and Norgestimate.

13) Testosterone is converted by 5α -reductase to dihydrotestosterone, which has a greater androgenic effect than testosterone, whereas testosterone itself has a greater anabolic effect than dihydrotestosterone. Loss of hair and prostatic hypertrophy are due to dihydrotestosterone; a 5α -reductase inhibitor such as Finasteride is used to treat prostate hypertrophy and to prevent androgen-dependent hair loss.

14) Flutamide is an androgen-receptor blocker and is useful to treat prostate cancer.

15) Somatropin and Somatrem are synthetic growth hormones and are used to promote physical growth.

16) Anabolic steroids are used to increase muscle size and strength, and to treat osteoporosis. They include Oxandrolone, Oxymetholone, and Stanozolol.

40. Drugs used in Gout

- 1) Allopurinol is converted by xanthine oxidase to oxypurinol (=alloxanthine), which in turn inactivates the same enzyme to block the formation of uric acid, the culprit of gout, from xanthine, a byproduct of nucleic acid degradation. Allopurinol is a DOC for chronic gout. Side effects of allopurinol include maculopapular skin rash and itching.
- 2) Colchicine binds to tubulin to block formation of microtubules, without which polymorphonuclear neutrophils and monocytes cannot migrate to the site of uric acid deposition. Hence, there is no phagocytosis and no release of lysosomal enzymes to induce gouty inflammation. Colchicine is a drug of choice in acute gout. Side effects of colchicine include bloody diarrhea. Indomethacin is another DOC for acute gout.
- 3) Sulfinpyrazone is a uricosuric acid that enhances urinary excretion of uric acid. It has some antithrombotic effects. Probenecid is another uricosuric agent but with weaker potency and milder side effects. Probenecid has no antithrombotic effect unlike Sulfinpyrazone.

41. Antianemic Drugs

- 1) Ferrous sulfate or ferrous fumarate is for the treatment of microcytic hypochromic anemia.
- 2) Folic acid is for the treatment of megaloblastic anemia, but not pernicious anemia. PABA (para-aminobenzoic acid) is a chemical component of folic acid.
- 3) Cyanocobalamin or hydroxocobalamin is for the treatment of pernicious anemia.

42. Vitamins

- 1) Thiamine (vitamin B-1) is required for oxidative decarboxylation of pyruvic acid in the process of formation of acetyl-CoA. Deficiency of this vitamin can produce beri-beri.
- 2) Riboflavin (vitamin B-2) is involved in oxidation of nutrients such as glucose, free fatty acids, and amino acids. Deficiency of the vitamin can produce cheilosis (inflammatory fissure at the surface of the lips).
- 3) Pyridoxine (vitamin B-6) is involved in the oxidative deamination and decarboxylation of amino acids, and transamination between an amino acid and alpha-ketoglutaric acid. Deficiency of this vitamin can lead to convulsions.
- 4) Ascorbic acid (vitamin C) is essential for the conversion of proline to hydroxyproline of collagen. Deficiency of this vitamin can produce scurvy.
- 5) Niacin (nicotinic acid) is involved in oxidation of nutrients such as glucose, free fatty acids, and amino acids. Deficiency of this vitamin can lead to pellagra (dermatitis, dementia and diarrhea).
- 6) Biotin is involved in carboxylation reactions, and is important for gluconeogenesis and for the synthesis of free fatty acids.
- 7) Vitamin A (retinol) is oxidized to retinal (= retinene) and further to retinoic acid. Deficiency of this vitamin can cause nyctalopia, xerophthalmia, acne, and psoriasis.
- 8) Tocopherol (vitamin E) is important as an antioxidant. Deficiency of this vitamin can lead to rupture of RBC membranes and destruction of skeletal muscle.
- 9) Vitamin K is important for blood coagulation. Phytonadione

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(vitamin K-1) and Menadiol Sodium Diphosphate (vitamin K-4) are clinically important. Among K-1, K-2, K-3, and K-4, Phytonadione (vitamin K-1) is the most potent, has the most prompt onset and a longer duration of action than others, and does not cause paradoxical bleeding. However, its intestinal absorption requires the presence of bile juice.

IX. Chemotherapeutic Agents

43. Chemotherapy & Sulfonamides

- 1) When a member of penicillins (a bactericidal drug) is used in combination with a tetracycline (a bacteriostatic drug) against pneumococcal meningitis, antibiotic antagonism can ensue.
- 2) Some antibiotics work by inhibition of bacterial cell wall synthesis. They include Penicillins, Cephalosporins, Bacitracin, and Vancomycin.
- 3) Some antibiotics work by change of cell membrane permeability. They include Polymyxin-B (antibacterial agent), Amphotericin-B and Nystatin (both antifungal agents).
- 4) Some antibiotics work by metabolic antagonism. They include sulfonamides (antifolates).
- 5) Some antibiotics work by inhibition of bacterial protein synthesis. They include Tetracyclines, Aminoglycosides, Chloramphenicol, Clindamycin, and Erythromycin and its derivatives such as Clarithromycin and Azithromycin.
- 6) Some antibiotics work by inhibition of bacterial RNA synthesis. They include Rifampin and Dactinomycin.
- 7) Some antibiotics work by inhibition of bacterial DNA synthesis. They include Nalidixic Acid and Mitomycin.
- 8) Sulfisoxazole or Sulfadiazine is a drug of choice for infections by *Nocardia* asteroids.

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9) Sulfamethoxazole and Trimethoprim, when used together, can generate a supra-additive antibacterial effect while bacterial resistance is reduced to them. Sulfamethoxazole works by inhibition of the enzyme dihydropteroate synthase, thereby inhibiting the formation of dihydrofolate; and Trimethoprim works by inhibition of dihydrofolate reductase, thereby inhibiting the formation of tetrahydrofolate. The combination is regarded as a DOC for *Pneumocystis jiroveci* (*carinii*) infections.

10) Side effects of sulfonamides include dermatitis (Stevens-Johnson type), bone marrow depression, hemolysis, and crystalluria.

11) Sulfonamides are inactivated by acetylation at the free amino group of their benzene ring.

12) The nitro group of Nitrofurantoin is reduced by susceptible bacteria during which a free radical is generated to destroy macromolecules of the bacteria. Acidic pH is required for urinary antiseptic effect of this drug. *Proteus* and *Pseudomonas* are resistant to this drug.

13) Ammonia and formaldehyde are generated from Methenamine Mandelate. Formaldehyde is toxic to susceptible bacteria. Acidic pH is required for the urinary antiseptic effect of this drug. *Proteus* and *Pseudomonas* are resistant to this drug.

14) Nalidixic Acid has a narrow spectrum antibacterial effect. Nalidixic Acid works only against sensitive Gram-negative bacteria by inhibition of DNA gyrase. It is active against *Proteus* but not active against *Pseudomonas*, nor active against Gram-positive bacteria.

15) Ciprofloxacin has broad spectrum antibacterial effects useful against urinary tract infections and respiratory infections. Its mechanism of action is by inhibition of bacterial DNA gyrase. Ciprofloxacin is a drug of choice for inhalation anthrax. Anaerobic

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germs such as Clostridium and Bacteroides are resistant to this drug, and some Streptococcus fecalis and Streptococcus pneumonia also may be resistant. Pseudomonas aeruginosa usually responds to this drug but resistance may soon develop. Gonorrhea may respond, but Syphilis and Chlamydia do not. Side effects of Ciprofloxacin include tendon rupture and erosion of cartilage at weight-bearing joints. For this reason, this drug is contraindicated in pregnant patients or in young children.

16) Ofloxacin is active against both Neisseria gonorrhoea and Chlamydia, to which Ciprofloxacin is not very active.

17) Side effects of Sparfloxacin include phototoxicity (sunburn-like dermatitis by ultraviolet light) and Q-T elongation (cardiotoxicity).

18) Trovafloxacin has the widest spectrum antibacterial activity among all fluoroquinolone antibiotics, acting against some anaerobic germs as well, but its side effects include serious hepatotoxicity.

19) Other fluoroquinolone antibiotics currently in use include Moxifloxacin and Levofloxacin.

44. Antibiotics 1: Penicillins & Cephalosporins

1) Penicillin G still remains the DOC for the treatment of syphilis by Treponema pallidum. It works by binding to PBP (penicillin binding proteins) and thereby inhibits the enzyme transpeptidase to oppose cross-linking between the two adjacent N-acetylmuramic acid pentapeptide chains.

2) Ampicillin is a DOC for infections by Listeria monocytogenes that may cause meningitis.

3) Amoxicillin is a DOC for Lyme disease. Another DOC for Lyme

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