SCOPE OF PHARMACOLOGY

A. History - It is of intellectual interest to the physician to know how drugs are discovered and developed. Often in the past, this was based on folklore or intelligent observation (e.g. digitalis leaf, penicillin). Nowadays, new drugs are mostly developed by the organic chemist working with a pharmacologist, increasingly from basic knowledge about key molecular targets. Usually some sort of biological screen is used to select among organic molecules for optimum pharmacological activity.

1. **Francois Magendie (1783-1855)**, a French physiologist laid down the dictum "Facts and facts alone are the basis of science." Experimental procedures with animals are the testing grounds for determination of drug action.

2. **Claude Bernard (1813-1878)** worked in Magendie's lab, investigated the plant extract curare and proposed a site of action for this agent.

3. **Rudolph Buchheim (1820-1879)**. In 1847 Buchheim established the first laboratory devoted to experimental pharmacology in the basement of his home in Dorpat which is known as the cradle of experimental pharmacology.

4. **Oswald Schmiedeberg (1838-1921)**. In 1872 Schmiedeberg set up an institute of pharmacology in Strasbourg, France (Germany at that time) which became a mecca for students who were interest in pharmacological problems.


6. **John J. Abel (1857-1938)** established the first chair of pharmacology in the U.S.A. (U. Michigan, 1891) after training in Germany. Able went to Johns Hopkins in 1893, and trained many U.S. pharmacologists. He is known as "The Father of American Pharmacology".

7. The second world war was the impetus for accelerated research in pharmacology (the war time antimalarial program) in the U.S., and introduced strong analytical and synthetic chemical approaches.

B. Chemistry - Chemical structures of drugs can provide information about mechanism of action, pharmacokinetics, stability, and metabolic fate.

1. **Structure-Activity Relationship** - A modification of the chemical structure of a drug may accentuate or diminish its pharmacological effects, often providing clues as to the mechanism of action. A picture
of the biological reactive site (the receptor) can be developed in such studies. Also, drugs are metabolized by body systems, which may convert the parent drug to a more active or a less active form. The drug structure can be modified to enhance or diminish the rate of metabolic conversion.

2. **Sites of Action** - The organ or cellular target of drug action.

3. **Drug Receptors** - Macromolecules in cells or cell membranes with which drugs interact to exert their effects. Usually the interacting forces are reversible ionic and Van der Waals bonds of relatively low energy, but sometimes covalent bonds are formed (e.g. organophosphate insecticides).

C. **Pharmacodynamics** - The effect of the drug on the body. Pharmacodynamics is the study of the relationship of drug concentration and the biologic effect (physiological or biochemical). For most drugs it is necessary to know the site of action and mechanism of action at the level of the organ, functional system, or tissue. For example, the drug effect may be localized to the brain, the neuromuscular junction, the heart, the kidney, etc. Often the mechanism of action can be described in biochemical or molecular terms. Most drugs exert effects on several organs or tissues, and have unwanted as well as therapeutic effects. There is a dose-response relationship for wanted and unwanted (toxic) effects. Patient factors affect drug responses - age, weight, sex, diet, race, genetic factors, disease states, trauma, concurrent drugs, etc.

D. **Pharmacokinetics** - The effect of the body on the drug. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Thus, it is important to know the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.

1. **Absorption** (oral or parenteral) - A drug must be absorbed and achieve adequate concentration at its site of action in order to produce its biological effects. Thus, when a drug is applied to a body surface (e.g., g.i. tract, skin, etc.), its rate of absorption will determine the time for its maximal concentration in plasma and at the receptor to produce its peak effect.

2. **Distribution** - The blood, total body water, extracellular, lymphatic and cerebrospinal fluids are involved in drug movement throughout the body. Depending upon its chemical and physical properties, the drug may be bound to plasma proteins or dissolved in body fat, delaying its progress to its sites of action or excretory mechanism.
3. **Metabolism** - This is how certain drugs are handled by the body in preparation for their elimination and includes the fate of drugs-biotransformation (e.g., hydrolysis, conjugation, oxidation-reduction).

4. **Excretion** - The kidney is the most important organ for drug excretion but the liver, lung and skin are also involved in drug elimination. Drugs excreted in feces are mostly derived from unabsorbed, orally ingested drugs or from metabolites excreted in the bile and not reabsorbed by the intestine. The physical and chemical properties, especially the degree of ionization of the drug, are important in the rate of excretion.

5. **Biological Factors Modifying Pharmacokinetic Aspects** - Normal variations occur in population pharmacokinetic constants (absorption rates, elimination rates). Other factors include age, weight, obesity, edema, concurrent diseases, other drugs (various interactions including effects on protein binding or metabolic rate), diet, dose interval and route of administration, genetic variations in elimination rate.

E. **Clinical Pharmacology and Therapeutics**

1. **Indications and Therapeutic Uses** - Emphasis is placed on the therapeutic use of drugs for the treatment of disease in clinical pharmacology, internal medicine and therapeutics. There are specific clinic disorders or disease entities for which a given drug may be prescribed and the physician must weigh the potential benefit of drug use against the risks of adverse effects.

2. **Contraindications and Factors (e.g., liver disease) May Modify Drug Action** - where detoxification of the drug by the liver is important. It is important to know that the presence of disease or organ pathology may influence the actions of a drug. Conditions such as age, pregnancy, concomitant administration of other drugs and disease may alter the patient's response to a given drug.

3. **Posology** - Is an archaic term describing dosage regimens. Consideration of dosage schedules is a part of pharmacokinetics.

4. **Bioavailability** - The fraction of drug administered which is actually absorbed and reaches the systemic circulation following oral dosing. Preparations of the same drug by different manufacturers may have a different bioavailability.

5. **Prescription writing** - It is important that the physician write clear, error-free directions for the drug provider (pharmacist) and for the patient. Physicians must guard against prescribing too many drugs, or
preparations of little value. Drugs of unproven clinical value should be avoided, as well as potentially toxic agents if drugs equally effective but less dangerous are available. Risk-benefit and cost-benefit should be considered. Drugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way. A particular manufacturer may be specified if the physician has reason to believe a better or more reliable preparation is available from that manufacturer.

6. **Drug Nomenclature** - In addition to its formal chemical name, a new drug is usually assigned a code name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the market, a United States Adopted Name (USAN) is selected by the USAN Council which is sponsored by:

   1) The American Medical Association
   2) The American Pharmaceutical Association
   3) The United States Pharmacopeial Convention

F. **Toxicology** - That aspect of pharmacology that deals with the adverse effects of chemical agents. Toxicology is concerned not only with drugs used in therapy but also with the other chemicals that may be responsible for household, environmental or industrial intoxication.

1. **Forensic Toxicology** - Addresses medicolegal aspects of the use of chemicals that are harmful to animals or man. Analytical chemistry and fundamental toxicological principles are hybridized to underlie this aspect of toxicology. Nonetheless accidental poisoning with drugs is a health problem of major significance. More than 1/4 of the fatalities and about 1/2 of all poisonings occur in children under 5 years of age. All common household articles that are poisonous should be made unavailable to children, and poisonous rodenticides and insecticides should not be placed in the home.

2. **Clinical Toxicology** - Focuses on toxic events that are caused by or are uniquely associated with drugs or other chemicals.

3. **Adverse Drug Reactions Toxicities and Side Effects** - No drug is free of toxic effects. Some untoward effects of drugs are trivial, but others are serious and may be fatal. Side effects often are predictable from a knowledge of the pharmacology of a particular drug. Examples of chemicals or drug-induced toxicities are given below:

   a. **Allergic reactions** - The number of serious allergic reactions to drugs involving antigen-antibody reactions is low but when they occur the physician must have sufficient knowledge to manage these problems.
b. **Blood dyscrasias** - These are very serious and sometimes fatal complications of drug therapy. They include: agranulocytosis, aplastic anemia, hemolytic anemia, thrombocytopenia and defects in clotting factors.

c. **Hepatotoxicity and nephrotoxicity** - Because many chemicals and drugs are eliminated and metabolized by the liver and kidney, damage to these organs is seen commonly.

d. **Teratogenic effects** - The thalidomide tragedy dramatically emphasized that drugs may adversely influence fetal development.

e. **Behavioral toxicity** - This is a term used to describe suppression of normal anxiety, reduction in motivation, impairment of memory and learning, distortion of judgement, impairment of reflexes, adverse effects on mood, etc.

f. **Drug dependence and drug abuse** - The repeated administration of some chemicals may lead to drug dependence. Drugs likely to be abused and upon which drug dependence may develop are the various psychopharmacological agents such as opiates, barbiturates, amphetamines, nicotine and ethanol. Dependence on tobacco (nicotine) is also well known.

g. **Carcinogenesis** - Carcinogenesis is a delayed type of toxicity with a latency of many years.

h. **Pharmacogenetic toxicities** - Certain genetically-predisposed individuals have a markedly toxic reaction to certain otherwise safe drugs. Examples are prolonged apnea after succinylcholine, or malignant hyperthermia associated with anesthetics.
Twelve contact hours are recommended at the beginning of the course to provide the foundation for reinforcement and application of these principles throughout the course.

1. **Introduction, Roots, and Definition of Terms**

   a. **Definition of Pharmacology**

      The discipline that is concerned with understanding the interactions of chemical substances with living systems, and the application of this understanding to the practice of medicine.

   b. **Relation to Other Disciplines**

      Basis in Chemistry, Physiology, Biochemistry, and Molecular Biology
      A foundation of medical practice, including historic perspective
      Relationship to Toxicology, Pharmacy, Therapeutics

   c. **Key Terms and Concepts**
1) Drug - a substance that acts, often by interaction with regulatory molecules, to stimulate or inhibit normal physiologic processes.

2) Drug Receptors - molecules with which a drug first interacts to eventually affect biological function. There is often a strict structural requirement for this interaction. Drug targets include receptors for endogenous substances (neurotransmitters, hormones, etc.), enzymes, transport proteins, ion channels etc. Some pharmacologists prefer the term "drug targets," and reserve the term "receptor" to describe the macromolecules that serve as receptors for endogenous substances.

3) Agonist (full, partial, inverse), antagonist (competitive and non-competitive).

4) Drug-receptor interactions – affinity, intrinsic activity

5) Selectivity of drug action - all drugs have multiple effects, both desirable (beneficial) and undesirable (adverse effects, or "side effects"). Selectivity is partly intrinsic to the nature of the drug-receptor interaction. The astute physician can maximize selectivity by attention to pharmacologic principles.

6) Pharmacodynamics - the study of drug effects on the body. The dose-response relationship(s) and drug-receptor interactions for each drug are of particular importance.

7) Pharmacokinetics - the study of the effects of the body on the drug, and its travels through the organism. The understanding of plasma drug concentration as a function of time is of particular importance.

8) Time-action relationships - function of dosing schedule and a combination of a drug's pharmacokinetic and pharmacodynamic properties

9) Dose-response relationships – graded and quantal

10) Efficacy, potency

11) Long-term effects of drugs (including tolerance, regulation of gene expression)

d. Course Goals

1) Describe the principles governing drug actions in humans

2) Describe the specific knowledge related to the different classes of drugs, and important distinctions among members of each class, in relation to the organ systems they affect, and the diseases for which they are used therapeutically.

3) Develop a basis for continued education in medicine

4) Establish a foundation on which to build a rational approach to the use of drugs in clinical practice
5) Develop a foundation to effectively use the medical literature to evaluate new drugs in the context of evidence-based medical practice

2. **Qualitative and Quantitative Pharmacokinetics**

a. **Chemical Aspects**

1) Weak acids and bases - the Henderson-Hasselbalch equation; relationship between pH and ionization of drugs
2) Lipid solubility of drug species; polar and nonpolar drugs
3) Properties of biological membranes, mechanisms of drug movement across membranes. Passive and active processes
4) Ion trapping of drugs. Specific examples of stomach contents and urine as ion-trapping compartments
5) Chirality - drugs that exist as mixtures of two or more stereoisomers

b. **Absorption**

1) Concept of therapeutic window
2) Relationship of lipid solubility, blood flow, and site of drug placement
3) Effect of pH- absorption of weak acids and bases from stomach vs. intestine - influence of age
4) Absorption from oral, IM, SC, and other routes
5) Manipulation of absorption - dosage form, depot preparations, delayed release preparations, transdermal patch
6) Special sites of absorption; buccal, pulmonary, rectal, transcutaneous sites
7) Systemic absorption of drugs applied for local effects: intraocular, intranasal, dermatologic preps
8) Concept of bioavailability as a function of absorption and first pass metabolism
9) Developmental, age-related, and disease-related changes in drug absorption

c. **Distribution**

1) Plasma protein binding, its effects on distribution
2) The lymphatic system and drug distribution
3) Factors affecting distribution: Tissue perfusion, ease of access, tissue binding and solubility coefficients
4) Distribution ("redistribution") as a mode of termination of drug action.
5) Distribution of drugs into special compartments. Nature of the capillary endothelium at the liver sinusoid, the skeletal muscle and brain. Why lipid solubility of a drug is important in the brain but not at the extracellular receptor of the neuromuscular junction. The blood-brain barrier and tight endothelial junctions. Drug penetration across the placenta.
6) Concept of apparent volumes of distribution; relationship to physiological volumes. One and two-compartment drug distribution models.
7) Developmental, age-related, and disease related changes in drug distribution.

d. Metabolism
1) Importance of drug metabolism for excretion (conversion of non-polar xenobiotics to polar metabolites which can be excreted in the urine).
2) Biotransformation: activation vs. inactivation (detoxification) of drugs: prodrugs, toxic metabolites
3) Major pathways of metabolism: Phase I vs. Phase II, general properties
   a) oxidation, reduction, hydrolysis
   b) conjugation -glucuronides, glycine, sulfate esters, acetylation, glutathione, mercapturic acids
4) The cytochrome P450 system. Liver, other tissues. Major P450s involved in drug metabolism: CYP1A2, CYP2B6, CYP2Cs, CYP2D6, CYP2E1, CYP3A4. (For isoforms see section on Pharmacogenetics)
5) Enzyme induction: mechanisms, time course, clinical implications, and examples of common inducers (e.g. phenobarbital, rifampin, polycyclic hydrocarbons, environmental factors)
6) Enzyme inhibition: clinical implications
7) Developmental, age-related, and disease-related changes in drug metabolism

e. Excretion
1) Definition of excretion as the loss of drug molecules from the body; excretion of parent drug vs. excretion of metabolites.
2) Major sites of drug excretion: renal, biliary/alimentary, pulmonary (a major route for inhalation agents only). Minor sites of drug excretion: sweat, milk
3) Renal excretion: role of filtration, secretion and reabsorption - importance of plasma protein binding, molecular size, polarity, weak acids and weak bases, urine pH

4) Biliary/alimentary excretion: biliary transport, direct secretion of drugs from blood to intestine, importance of plasma protein binding, molecular size, polarity, weak acids and weak bases. Consequences of enterohepatic circulation.

5) Developmental, age-related, and disease-related changes in drug and metabolite excretion

6) Differentiate excretion from pharmacologic concept of elimination (the sum of metabolism and excretion)

7) Clearance as the pharmacologic parameter that characterizes the efficiency of elimination process
a) general definition of clearance: \( Cl = \frac{\text{rate of elimination}}{[C]} \)
b) additivity of organ clearances, e.g. \( Cl_{tot} = Cl_{hepatic} + Cl_{renal} + Cl_{other} \)
c) organ clearance -- extraction ratio and blood flow \( Cl = E \times Q \), high and low extraction ratios and effects of changes in blood flow and plasma protein binding

f. Quantitative Pharmacokinetics

1) First order, dose-independent kinetics
a) single IV bolus dose, one and two compartment systems
i. definition of first order process, explanation of why metabolism and renal elimination are often first order, distribution and elimination phases of log C vs. time plot
ii. pharmacokinetic parameters that determine the plot and can be estimated from it, and their interrelationships: \( V_{d1}, V_{d\text{extrap}}, V_{d\text{area}}, AUC, k_e, \) elimination \( t_{1/2, Cl} \)
b) single oral (or other non IV dose), one compartment
i. effect of \( k_a, k_e, \) and dose on \( C_{\text{max}}, t_{\text{max}}, \) and AUC
ii. estimation of bioavailability by ratio of AUCs
c) constant IV infusion, one compartment
i. definition of steady state, the plateau principle, \( C_{ss} = \frac{IR}{Cl} \)
ii. time to steady state as a function of half-life and effects of stopping infusion or changing infusion rate
iii. calculation of loading dose
d) repeated dosing one compartment
i. drug accumulation and plateau principle: \[ C_{av} = \frac{Dx}{T} \times Cl \] independent of \( k_a \)

ii. peak to trough variation as a function of dose, \( F \), \( t_{1/2} \), dosing interval(\( T \)), and \( k_a : k_e \) ratio

2) Deviations from first order (dose-independent) kinetics
   a) Zero order and "Michaelis-Menten" elimination kinetics, definition, and implications (dose-dependent kinetics)
   b) Saturation of plasma protein binding, implications
   c) Dose-dependent absorption and bioavailability

3. **Pharmacodynamics - Relationship of Distributional Factors and Protein Binding, to Concentration of Drug at the Receptor Site**

a. Receptor Theory

   1) Introduction
      a) Historical development
      b) Definition of a receptor (signal transduction)
      c) Occupancy theory: \( E_A / E_M = [A] / ([A] + K_A) \)

   2) The log concentration-response relationship

   3) Agonists
      a) Interpretation of log concentration-response curves
      b) Potency (ED50 and EC50) vs affinity (\( K_A \))
      c) Intrinsic activity vs efficacy
         i. Partial agonists
         ii. Inverse agonists

   4) Antagonists
      a) Competitive, reversible, surmountable
      b) Non-competitive, irreversible, unsurmountable

   5) Receptor reserve

b. Quantal Response Relationships

   1) ED50 (potency) vs LD50 or TD50
   2) Therapeutic indices

c. Structure-activity relationship (SAR) as a mechanism for modeling receptors, active sites, and developing modified drugs.

d. Types and subtypes of receptors - therapeutic action vs side effects

   1) Receptor superfamilies and mechanisms
      a) Ligand-gated ion channels
         i. Nicotinic ACh receptor
         ii. GABA-A receptor
2) G Protein coupled receptors
   a) Muscarinic ACh receptors
   b) Three major types of adrenergic receptors (alpha-1, alpha-2, beta)
   c) Guanine nucleotide regulatory binding proteins
3) Tyrosine kinase receptors
   a) Insulin
   b) PDGF
4) Transcription factor receptors
   a) Receptors for steroid hormones

e. Receptor Regulation
   1) Down-regulation and desensitization
      a) Inverse relationship between agonist concentration and receptor levels
   2) Up-regulation and sensitization

f. Non-receptor targets as sites of drug action
   1) Enzymes - acetylcholinesterase
   2) Nucleic acids as site of action of drugs - actinomycin D
   3) Target uniqueness as a basis for selective chemotherapy - penicillin

4. Pharmacogenetics/genomics
   a. Pharmacogenetics is the genetic basis for differences among the human population in drug therapeutic response and/or toxicity. Pharmacogenomics is the application of genomic information towards the discovery and development of drugs with new and more specific targets. Rational, individualized selection of drug and/or drug dose based on patient's genetic information will increasingly replace the paradigm of one drug and/or one dose fits all. The pharmacogenetics knowledge base is expanding exponentially since the publication of the human genome. The "idiosyncratic" drug response will increasingly be predictable, preventable, and unacceptable (i.e., considered malpractice). Effective drugs previously discarded because of a high incidence of toxicity will be useful when targeted to patients of appropriate genetic profile.

   b. All proteins are gene products and many (perhaps most) exhibit genetic polymorphism. Single nucleotide polymorphisms (SNPs), gene deletions, gene amplifications determine protein structure, configuration, and/or concentration. When a protein is important
in drug action or disposition, then genetic differences between individuals in that drug's action or disposition are expected.

c. Differentiate genotype and phenotype. Discuss methods to determine phenotype and genotype. Discuss polymerase chain reaction, restriction fragment length polymorphism; allele-specific amplification; DNA microarrays.

d. Pharmacogenetic polymorphisms affect drug response as well as drug disposition and toxicity. Examples should be provided illustrating both drug disposition and toxicity (i.e., NAT2, CYP2D6) and drug action (i.e. beta adrenergic receptors).

e. Monogenic pharmacogenetic traits often discriminate populations into discrete phenotypes (polymorphic distribution). Polygenic pharmacogenetic traits usually provide monomorphic distributions.

f. Frequency of pharmacogenetic polymorphisms often differs with ethnic group. Polymorphisms are genetic differences in germ-line DNA and are not "mutations." Individuals with polymorphisms are healthy and are not "aberrant" or "abnormal" unless challenged with inappropriate drug or drug dose.

g. Illustrate clinical relevance with examples such as:

1) NAT2; isoniazid, procainamide
2) CYP2D6; debrisoquine, codeine
3) CYP2C19; mephenytoin
4) CYP2C9; warfarin
5) Serum cholinesterase; succinylcholine
6) Glucose-6-phosphate dehydrogenase; analgesics; antimalarials
7) Thiopurine-S-methyltransferase; 6-mercaptopurine
8) Beta-2 adrenergic receptors; albuterol
9) Dopamine receptors; antipsychotics
10) Malignant hyperthermia; inhalation anesthetics

5. **Principles of Drug Interactions**

a. Prevalence of multi-drug therapy; importance of complete drug history including herbal and other complementary medicine and recreational drugs
b. Types of interactions by mechanism--pharmaceutic, pharmacokinetic, pharmacodynamic-- with illustrative examples

c. Types of interactions by outcome--additivity, synergy, potentiation, antagonism-- with illustrative examples

d. Not all drug interactions are bad: beneficial, planned interactions vs. unintended adverse interactions

e. Awareness of drug-food interactions, and drug interference with diagnostic tests

6. Development, Evaluation and Control of Drugs

a. Preclinical Development. The goal is to develop therapeutic agents with known mechanism(s) of action, maximal therapeutic indices, and favorable pharmacokinetic properties. Drugs emerge from both rational design as well as serendipity. Rational drug design involves structure-activity considerations, modeling, and computational chemistry. Advantages and limitations of in vitro and in vivo screening. Difficulty of extrapolating animal toxicity studies to humans. FDA criteria for clinical trials approval.


c. Regulatory System. Legal mandates of the FDA and DEA. Classification (Scheduling) of drugs with addiction potential. Influence of drug scheduling on medical practice.

d. Post-Marketing Surveillance of Drugs. Adverse drug reaction reporting mechanism. Problems with subpopulations such as children, the elderly, the mentally impaired, pregnant or lactating women. Limitations of statistical analysis.

e. Drug Information for Practitioners. Textbooks, journals, FDA alerts, poison control centers, and electronic databases.

f. Pharmaceutical Industry: Duration of drug patents; branded verses generic drugs.
Influence of marketing (from sales representatives to television advertising) on medical practice.
In general, medical students enter medical pharmacology courses with a sound background in the anatomy of the ANS, but a somewhat inadequate grasp of its physiology. Therefore, we need to spend considerable time on the latter and little time on the former in ANS pharmacology. The importance of autonomic pharmacology is greater than that of its collective therapeutic agents. It is the foundation for understanding other areas such as cardiovascular pharmacology and pharmacology of the central nervous system. Autonomic nerves and/or their effector cells are the sites of action responsible for the side effects of many drugs whose primary sites of action are elsewhere.

1. **Introduction to the Autonomic Nervous System (1)**
   
   a. **History**
      
      1) Describe the anatomical projections of the sympathetic and parasympathetic autonomic nervous system.
      
      2) Describe the evidence for development of the concept of neurotransmitters, cotransmitters, and end-organ receptor specificity.

   b. Define words containing the suffixes, -ergic,-mimetic, -lytic and -ceptive.
c. Describe homeostasis, fight-or-flight and rest-and-repair with regard to sympathetic and parasympathetic activity.

d. Describe the central control of the autonomic nervous system.

e. List and describe the responses of end organs to activation of the sympathetic and parasympathetic nervous systems.

f. Describe the concept of predominant tone.

2. **Cholinergic Neurotransmission and Muscarinic Agonists (1)**

   a. List the steps in the synthesis, storage, release and inactivation of acetylcholine, and drugs that interface with those processes. Explain their mechanisms. Describe the types of receptors, nicotinic and muscarinic.

   b. Acetylcholine-muscarinic and nicotinic receptor sites

      1) List the locations of and the differences between muscarinic and nicotinic receptors.
      2) List the therapeutic uses of muscarinic agonists.
      3) List the adverse side effects of muscarinic agonists.
      4) Important or prototypic drugs: acetylcholine, bethanechol, and pilocarpine.

3. **Anticholinesterases (1)**

   a. Compare the two major cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) as to anatomical locations, sites of synthesis and function.

   b. Explain the chemical makeup of the active site of AChE (anionic and esteratic) as to attraction, attachment and rates of breakdown of various substrates and inhibitors.

   c. Relate the onset of action of anticholinesterases, routes of administration, and the duration of action of anticholinesterases with sites and type of attachment to the enzyme.

   d. Explain why anticholinesterases are reversible or irreversible, and indicate which anticholinesterases are in each category.

   e. Describe the effects of accumulated acetylcholine at muscarinic and nicotinic receptors in the periphery and the central nervous system.
f. List therapeutic uses for and adverse side effects of anticholinesterases.

g. Distinguish the mechanism by which pralidoxime reactivates phosphorylated AChE.

h. Explain the role of enzyme aging in the enzyme-inhibitor interaction.

i. Explain why anticholinesterase agents can be used as insecticides (malathion, parathion) and chemical warfare agents (sarin, VX series). Explain why PRALIDOXIME is not effective reactivating all phosphorylated AChE. Explain the concept of differential toxicity of malathion and parathion in different species.

j. Important or prototypic drugs: physostigmine, neostigmine, edrophonium, pyridostigmine, echothiophate and pralidoxime.

4. **Antagonists at Muscarinic Receptor Sites (1)**

   a. Describe the mechanism of action.

   b. Explain the rationale for the therapeutic use in diseases such as bronchoconstriction, excessive salivation, and motion sickness. Explain the rationale for the therapeutic use to produce mydriasis and cycloplegia.

   c. Explain why muscarinic antagonists cause xerostomia, blurred vision, photophobia, tachycardia, anhidrosis, difficulty in micturition, hyperthermia, glaucoma and mental confusion in the elderly.

   d. Explain why muscarinic antagonists are contraindicated in glaucoma, obstructive disease of the gastrointestinal tract or urinary tract, intestinal atony.

   e. Important or prototypic drugs: atropine, scopolamine, tolterodine and ipratropium.

5. **Drugs Acting at Autonomic Ganglia (0.5)**

   a. Nicotine

      1) Describe nicotine’s agonist and antagonist properties.
2) Explain why it is not used clinically (except as a smoking deterrent), and its historical, social and toxicological significance.

b. Antagonists acting at ganglionic nicotinic receptor sites

1) Describe the pharmacological effects, and understand the role of predominant tone.
2) Explain rationale for original uses in treatment of hypertension and autonomic hyperreflexia.
3) List the adverse side effects.
4) Important drug: trimethaphan

6. Antagonists at Nicotinic Receptor Sites in the Skeletal Neuromuscular Junction (NMJ) (0.5)

a. Describe the selectivity of drugs between ganglionic and neuromuscular nicotinic receptors.

b. Describe the physiology and pathophysiology of transmission at NMJ.

c. Classes of neuromuscular antagonists

1) Depolarizing agent
   Explain the uses and limitations.
2) Competitive antagonists at NMJ
   List the adverse side effects.
3) Important-prototypic drugs: succinylcholine, tubocurarine, mivacurium.
4) Contrast and compare the depolarizing and competitive NMJ blocking drugs.

d. Explain the rationale for the combination use of antimuscarinic and anticholinesterase agents in reversal of neuromuscular blockade.

7. Sympathetic Neurotransmission, and the Adrenal Medulla (1)

a. List the steps in the synthesis, storage, release and inactivation of norepinephrine and epinephrine, and the drugs that interfere with those processes. Explain their mechanisms.

b. Describe the types and subtypes of adrenergic receptors, their locations, and physiologic response to activation.
c. Describe the receptor selectivity of norepinephrine and epinephrine.

d. Important or prototypic drugs: epinephrine, norepinephrine, monoamine oxidase inhibitors, metyrosine, reserpine, and guanadrel.

8. **Indirectly Acting Sympathomimetic Agents (1)**

a. Describe the difference between actions of direct and indirect adrenergic drugs.

b. Explain the mechanism of indirect acting adrenergic drugs.

c. List the therapeutic uses.

d. Important or prototypic drugs: tyramine, ephedrine, pseudoephedrine, cocaine, amphetamine, and methamphetamine.

9. **Alpha Adrenergic Agents (1.5)**

a. Alpha-1 Adrenergic Agonists

1) Explain why alpha-1 adrenergic agonists are important in the treatment of nasal congestion, hypotension, paroxysmal atrial tachycardia, and are used to cause mydriasis and vasoconstriction (with local anesthetics).

2) List the adverse side effects.

3) Explain drug interactions with oxytocic drugs and monoamine oxidase inhibitors.

4) List the contraindications.

5) Important-prototypic drugs: epinephrine, norepinephrine, and phenylephrine.

b. Alpha-2 adrenergic agonists

1) Explain the mechanism for the use of alpha-2 adrenergic agonists in the treatment of hypertension, and for the topical treatment of glaucoma.

2) List the adverse side effects.

3) Important or prototypic drug: clonidine

c. Nonselective alpha-1, alpha-2 adrenergic antagonists
1) Explain the limitations of the use of nonselective alpha-1, alpha-2 adrenergic antagonists in the treatment of hypertension.
2) List the adverse side effects.
3) Important or prototypic drugs: phentolamine, phenoxybenzamine.

d. Alpha-1 adrenergic antagonists
1) Explain why alpha-1 adrenergic antagonists are used to treat hypertension and benign prostatic hypertrophy.
2) List the adverse side effects.
3) Important or prototypic drugs: prazosin, terazosin, tamsulosin

10. Beta Adrenergic Agents (1.5)

a. Nonselective beta adrenergic agonists
Compare and contrast the pharmacology of epinephrine and isoproterenol.

b. Selective beta adrenergic agonists
1) Compare and contrast the pharmacology of beta selective adrenergic agonists isoproterenol, albuterol, salmeterol, and dobutamine.
2) Explain the mechanisms for the use of these drugs in diseases such as cardiac decompensation, asthma, premature labor, bronchospasm and emphysema.
3) List the adverse side effects.

c. Beta adrenergic antagonists
1) Compare and contrast the pharmacology of propranolol, metoprolol and atenolol.
2) List the adverse side effects.
3) Important or prototypic drugs: propranolol, metoprolol and atenolol.

d. Compare and contrast the pharmacology of the nonselective alpha and beta blocking drug labetalol, with selective beta blocking drugs.
Minimum list of drugs in autonomic and neuromuscular pharmacology

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<tr>
<th>PRIMARY DRUGS</th>
<th>SECONDARY DRUGS</th>
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<td>TYRAMINE</td>
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 PRIMARY DRUGS - All uppercase letters
 Secondary drugs - lowercase letters
## DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM (21)

### Subcommittee:

<table>
<thead>
<tr>
<th>NAME</th>
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1. Neurotransmitters, receptors and neurochemistry (1.5)
2. General anesthetics (2)
3. Local anesthetics (1)
4. Opioid analgesics, agonist-antagonists, antitussives & expectorants, other pain-relieving agents (3)
5. Drugs used in treatment of motor disorders (1)
6. Antiepileptics (1)
7. Antidepressants and mood stabilizing drugs (2)
8. Antipsychotics (Neuroleptics) (2)
9. Sedative-Hypnotics, anxiolytics, and centrally acting muscle relaxants (3 hr)
10. Substance Abuse (4.5)
   a. Drug dependence (0.5)
   b. Stimulants and anorexigenic agents (0.5)
   c. Ethanol and alcoholism (1.0)
   d. Hallucinogens and designer drugs (0.3)
   e. Marijuana (0.3)
   f. Organic solvents, inhalants (0.3)
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   h. Drugs and the law (0.5)
11. Treatment of Alzheimer’s Disease (.25)

### Introduction to Pharmacology of the Central Nervous System
Understanding how drugs affect the central nervous system depends upon an integral knowledge of neuroanatomy, biochemistry, physiology, and basic pharmacological principles. A core medical curriculum in pharmacology of the central nervous system requires at least 25 hours.

1. **Neurotransmitters, Neuromodulators, and Receptors**
   
a. List the major neurotransmitters in the brain, their predominant anatomical pathways, and their associated relevant disorders.

b. Compare and contrast G protein coupled receptors and ligand gated ion channels.

c. Describe how neurotransmitter receptor function may be altered as a consequence of chronic agonist or antagonist administration.

d. Identify the molecular, cellular, and biochemical sites where drugs can act to affect neuronal function.

e. List the factors that determine whether a drug will gain access to the central nervous system.

1) **Endogenous Agents**
   
   ACETYLCHELINE (ACH)
   
   ADENOSINE TRIPHOSPHATE (ATP)
   
   aspartate (Asp)
   
   beta-amyloid
   
   beta-endorphin
   
   bradykinin
   
   DOPAMINE (DA)
   
   epinephrine
   
   dynorphins
   
   endomorphins
   
   enkephalins
   
   5-HYDROXYTRYPTAMINE (5-HT)
   
   GAMMA-AMINOBUTYRIC ACID (GABA)
   
   GLUTAMATE (glu)
   
   glycine
   
   histamine
   
   leptin
   
   nerve growth factor (and other growth factors)
   
   NOREPINEPHRINE
   
   nitric oxide
   
   SUBSTANCE P
2. **General Anesthetics (2)**

   a. Define the terms “general anesthesia”, “neuroleptic analgesia”, and “dissociative anesthesia.”

   b. State the objectives of general anesthesia, characteristics of an ideal anesthetic, and the stages of general anesthesia.

   c. Explain how the solubility of a gas in a liquid is defined. List the conditions that must be specified to determine the concentration of gas in the liquid phase.

   d. Define MAC (minimal alveolar concentration), name the physical property of an inhalation anesthetic that correlates best with its MAC, and explain how the concept of MAC is used in anesthesiology.

   e. Describe how the physical properties of inhalation anesthetics influence the rate of equilibration of anesthetic in the inspired air to anesthetic in alveoli, blood, brain, muscle and fat. Explain how this information is related to onset and recovery from inhalation anesthesia.

   f. Define “second gas effect” and explain why it occurs.

   g. List and explain the complications that may ensue with the use of Nitrous Oxide as a direct result of the high concentrations at which it is administered and its solubility in blood relative to that of nitrogen.

   h. List the current theories of the mechanisms of action of inhalation anesthetics, of intravenous anesthetics.

   i. Compare the available inhalation anesthetics with respect to their pharmacokinetic properties, effects on various organ systems, biotransformation, and disadvantages and advantages.

   j. Compare and contrast commonly used intravenous induction agents—their adverse effect profile, speed of onset, and duration of action. Describe the relative roles of distribution and metabolism in determining duration of action and how duration of action may change with repeated administration of an iv anesthetic.

   k. List clinical conditions that make general anesthesia hazardous and alternative means for preparing patients for surgery.
l. Describe malignant hyperthermia, list some common triggering agents, and discuss its prevention and treatment.

m. Describe the utility and adverse effects of drugs commonly used as preanesthetic medications or as adjuncts to anesthesia. Include: atropinics, neuromuscular blocking agents, benzodiazepines, and opioids in your discussion. Indicate how the concomitant use of these drugs may affect the concentrations of inhaled anesthetics used to maintain the anesthetic state.

**Drugs to Consider:**
alfentanil
desflurane
enflurane
etomidate
FENTANYL
HALOTHANE
ISOFLURANE
KETAMINE
methohexital
methoxyflurane
MIDAZOLAM
MORPHINE
NITROUS OXIDE (N₂O)
PROPOFOL
SEVOFLURANE
sufentanil
THIOPENTAL

3. **Local Anesthetics (1)**

   a. Discuss the mechanism of action of local anesthetics. Explain how the actions of clinically used anesthetics might be influenced by the frequency of impulse transmission in peripheral nerves, pH, and by the vascularity of the injected area.

   b. List the factors that influence the sensitivity of different classes of nerve fibers to local anesthetics. Explain how this relates to the order in which function is lost upon application of local anesthetic to a peripheral nerve.

   c. List the significant differences between amide and ester-type local anesthetics.
d. List the common adverse effects of local anesthetics and indicate appropriate treatments should they occur.

e. Describe the common routes of administration of local anesthetics. List anesthetics that cannot be used topically, that cannot be used for infiltration. Explain why these routes are not effective.

f. Describe methods used to restrict local anesthetics to a desired site of action and indicate how these methods reduce adverse effects.

g. Discuss epidural and intrathecal administration of selected opioids and local anesthetics

**Drugs to Consider:**
- BENZOCAINE
- BUPIVACAINE
- cocaïne
- LIDOCAINE
- prilocaine
- PROCAINE
- ROPIVACAINE
- tetracaine

4. **Opioid Analgesics, Agonist-antagonists, and Antitussives (3.0)**

   a. Opioid Analgesics and Antagonists(2.0)

      1) Present the clinical indications for the opioids and opioid antagonists and explain the basis for their use.
      2) Describe the pharmacologic responses associated with the stimulation of the Mu-, Kappa-, and Delta-opioid receptor subtypes. Correlate with the pharmacological characteristics of the various endogenous opioid agonists (endorphins, dynorphins, enkephalins, endomorphins).
      3) Describe the distribution of opioid receptors in relation to the types of pain and—pain perception, and how morphine interferes with these processes.
      4) List and explain the advantages and disadvantages of using mixed opioid agonists/antagonists.
      5) Describe the pharmacological effects and sites of action of the prototype opioid agonist, morphine, and its utility in relieving different types of pain. In the description of morphine’s pharmacology include its actions and major adverse actions on the following systems: CNS, Cardiovascular, G.I.-biliary, respiratory, genitourinary.
6) Describe the pharmacokinetic processes affecting morphine, absorption, distribution, metabolism, excretion and how these are relevant to its therapeutic use. Describe the distribution of opioids in the body, including their ability to cross the blood-brain barrier and the placenta.

7) Discuss the salient differences in pharmacology between morphine and each of the following full agonists: meperidine, fentanyl, methadone. List other opioid agonists that are metabolized to morphine and indicate the salient differences in their pharmacology from that of morphine.

8) List and explain the major drug interactions of morphine.

9) Contrast the analgesic effects of morphine with those of the nonsteroidal antiinflammatory drugs, with those of antidepressants, and with those of carbamazepine. Discuss the rationale for using mixtures of opioid analgesics and NSAIDS.

10) Explain how agonist-antagonists and partial agonists differ in their utility and adverse effect profile when compared to morphine. Contrast the pharmacology of pentazocine with morphine. Describe why TALWIN-NX is useful in reducing the abuse of pentazocine.

11) List the contraindications for morphine and its surrogates.

12) Describe the characteristics of opioid tolerance and dependence. Describe the opioid abstinence syndrome and how it differs from that for sedative-hypnotics.

13) Discuss abuse liability for opioids and how it differs among the various drugs.

14) Describe the symptoms of morphine and heroin overdose and how they are managed.

15) Discuss the salient differences between naloxone and naltrexone and how these are reflected in clinical use of these drugs.

16) Define precipitated abstinence and indicate under what circumstances it might occur following the clinical use of opioid analgesics or antagonists.

17) Explain the rationale for using methadone to treat heroin abusers. List the aspects of methadone’s pharmacokinetics and pharmacodynamics that make it useful for this purpose.

**Drugs to Consider:**

a) **Agonists**
   - codeine
   - diphenoxylate
   - fentanyl
   - heroin
   - hydrocodone
l-alpha-acetyl-methadol
levomethadyl acetate
loperamide
MEPERIDINE
METHADONE
MORPHINE
OXYCODONE
d-propoxyphene
combinations - opioids plus acetaminophen and ASA
TRAMADOL

b) Agonist/Antagonists and Antagonists
BUPRENORPHINE
butorphanol
nalbuphine
nalorphine
NALOXONE
NALTREXONE
nalmefene
pentazocine

b. Antitussives, Expectorants and Mucolytics (0.5)

Describe the cough reflex and the sites of action of antitussive drugs, expectorants and mucolytic agents.

Discuss the mechanism of action of antitussive drugs.

**Drugs to Consider:**
CODEINE
DEXTROMETHORPHAN
HYDROCODONE

5. **Drugs Used in the Treatment of Motor Disorders (1)**

a. Describe the major anatomical pathways and neurotransmitter systems involved in control of motor function.

b. Understand how the “Balance Hypothesis of Stratal Function” predicts management and side effects of all extra-pyramidal movement disorders.

c. Discuss current hypotheses about the etiology and pathophysiology of Parkinson's disease.

d. Describe the rationale for the use of levodopa in Parkinson's disease and the rationale for its use in combination with
peripheral L-amino acid decarboxylase inhibitor. Discuss how the drug combination alters levodopa's therapeutic and adverse effect profiles.

e. Differentiate the two major classes of direct DA receptor agonists, and indicate how they are used therapeutically and any significant differences in their adverse effects.

f. Discuss the use of other classes of drugs in treating Parkinson's disease: anticholinergics, MAO inhibitors, COMT inhibitors, amantadine.

g. Discuss drugs that can induce Parkinson's disease and specific treatments.

h. Describe Huntington's Chorea and discuss drugs available for its treatment and their effectiveness.

i. Discuss the pathophysiological basis of spasticity and muscle spasm.

j. List drugs useful for treatment of spasticity and compare and contrast the mechanisms of action and adverse effects of benzodiazepines, baclofen and dantrolene when used for this purpose.

k. Describe how the therapeutic utility of cyclobenzaprine for treatment of muscle spasm differs from that of baclofen and benzodiazepines.

**Drugs to Consider:**

AMANTADINE
BACLOFEN
BENZODIAZEPINES
BENZTROPINE
BROMOCRIPTINE
CARBIDOPA
cyclobenzaprine
dantrolene
DOPAMINE
ENTACAPONE
haloperidol
L-DOPA
pergolide
PRAMIPREXOLE
ropinerole
SELEGILINE (deprenyl)  
trihexyphenidyl

6. **Antiepileptics (1 hr)**

a. Describe the pathophysiology of seizures, and the types and incidence of epilepsy.

b. Discuss each of the following with respect to their possible relevance to the initiation and spread of seizure activity: mirror foci, kindling, post-tetanic potentiation, long-term potentiation, paroxysmal depolarizing shift.

c. List the major classes of antiepileptic drugs, the seizure types against which they are effective, their cellular mechanisms of action, and how these actions might be relevant to their roles as antiepileptic agents.

d. Describe the pharmacokinetic factors relevant to appropriate therapy with antiepileptic drugs. Explain why the clearance of phenytoin changes with dose. Discuss the rationale for the common practice of monitoring plasma concentrations of many antiepileptic drugs.

e. List the antiepileptic medications that induce of hepatic enzymes and describe the consequences for treatment of epilepsy and for interactions with drugs used for other conditions.

f. List and describe the adverse and teratogenic effects of the major antiepileptic drugs.

g. Define status epilepticus and explain how it is managed pharmacologically.

h. Discuss the therapeutic use of antiepileptic drugs for conditions other than epilepsy, including their use as analgesics and as mood stabilizers.

**Drugs to Consider:**
acetazolamide  
CARBAMAZEPINE  
clonazepam  
DIAZEPAM  
ETHOSUXIMIDE  
felbamate  
GABAPENTIN
7. **Drugs Used In Affective Disorders (1 hr)**

   a. Describe the concept of affect, the current neurochemical theories regarding affect and how it can be altered by drugs.

   b. Define depression and list its symptoms, signs and causes. Define bipolar disorder and its subtypes, and describe its signs and symptoms and its natural history. Describe manic disorder.

   c. List the major classes of antidepressant drugs and their primary cellular targets. (Tricyclic ADs, SSRIs, SNRIs, atypical antidepressants, and MAO inhibitors)

   d. Explain and contrast the time course for the neurochemical mechanisms and therapeutic action of the different classes of antidepressant drugs. Discuss the importance of active metabolite formation.

   e. Describe and compare the most common adverse effects of the major classes of antidepressants, and where known, explain the mechanism for these effects. Identify significant drug and dietary interactions.

   f. Describe the signs and symptoms of overdose with each of the major classes of antidepressants and the appropriate treatment tricyclic antidepressant toxicity, serotonin syndrome, tyramine effect).

   g. Discuss the utility of the various classes of antidepressants for other indications: Obsessive compulsive disorder, neuropathic pain, smoking cessation, enuresis.

   h. Discuss the use of herbal antidepressants, such as St. John’s wort.
i. List drugs useful for treating mania and describe the major
theories explaining their presumed mechanisms of action
(lithium, antiepileptics, antipsychotics). Describe the effects of
lithium on CNS neurotransmitter systems. Distinguish between
acute control of a manic episode and prevention of cycling.

j. Discuss the pharmacokinetics of lithium and its relationship to the
following: alteration in dietary sodium, effects of exercise, use of
diuretics, monitoring of plasma lithium levels, and treatment of
lithium overdose.

k. Differentiate adverse side effects of lithium from signs and
symptoms of lithium overdose. Explain why there is a
contraindication to the use of lithium in patients with impaired
renal function or cardiovascular disease.

l. Discuss the use of antiepileptic drugs for treatment of bipolar
disorder, their efficacies and toxicities relative to that of lithium.

Drugs to Consider:

1) Antidepressants
   AMITRIPTYLLINE
   BUPROPION
   citalopram
   clomipramine
   desipramine
   FLUOXETINE
   fluvoxamine
   IMIPRAMINE
   NORTRIPTYLLINE
   PAROXETINE
   phenelzine
   SERTRALINE
   TRAZODONE
   TRANYLCPROMINE
   VENLAFAXINE

2) Antimanic drugs
   CARBAMAZEPINE
   LITHIUM CARBONATE
   VALPROIC ACID

8. **Antipsychotics (neuroleptics) (2 hrs)**

   a. Describe schizophrenia and discuss the theories regarding the
      underlying neurochemical basis.
b. Discuss the current theories regarding the therapeutic mechanism of action of antipsychotic drugs. Include in this discussion acute and chronic effects of these drugs on major dopaminergic systems in the CNS. Distinguish the properties, relative efficacies and side effects of the major classes of classical (or typical antipsychotic drugs, the low potency and the high potency.

c. Describe the time course and symptoms of antipsychotic drug-induced acute dystonia, akathesia, Parkinson’s syndrome, tardive dyskinesia, and neuroleptic malignant syndrome. Discuss the management of these conditions. Where known, discuss the receptors/pathways mediating the drug effects.

d. Explain how atypical antipsychotics differ from classical antipsychotics in their cellular actions, efficacies and side-effect profiles. Contrast the mechanisms of action of phenothiazines and haloperidol with clozapine, risperidone, and olanzapine. Describe the implications for the theories of the mechanism of antipsychotic action.

e. Discuss the hypersensitivity reactions to antipsychotic drugs including those affecting liver, blood and skin.

f. List nonpsychiatric uses of phenothiazines and butyrophenones.

g. Discuss the use of dopamine antagonists in Tourette’s Syndrome.

Drugs to Consider:
CHLORPROMAZINE (CPZ)
CLOZAPINE
FLUPHENAZINE
HALOPERIDOL
OLANZAPINE
quetiapine
RISPERIDONE
sertindole
thioridazine
thiothixene
ziprasidone

9. **Sedative-Hypnotics, Anxiolytics, and Centrally Acting Muscle Relaxants (3 hr)**

a. Sedative-Hypnotics
1) Briefly describe the concepts of sedation, hypnosis, anesthesia, and coma. List and describe the stages of sleep.

2) Briefly discuss benzodiazepine action, and the action of non-benzodiazepines acting at the benzodiazepine site, as they pertain to the induction of sleep; explain the mechanism of action; and describe the primary side effects (an expanded discussion of benzodiazepine is included in the section on antianxiety agents).

b. Barbiturates

1) Discuss the relationship between the chemical structure of barbiturates and their pharmacokinetics (absorption, distribution, biotransformation, elimination).

2) Describe the actions of the barbiturates on the CNS, (including tolerance), respiration, cardiovascular system, kidney, and liver.

3) Discuss the consequences of barbiturate and benzodiazepine induction of enzymes, specifically on aminolevulinic acid synthetase (porphyria) and on vitamin D metabolism (osteomalacia). Explain the significance of redistribution vs. metabolism on duration of action.

4) List the therapeutic uses of barbiturates, and indicate a prototype for each use; discuss adverse reactions.

5) Describe the interactions of barbiturates with other CNS agents and their effects on the metabolism of other drugs. Indicate the effects of combining barbiturates with alcohol and other CNS depressants on CNS function.

6) Describe the effects of ionization and lipid solubility on tissue distribution and duration of action of barbiturates. Describe the effects of altering urinary pH on the rate of barbiturate elimination.


8) Discuss tolerance development and physical dependence to barbiturates. Describe the symptoms of barbiturate withdrawal and treatment in a barbiturate dependent subject.

c. Non-barbiturate, non benzodiazepine sedatives and hypnotics

1) Discuss the use of non-barbiturate, non-benzodiazepine sedative/hypnotics (chloral hydrate, hydroxyzine) and compare therapeutic application and side effects to benzodiazepines and barbiturates.

Drugs to Consider:
alprazolam
chloral hydrate
diphenhydramine
FLUMAZENIL
FLURAZEPAM
hydroxyzine
lorazepam
oxazepam
phenobarbital
TEMAZEPAM
TRIAZOLAM
zaleplon
ZOLPIDEM

d. Drugs use in the treatment of anxiety disorders

1) Present the general pharmacology of benzodiazepines and buspirone (other categories of agents, i.e. antidepressants are referenced but their complete pharmacology is presented in another sections).

2) Define anxiety, its relationship to the amygdala, and differentiate the major anxiety disorders.

3) Discuss drugs other than the benzodiazepines and buspirone that are used for treating various anxiety disorders: generalized anxiety, panic disorder, obsessive compulsive disorder, specific phobias

4) Discuss the relationship between benzodiazepines and the GABA<sub>A</sub> receptor. Describe how benzodiazepine action differs from that of drugs acting at the GABA recognition site. Define inverse agonism at the benzodiazepine receptor.

5) List the therapeutic uses of benzodiazepines, and how the pharmacokinetics of the various benzodiazepines is related to their particular therapeutic uses (short, intermediate, and long-acting active metabolites).

6) Compare the dependence liability, toxicity, side effects, and therapeutic actions of benzodiazepines the barbiturates and hypnotics.

7) Describe the effects of benzodiazepines on sleep architecture and anterograde amnesia.

8) Describe the interactions of the benzodiazepines with other CNS depressants.

9) Describe the mechanism of action of flumazenil and its uses.

10) Describe the pharmacology of buspirone and compare it to the pharmacology of diazepam.

e. Centrally-acting skeletal muscle relaxants
1) Discuss the pathophysiological basis of rigidity, spasticity, muscle spasm (if not previously discussed under motor dysfunction) and the assorted agents that are used to promote skeletal muscle relaxation.

**Drugs to Consider:**
ALPRAZOLAM
chlorazepate
chusldiazepoxide
DIAZEPAM
FLUMAZENIL (antagonist)
LORAZEPAM
OXAZEPAM

2) Non-benzodiazepine
BUSPIRONE

**10. Substance Abuse (4.5)**

a. Drug dependence (.5)

1) Define and describe physical dependence and tolerance on drugs. Discuss drug craving and positive conditioning as an issue in maintaining substance dependence.
2) Discuss the economic - social issues of drug dependence.
3) Describe the personality characteristics of an individual susceptible to substance abuse. Discuss the role of the nucleus accumbens in reward gratification and dependence liability.
4) Describe the clinical characteristics of drug dependence, and understand the concept of ‘gateway” drugs.
5) Describe the withdrawal and detoxification techniques for different drugs of abuse.
6) Review the mortality and morbidity of dependence to various drugs.
7) Compare dependence on and associated abstinence signs of opioids, CNS depressants, stimulants and other drugs subject to abuse

b. Psychostimulants (cocaine, amphetamine, methylphenidate) and anorexigenic agents

1) Discuss the major groups of psychostimulant drugs, and discuss current theories of their mechanisms of action.
2) Discuss the therapeutic uses of central and psychostimulants as appetite suppressants, in attention deficit hyperactivity disorder, and in narcolepsy.
3) Discuss the current theories of substance dependence on stimulant drugs and the influence of pharmacokinetics on dependence liability.
4) Describe the adverse effects of stimulants on the CNS and on other organ systems.
5) Discuss the role of adenosine receptor antagonism in the action of caffeine.
6) Discuss the effects of caffeine’s actions as a phosphodiesterase inhibitor on its CNS and peripheral nervous system effects.
7) Describe the major differences in mechanisms between the psychostimulants and anorexigenic agents.

Drugs to Consider:
AMPHETAMINE
CAFFEINE
COCAINE
ephedrine
METHAMPHETAMINE
METHYLPHENIDATE
phentermine
sibutramine

c. Ethanol - alcoholism (1 hr).

1) Summarize the therapeutic applications of ethanol.
2) Describe the acute CNS actions of ethanol and discuss their relationship to blood alcohol levels.
3) Discuss current theories about the mechanism of action of alcohol in the CNS.
4) Describe the pharmacokinetics of ethanol, its absorption, distribution, metabolism and excretion.
5) Describe the acute and chronic organ toxicities of ethanol.
6) List drugs with which ethanol shows cross-tolerance and cross-dependence.
7) List drugs, both prescription and over the counter, that would entail a patient refraining from the use of alcoholic beverages. Explain the nature of the potential interactions.
8) List the signs and symptoms of the ethanol abstinence syndrome. Compare and contrast these with abstinence syndromes following barbiturates, benzodiazepines, and opioids.
9) Discuss the treatment options for acute ethanol intoxication, and for the ethanol abstinence syndrome.
10) Discuss the use of disulfiram and naltrexone in the treatment of chronic alcoholics. Describe their effects and the mechanistic rationale for their use.
11) Summarize the therapeutic applications of ethanol.
12) Discuss the mechanism for the synergism between chloral hydrate and ethanol.
13) Discuss the management of methanol toxicity.

**Drugs to Consider:**
DISULFIRAM
ETHANOL
METHANOL
naltrexone

**d. Hallucinogens and Designer Drugs (0.3)**

1) List the major classes of hallucinogens and describe their mechanisms of action.
2) Describe salient differences among the behavioral and hallucinogenic effects of the various drugs and compare and contrast drug-induced states with endogenous psychoses. Describe the cognitive, somatic, and sensory effects of the hallucinogens.
3) What are the three chemical classes of hallucinogens?
4) Discuss the variability in inter-individual responses to hallucinogens and the interaction between the social setting in which hallucinogens are taken and their behavioral effects.
5) Discuss tolerance to and cross-tolerance among the various hallucinogens.
6) Describe how the pharmacokinetics of different drugs may influence their duration of action and their detection by screening tests for illicit drug use.
7) Describe general principles of treatment for anxious/agitated patients with known ingestion of hallucinogens
8) Describe how the effects of the anticholinergics differ from those of the hallucinogens.
9) What are the common side effects of the anticholinergics?
10) Know what a designer drug is and how it differs from a hallucinogen
11) Discuss the differences and similarities among anticholinergic, hallucinogen, and designer drug overdose.
12) Discuss the social use and abuse of hallucinogens.
13) Discuss legislative control of designer drugs.
14) What are the effects of ketamine and PCP on the NMDA receptor/sigma receptor

**Drugs to Consider:**
- atropine, scopolamine
- KETAMINE
- LYSERGIC ACID DIETHYLAMIDE (LSD)
- MDMA (methylene dioxy-methyl amphetamine)
- MESCALINE
- PHENCYCLIDINE (PCP)

**e. Marijuana**

1) Discuss cannabinoid receptors and their proposed effects in brain
2) Understand the role of genetic source and growing environment in THC content
3) Understand the difference in THC content among marijuana, hashish, and 2nd hash oil
4) What are the proposed health benefits of marijuana? What are THC’s health consequences?

**Drugs to Consider:**
- donabinol
- MARIJUANA/THC

**f. Organic solvents, inhalants (gasoline, glue, fire extinguisher accelerants, nitrous oxide, toluene, carbon tetrachloride, fluoro carbons)**

1) Describe the relationship between abuse of these drugs, hypoxic effects, and the ability to uncouple oxidative phosphorylation of these drugs.
2) Describe the toxicities of these agents according to their particular type.

**g. Discuss opioids, sedative-hypnotics, and antianxiety agents with respect to their substance abuse aspects.**

**Drugs to Consider:**
- HEROIN/other opioids
- MARIJUANA/THC
- Organic solvents
- NICOTINE
- pentobarbital
h. Drugs and the law (0.5 hr).

1) Define the characteristics of drugs in each of the Drug Enforcement Administration classification of controlled substances into Schedules I, II, III, and IV, and give examples of some specific drugs that are included in each schedule. Discuss the ways in which this classification affects the clinical use of drugs.

11. Treatment of Alzheimer’s Disease

a. Discuss the drugs used for the treatment of Alzheimer's disease, their presumed mechanisms of action, their efficacy and their adverse effects.

Drugs to Consider:  
DONEPEZIL  
GALANTAMINE  
RIVASTIGMINE  
tacrine
AUTACOIDS/NONSTERoidal ANTIINFLAMMATORY/ASTHMATIC DRUGS

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1. **Histamine (0.5 hr)**
   - a. Distribution and synthesis
   - b. Storage and release (immunologic and nonspecific)
   - c. Metabolism and elimination
   - d. Receptors (H₁, H₂ and H₃)
   - e. Pharmacologic actions: smooth muscles, exocrine glands, cardiovascular, and sensory nerve endings

**Drugs to Consider:**
- betazole
- HISTAMINE

2. **Antihistaminic Drugs (1 hr)**
   - a. Mechanisms of action: on receptor subtypes (H₁, H₂ and H₃)
   - b. Pharmacological properties and side effects (desirable/adverse)
   - c. Therapeutic uses

**Drugs to Consider:**
- H₁-antagonists:
  - brompheniramine
- CHLORPHENIRAMINE
- DIPHENHYDRAMINE
- FEXOFENADINE
- hydroxyzine
- loratadine
- promethazine
H$_2$-antagonists:
CIMETIDINE
FAMOTIDINE
nizatidine
RANITIDINE

Antidegranulating drugs:
CROMOLYN SODIUM
nedocromil sodium

3. **Anti-motion Sickness Drugs (0.5 hr)**
   a. Understand the mechanisms of motion sickness and the differences in mechanism and action between the phenothiazine neuroleptics and those drugs that affect the vestibular pathway.

   **Drugs to Consider:**
   DIMENHYDRINATE
   promethazine
   scopolamine

4. **Serotonin (5-HT) and Pharmacology of Migraine (0.5 hr)**
   a. Distribution and synthesis
   b. Storage and release
   c. Metabolism, elimination
   d. Receptors
   e. Pharmacological actions (cardiovascular, cerebral vasculature, gastrointestinal, sensory neurons)
   f. Treatment of migraine (drugs for prophylactic and abortive therapies, relative efficacies, their pharmacokinetics and adverse effects, and primary cellular sites of action)
   g. Treatment of chemotherapy-induced emesis

   **Drugs to Consider:**
   antiemetics (metoclopramide, ONDANSETRON)
   ß-adrenergic antagonists (atenolol, propranolol)
   caffeine
   calcium channel blockers (amlodipine, verapamil)
   cyproheptadine
ergot derivatives (ERGOTAMINE, dihydroergotamine)
METHYLSERGIDE
NSAIDs and analgesics (aspirin, acetaminophen, ibuprofen, indomethacin, naproxen)
phenelzine
tricyclic antidepressants (amitriptyline, nortriptyline)
triptans (SUMATRIPTAN, zolmitriptan)

5. **Nitric Oxide, Donors and Inhibitors (0.5 hr)**
   
   a. EDRF
   
   b. Synthesis (nNOS, eNOS, iNOS); constitutive vs inducible
   
   c. Pharmacological actions (cGMP; vasculature; erectile dysfunction etc)

   **Drugs to Consider:**
   - nitrates
   - nitrites
   - SILDENAFIL
   - sodium nitroprusside

6. **Eicosanoids (0.5 hr)**
   
   a. Synthesis of prostaglandins, thromboxanes, and leukotrienes from arachidonic acid. Know which are the key enzymes in the overall pathway and what drugs affect each enzyme.
   
   b. Pharmacological actions of PGE$_2$, PGF$_2$, PGI$_2$ (PROSTACYCLIN), TXA$_2$, and the leukotrienes (LTA$_4$ thru LTE$_4$): vascular, airway, uterine, and GI smooth muscle; microvascular permeability; platelet function; sensory nerve endings; gastric and intestinal secretions; temperature regulation center.
   
   c. Termination of action.

   **Drugs to Consider:**
   - alprostadil
   - dinoprostone
   - epoprostenol
   - misoprostol
   - montelukast
   - ZAFIRLUKAST
   - ZILEUTON
7. **Treatment of Asthma (1.0 hr)**

a. Know the disease process of asthma involving airway inflammation, bronchial smooth muscle constriction and mast cell degranulation

b. Mediators (histamine, acetylcholine, proteases, leukotrienes C₄, D₄; prostaglandins; cytokines)

c. Describe the mechanisms of action, adverse effects of each anti-asthmatic drug

d. Know the routes and limitations of drug administration, systemic and inhalant

e. Describe the types of therapy available: short term relief and long-term control

**Drugs to Consider:**
- β-adrenergic agonists (non-selective, epinephrine; selective short-acting, ALBUTEROL, bitolterol, METAPROTERENOL; selective long-acting, SALMETEROL)
- anticholinergics (IPRATROPIUM bromide)
- antidegranulating agents (CROMOLYN SODIUM, nedocromil sodium)
- glucocorticoids (BECLOMETHASONE, budesonide, flunisolide, FLUTICASONE)
- leukotriene inhibitors (montelukast, ZAFIRLUKAST, ZILEUTON)
- methylxanthines (THEOPHYLLINE, aminophylline)

8. **Hypersensitivity and Immunopharmacology (0.5 hr)**

a. Role of immunoglobulins (IgE, IgG, IgM) in drug allergy

b. Differentiate different types of allergic reactions (Type I-IV) and factors (e.g. cytokines, MHC) involved

c. Learn the release of allergic mediators, and process leading to hypersensitivity

d. Understand the site of action of selected immunosuppressive agents on the immune response.

**Drugs to Consider:**
- CYCLOSPORINE
- mycophenolate mofetil
- PREDNISONE
9. **Bradykinin (0.5 hr)**

a. Synthesis and metabolism of kinins: know what pathophysiological factors trigger kinin formation and how bradykinin can influence the eicosanoid and EDRF pathways.

b. Pharmacological actions: compare and contrast with actions of histamine and eicosanoids.

**Drugs to Consider:**
aprotinin
BRADYKININ

10. **Analgesic, Antipyretic, Antiinflammatory Drugs (2.0 hr)**

a. Antipyretic-analgesic drugs

1) Understand the physiological basis of body temperature control and peripheral sensory pain fibers.

2) Understand the role of eicosanoids and bradykinin in causing local pain, edema and fever.

3) Opiate analgesics (morphine, etc.) are covered under CNS drugs.

4) Understand the difference in mechanisms of action between acetaminophen and aspirin.

5) Compare the pharmacological properties of acetaminophen and aspirin.

6) Understand the metabolism of acetaminophen, the role of cytochrome P450, and the mechanism of acetaminophen toxicity, as well as its reversal by N-acetylcysteine.

7) Understand the adverse effects of aspirin, as well as the acute toxic effects of aspirin overdose.

8) Understand the factors that affect the absorption and elimination of aspirin.

9) Understand the hepatic metabolism of aspirin.

10) Understand the potentially detrimental consequences of plasma protein binding, zero-order metabolism, and irreversible cyclooxygenase inhibition shown by aspirin.

11) Understand the adverse drug interactions possible with aspirin (coumadin anticoagulants, oral hypoglycemic drugs, alcohol, others).

12) Understand the principles of treatment of salicylate intoxication.
Drugs to Consider:
ACETAMINOPHEN
ASPIRIN and related salicylates
NSAIDs other than aspirin

b. Antiinflammatory drugs (NSAIDs and glucocorticoids)

1) Understand the pathophysiology of acute and chronic inflammation.
2) Understand the adverse effects and potential adverse drug interactions associated with inhibition of the COX1 pathway.
Understand the significance of COX2.
3) Glucocorticoids are covered under steroid hormones

Drugs to Consider:
ASPIRIN and salicylates
CELECOXIB
DICLOFENAC SODIUM
fenoprofen
IBUPROFEN
INDOMETHACIN
KETOROLAC
KETOPROFEN
meclofenamate
NABUMETONE
NAPROXEN
OXAPROZIN
piroxicam
ROFECOXIB
sulindac
tolmetin

c. Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

1) Understand that these drugs have no analgesic or antipyretic activity; their mechanisms of action are largely unknown.
2) Understand that their onset of action is very long and the drugs are very toxic.
3) Understand the role of TNF in chronic inflammation.

Drugs to Consider:
azathioprine
chloroquine and HYDROXYCHLOROQUINE
ETANERCEPT
gold salts (auranofin, aurothioglucose)
INFLIXIMAB
methotrexate
d-penicillamine
d. Drugs used to treat gout

1) Understand the causes and pathophysiology of acute gouty arthritis and chronic tophaceous gout.
2) Compare and contrast the mechanisms of action of colchicine, allopurinol, probenecid, and sulfinpyrazone.
3) Understand the dangerous side effects of colchicine.
4) Understand the cause and treatment of acute gouty flare-ups associated with the use of allopurinol or probenecid in treating chronic tophaceous gout.
5) Understand that NSAIDs except aspirin may be used as substitutes for colchicine. Why is aspirin contraindicated?
6) Understand the potential adverse drug interactions with allopurinol (i.e. 6-mercaptopurine).

Drugs to Consider:
ALLOPURINOL
COLCHICINE
NSAIDs (except aspirin)
PROBENECID
SULFINPYRAZONE

11. Pharmacology of Migraine (0.5)

a. Discuss the classes of drugs used to treat patients with migraine headache, their primary cellular sites of action, and their relative efficacies as prophylactic vs abortive therapy.

b. Discuss pharmacokinetic aspects of abortive therapy for migraine.

c. List the major adverse effects of ergot alkaloids used the treatment of migraine, and sumatriptan and related drugs.

Drugs to Consider:
butorphanol
CAFFEINE
calcium channel blockers
CLONIDINE
ERGOTAMINE
METHYSERGIDE
PROPRANOLOL
### Drugs to Consider:

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1. **Review of Cardiovascular Physiology (2)**

Review properties of the heart including contractility (e.g., excitation-contraction coupling) and electrical activity (e.g., the action potential, automaticity, excitability, refractory period, conduction and the relationship to the electrocardiogram).

Review neuroendocrine properties of the heart (both response and output).

Discuss mechanisms of growth, hypertrophy and signal transduction.

Review the intrinsic and extrinsic regulation of the cardiovascular system.

Describe cardiac and vascular smooth muscle cellular pathobiology including mechanisms of apoptosis and responses to hypoxia, reperfusion, ischemia and mechanical and oxidative stress.
2. Cardiac Drugs

a. Anti-Arrhythmic Agents (3)

1) Drugs and Drug Classes to Consider:
   - Adenosine
   - Amiodarone
   - Atropine
   - \(\beta\)-Adrenergic Antagonists (e.g. Metoprolol; Sotalol)
   - Calcium Channel Blockers (e.g. Diltiazem)
   - Digoxin
   - Disopyramide
   - Dofetilide
   - Flecainide
   - Lidocaine
   - Mexiletine
   - Moricizine
   - Procainamide
   - Propafenone
   - Quinidine
   - Tocainide

2) Principles and knowledge objectives:
   a) Mechanism of action
      - Describe the pathophysiologic mechanisms of cardiac arrhythmias (abnormal automaticity, triggered rhythms, reentrant rhythms and abnormal impulse conduction).

      Classify antiarrhythmic drugs according to classes I, II, III and IV including other miscellaneous agents, though recognizing the limitations of this classification system.

      Describe the slow (calcium-dependent) and fast (sodium-dependent) responses, their relevance to sinoatrial, atrial, AV-nodal and ventricular tissues, and their alteration by antiarrhythmic drugs.

      Describe the electrophysiologic actions of antiarrhythmic drugs in normal and abnormal myocardial and conduction tissue, and their effect on the phases of the cardiac action potential.

      Describe the indirect autonomic actions of these drugs.

      Describe the effect of age on fast and slow channels and on the agents affecting these channels.
Discuss the pharmacogenomics of long QT syndrome and the relationship of genetics to drug selection.

Know the two forms of this disorder (i.e. drug-induced [or acquired LQT] and congenital) and which ion channels are responsible for each.

Know the classes of drugs that can produce acquired LQTS and that the therapeutic management of congenital LQTS depends on the genotype, despite a uniform phenotype.

b) Actions on organ systems
Describe the relevant extracardiac actions of antiarrhythmic drugs with special reference to amiodarone.

c) Pharmacokinetics
Describe the routes of administration, biotransformation and excretion of selected antiarrhythmic drugs.

Describe the pharmacokinetics and time-course of the cardiac actions of antiarrhythmic drugs (onset and duration of action).

Discuss the impact of reduced cardiac output due to myocardial infarction on drug half-life and pharmacodynamics.

Describe the influence of age on pharmacokinetic parameters, i.e., liver metabolism (lidocaine, procainamide, and propranolol) and elimination through kidney (digoxin and sotalol).

d) Therapeutic indications
Describe the use of antiarrhythmic drugs in supraventricular arrhythmias (atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia, junctional arrhythmias).

Describe the use of antiarrhythmic drugs in ventricular arrhythmias (ventricular premature beats, ventricular tachycardia, ventricular fibrillation).

Discuss the utility of antiarrhythmic drugs in combination with electrical cardioversion or implantable converters-defibrillators.

e) Adverse effects, drug interactions and contraindications
Describe the cardiac and extracardiac manifestations of toxicity from antiarrhythmic drugs.

Describe the beneficial and adverse interactions among antiarrhythmic drugs and between antiarrhythmic drugs and cardiac glycosides.

Describe the significance of electrolyte and acid-base imbalance in arrhythmia generation and their influence on antiarrhythmic drug action.

Describe the possible contraindications of antiarrhythmic drugs in the presence of heart block or congestive heart failure, and the precautions and contraindications in other conditions.

b. Management of Acute and Chronic Heart Failure (2)

1) Introduction to cardiac inotropism
   Describe the acute inotropic, dromotropic and chronotropic effects of catecholamines (e.g. epinephrine, norepinephrine, dopamine, isoproterenol).
   Compare and contrast the management of acute and chronic heart failure.

2) Drugs and Drug Classes to Consider:
   ACE INHIBITORS (e.g. ENALAPRIL)
   ANGIOTENSIN RECEPTOR ANTAGONISTS (e.g. LOSARTAN)
   Amrinone
   β-ADRENOCEPTOR ANTAGONISTS (e.g. CARVEDILOL; METOPROLOL)
   β-ADRENOCEPTOR AGONISTS (e.g. DOBUTAMINE)
   CARDIAC GLYCOSIDES (e.g. DIGOXIN)
   DIURETICS (e.g. furosemide)
   PHOSPHODIESTERASE INHIBITORS (e.g. MILRINONE)
   NESIRITIDE
   VASODILATORS (e.g. HYDRAZINE)

3) Principles and knowledge objectives.
   a) Mechanism of action
      Describe the basic pathophysiology of heart failure and the cardiac and extracardiac compensatory mechanisms that are activated.
      Describe the effects of cardiac glycosides on myocardial contractility.
Explain the ionic basis for the mechanism of action of the cardiac glycosides – Na\(^+\), K\(^+\)-ATPase inhibition; Na\(^+\)/Ca\(^{2+}\) exchanger.

Describe the electrophysiologic effects of cardiac glycosides on atrial and ventricular muscle and specialized conducting tissue.

Explain the significance of direct and indirect (autonomic) actions of the cardiac glycosides.

Describe the positive inotropic effects of the β-adrenoceptor-agonists and phosphodiesterase inhibitors.

Explain the effects of β-adrenoceptor antagonists and ACE-inhibitors on cardiac function and ventricular remodeling in the setting of heart failure.

b) Actions on organ systems
Describe the hemodynamic actions of cardiac glycosides in the failing heart.

Describe the extracardiac actions of cardiac glycosides.

Explain the effects of the vasodilators on pre-and afterload.

Describe the extracardiac actions of the β-adrenoceptor agonists, β-adrenoceptor antagonists, phosphodiesterase inhibitors and ACE-inhibitors.

c) Pharmacokinetics
Describe the routes of administration, the extent of oral absorption and bioavailability, the routes of elimination and extent of biotransformation of the cardiac glycosides and other drugs used in heart failure.

Relate these to physicochemical properties of cardiac glycosides.

Contrast the pharmacokinetics of cardiac glycosides in young and old patients.

Describe the time-course of the cardiac actions of cardiac glycosides (onset and duration of action) with reference to differences between digoxin and digitoxin.
Explain the concept of digitalization (loading dose) and maintenance therapy.

Review the "plateau principle" with regard to maintenance therapy without a loading dose.

d) Therapeutic indications
Describe the use of cardiac glycosides in congestive heart failure.

Describe the role of β-adrenoceptor agonists, β-adrenoceptor antagonists, vasodilators, diuretics and ACE-inhibitors in the treatment of acute and chronic heart failure.

e) Adverse effects, drug interactions and contraindications
Describe the cardiac (delayed after depolarizations and arrhythmias) and extracardiac manifestations of digitalis toxicity.

Describe the significance of changes in serum electrolyte levels (potassium, sodium, calcium, magnesium) with regard to digitalis toxicity.

Discuss the potential adverse effects with concomitant use of diuretics in the elderly or in patients with congestive heart failure, hypothyroidism and renal disease.

Describe the interactions of digitalis glycosides and quinidine, verapamil, and other relevant drugs.

Describe the cardiac and extracardiac side effects and limitations of the antagonist agents, vasodilators, phosphodiesterase inhibitors, and ACE-inhibitors.

c. Antihypertensive and Related Drugs (4)

1) Drugs and Drug Classes to consider:
- **α-ADRENOCEPTOR ANTAGONISTS** (e.g. PRAZOSIN)
- **ACE INHIBITORS** (e.g. ENALAPRIL; BENazeprIL CAPTOPRIL; FOSINOPRIL; LISINOprIL; QUINAPRIL)
- **ANGIOTENSIN RECEPTOR ANTAGONISTS** (e.g. LOSARTAN; VALSARTAN; CANDASARTAN)
- **β-ADRENOCEPTOR ANTAGONISTS** (e.g. ATENOLOL; PROPRANOLOL; TIMOLOL; NADOLOL; LABETOLOL)
CALCIUM CHANNEL BLOCKERS (e.g. AMLODIPINE; FELODIPINE; NICARDIPINE; NIFEDIPINE)
CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS (e.g. CLONIDINE),
DIURETICS (e.g. HYDROCHLOROTHIAZIDE; INDAPAMIDE)
VASODILATORS (e.g. NITROPRUSSIDE; HYDRALAZINE;)

2) Principles and knowledge objectives
List the types of hypertension and the relative prevalence of each.

Review the determinants of systemic arterial blood pressure including the role of the autonomic nervous system and the renin-angiotensin system.

Describe the current views for the etiology of essential hypertension.

a) Mechanism of action
Discuss the mechanism of action of each of the several classes of agents used to manage hypertension according the site of action within the pathogenesis of hypertension.

Describe the mechanism by which each antihypertensive drug or drug class exerts its therapeutic function.

b) Actions on organ systems
Review the end organ effects of hypertension and the beneficial effects achieved by therapeutic management of the disease.

Describe the actions of antihypertensive drugs on the heart, renal blood flow and renal function.

Describe the relevant actions of antihypertensive drugs in other organ systems (CNS, other).

c) Pharmacokinetics
Describe the use of antihypertensive drugs in mild, moderate and severe essential hypertension.

Describe the time-course of their antihypertensive activity (onset and duration of action) for each class of agents.

d) Therapeutic indications
Discuss the role of non-pharmacological treatment modalities in the management of hypertension.
Describe the use of antihypertensive drugs in mild, moderate and severe essential hypertension.

Describe the use of antihypertensive drugs in hypertensive emergencies.

Describe the use of antihypertensive drugs in pheochromocytoma.

Discuss subgroups with special antihypertensive drug considerations (e.g. African-Americans, diabetics, isolated systolic hypertension esp. in elderly patients, renal failure patients).

e) Adverse effects, drug interactions and contraindications
Describe the cardiac and extracardiac side effects of antihypertensive drugs.

Describe the beneficial and adverse interactions between antihypertensive drugs and between antihypertensive drugs and other therapeutic agents.

d. AntiAnginal Drugs (1)

1) Drugs and Drug Classes to consider:
   - ANTIPLATELET AGENTS (e.g. clopidogrel)
   - β-ADRENOCEPTOR ANTAGONISTS (e.g. propranolol)
   - CALCIUM CHANNEL BLOCKERS (e.g. nifedipine)
   - VASODILATORS (e.g. nitroglycerin)

2) Principles and knowledge objectives
   a) Mechanisms of action
   Describe the normal regulation of coronary blood flow and the relationship to the events of the cardiac cycle.

   Describe the basic pathophysiology of myocardial ischemia.

   Explain the significance of atherosclerotic coronary artery disease and coronary artery spasm (Prinzmetal's) in the production of myocardial ischemia and angina pectoris.

   Describe the hemodynamic actions of antianginal drugs, including their coronary and peripheral vasodilator actions.
Describe the effects of each antianginal drug or drug class on the determinants of myocardial oxygen consumption (heart rate, myocardial wall tension, etc.) and/or oxygen supply (coronary blood flow).

Describe the effects of the antianginal drugs at the cellular level.

b) Actions on organ systems
Describe the cardiac actions of antianginal drugs (electrophysiologic, coronary vasodilator, inotropic actions).

Describe the actions of antianginal drugs on the peripheral circulation (arterial, venous) and their effects on ventricular preload and afterload.

Pharmacokinetics
Describe the routes of administration, biotransformation and excretion of antianginal drugs.

Describe the significance of a "first-pass effect" for orally administered antianginal drugs.

Describe the time-course of antianginal activity (onset and duration of action).

Describe the problem of dose intervals and tolerance development with the nitrates.

d) Therapeutic indications
Describe the use of antianginal drugs in classic (effort-related) angina pectoris and vasospastic angina pectoris.

Describe the concept of "myocardial preservation" and discuss the use of antianginal drugs in the context of acute myocardial infarction with particular emphasis on β-adrenoceptor antagonists.

e) Adverse effects, drug interactions and contraindications
Describe the cardiac and extra-cardiac side effects of antianginal drugs.

Describe the beneficial and adverse interactions between antianginal drugs and between antianginal drugs and other cardiovascular drugs.

e. Drugs for hyperlipidemias (1)
1) **Drugs and Drug Classes to consider:**
- CHOLESTYRAMINE
- Colestipol
- CLOFIBRATE
- Fenofibrate

**HMG CoA REDUCTASE INHIBITORS** (e.g. ATORVASTATIN; CERIVASTATIN, LOVASTATIN; PRAVASTATIN)
- GEMFIBROZIL
- Nicotinic acid
- Long-acting niacin
- Probucol

2) **Principles and Knowledge Objectives**
   a) **Mechanism of action**
      Discuss cholesterol synthesis, transport, export, excretion, and receptor-mediated cellular uptake.

      Review “normal” values.

      Discuss the relevant hypotheses regarding the etiology of hyperlipidemias (e.g. “cholesterol” or “infectious agent” hypotheses).

      Describe the basic pathophysiology of atherosclerotic vascular disease and its relationship to the hyperlipidemias.

      Describe the types of hyperlipidemias (I, II, III, IV, and V) and the alterations in serum lipids in each type (triglycerides, cholesterol, LDL, HDL, LDL, lipoproteins).

      Discuss the lipid profile characteristic of insulin-resistant diabetics.

      Discuss genetic conditions leading to hyperlipidemia.

      Describe the concept of “plaque stability”.

      Describe the actions of each drug class on serum lipids, and compare and contrast the mechanism of each of these actions.

      Characterize these agents according to their action to reduce lipid synthesis or enhance removal.
Identify the role of antioxidants in the management of hyperlipidemia.

b) Actions on organ systems
Describe the relevant actions of these drugs, other than on lipid metabolism (e.g. pleitrophic effects).

Discuss drug-induced hyperlipidemia (e.g. protease inhibitors).

Discuss the role of the HMG CoA reductase inhibitors in preventing acute coronary events and stroke.

c) Pharmacokinetics
Describe the routes of administration, biotransformation and excretion of drugs for hyperlipidemias.

Compare and contrast the pharmacokinetics of nicotinic acid and fibric acids.

d) Therapeutic indications
Describe the non-pharmacological management of hyperlipidemia (i.e. life style modifications that benefit the patient).

Describe the use of these agents in familial and acquired hyperlipidemias, and their efficacy in atherosclerotic vascular disease.

Discuss important multicenter clinical trial data documenting efficacy in multiple patient groups.

Discuss new NCEP guidelines for lowering LDL.

Discuss the apparent lack of a threshold effect (lower is always better, even in the normal range of LDL).

e) Adverse effects, drug interactions and contraindications
Describe the cardiovascular and other systemic side effects of these drugs with special reference to the muscle and liver toxicities.

Describe the beneficial and adverse interactions between these drugs, and their interactions with cardiac glycosides, oral anticoagulants, and other relevant drugs.

f. Thrombolytic and Hemorrheologic Agents in the Management of Myocardial Infarction / Acute Coronary Syndrome and Chronic Treatment of Cardiovascular Diseases (1)
See Section I Drugs Acting on the Blood and Blood-forming Organs for Thrombolytics, Anticoagulants and Antithrombotic Drugs.

1) **Drugs and Drug Classes to Consider:**
   - **ANTIPLATELET AGENTS** (e.g. CLOPIDOGREL)
   - **HEPARINS** (e.g. ENOXAPARIN)
   - COUMADIN
   - **CORTICOSTEROIDS** (DEXAMETHASONE)
   - **β₂-ADRENOCEPTOR AGONISTS** (e.g. terbutaline)

2) **Principles and Knowledge Objectives**
   a) **Mechanism of action**
      Describe the use of thrombolytic agents as first-line in the therapy of acute post-myocardial infarction and stroke. Discuss the role of acute catheter-mediated intervention as an alternative or complementary strategy.

      Consider the spectrum of agents available for cardioprotection and plaque stabilization in the setting of acute coronary syndrome.

   b) **Action on Organ Systems**
      Discuss the long-term use of antiplatelet agents (e.g. acetylsalicylic acid, PENTOXIPHYLLINE and clopidogrel) in patients with claudication associated with chronic occlusive peripheral arterial disease and stroke.

      Describe the use of thrombolytic agents as first-line agents in the acute therapy of post-myocardial infarction and as adjuncts in the nonpharmacological management of coronary artery disease (e.g. surgical stent implantation).

      Consider the proper use of morphine in the pain of MI, the long-term use of acetylsalicylic acid (antiplatelet activity) as prophylaxis and the use of adrenergic blocking agents for cardiac protection.

   c) **Pharmacokinetics**
   d) **Therapeutic Indications**
   e) **Adverse effects, drug interactions and contraindications**
3. **Management of Asthma and Chronic Obstructive Pulmonary Disease (1)**

a. **Drugs to Consider:**

- **β-ADRENOCEPTOR AGONISTS** (e.g. ALBUTEROL; EPINEPHRINE; SALMETEROL)
- **CROMOLYN**
- **CORTICOSTEROIDS** (e.g. BECLOMETHASONE; FLUTICASONE)
- **IPRATROPIOUM**
- **Nedocromil**
- **LEUKOTRIENE INHIBITORS** (e.g. MONTELUKAST; ZAFIRLUKAST; ZILEUTON)
- **METHYLXANTHINES** (e.g. THEOPHYLLINE)

b. **Principles and knowledge objectives**

Characterize the role of the inflammatory process in the pathogenesis of asthma.

Describe the endogenous chemical mediators and their receptors that function to regulate bronchial smooth muscle tone.

Describe the role of cyclic AMP, leukotrienes and nitric oxide in regulation of bronchiolar smooth muscle and pulmonary vasculature.

Identify the relationship of bronchial smooth muscle reactivity to the pathogenesis of asthma.

1) **Mechanism of action**

Describe the mechanism of action of each of the major classes of agents relative to the component of the pathogenesis that is involved.

2) **Actions on organ systems**

Describe the relevant actions of these drugs on other physiological systems.

3) **Pharmacokinetics**

Identify the factors that influence the plasma levels of theophylline?

Know the appropriate route of administration of the various bronchodilators relative to the physico-chemical characteristics and the pharmacological action of the drug.

4) **Therapeutic indications**

Compare and contrast the management of acute and chronic asthma and obstructive pulmonary disease.
Discuss the developing approaches to the management (e.g. monoclonal antibodies).

5) Adverse effects, drug interactions and contraindications
Discuss the adverse effects and contraindications for each of the six classes of agents.

**List of Cardiovascular Drugs to Consider** *(Classes of Agents are identified in Bold Print)*:

ADENOSINE

**Ace inhibitors:**
BENAZEPRIL*
CAPTOPRIL*
cilazapril
ENALAPRIL*
enalaprilat
FOSINOPRIL*
LISINOPRIL*
moexipril
perindopril
QUINAPRIL*
RAMIPRIL*
trandolapril

**α-Adrenoceptor Blockers:**
CARVEDILOL*
DOXAZOSIN*
Indoramin
LABETALOL*
phenoxybenzamine
phentolamine
PRAZOSIN*
TAMSULOSIN*
TERAZOSIN*
tolazoline

AMIODARONE*
amyl nitrate

**ANGIOTENSIN RECEPTOR ANTAGONISTS:**
candesartan
IRBESARTAN*
LOSARTAN*
telmisartan
VALSARTAN*

ANTIPLATELET AGENTS:
abciximab
aspirin
cilostazol
CLOPIDOGREL*
eptifibatide
ridogrel
ticlopidine
tirofiban

β-ADRENOCEPTOR AGONISTS:
dobutamine
dopamine
epinephrine
isoproterenol

β2-ADRENOCEPTOR AGONISTS:
ALBUTEROL*
bitolterol
fenoterol
formoterol
isoetharine
levalbuterol
metaproterenol
pirbuterol
procaterol
ritodrine
salmeterol
terbutaline

β-ADRENOCEPTOR ANTAGONISTS:
carvedilol
carteolol
labetalol
nadolol
oxprenolol
penbutolol
pindolol
PROPRANOLOL*
sotalol
timolol

β1-ADRENOCEPTOR ANTAGONISTS:
acebutolol
ATENOLOL*
betaxolol
bretylium
bisoprolol
celiprolol
ESMOLOL*
METOPROLOL*

CALCIUM CHANNEL BLOCKERS:
AMLODIPINE*
bepridil
DILTIAZEM*
FELODIPINE*
flunarazine
isradipine
lacidipine
nicardipine
NIFEDIPINE*
nimodipine
nisoldipine
VERAPAMIL*

CARDIAC GLYCOSIDES:
DIGOXIN*
digitoxin

CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS:
apraclonidine
CLONIDINE*
guanfacine
guanabenz
methyldopa

CHOLESTYRAMINE*
clofibrate
colestipol

CORTICOSTEROIDS:
BECLOMETHASONE*
budesonide
DEXAMETHASONE*
flunisolide
FLUTICASONE*
mometasone
TRIAMCINOLONE*
COUMADIN*
CROMOLYN*
dipyridamole
disopyramide

**DIURETICS:**
amiloride
bumetanide
chlorothiazide
chlorothalidone
FUROSEMIDE*
HYDROCHLOROTHIAZIDE*
INDAPAMIDE*
metolazone
SPIRONOLACTONE*
torsemide
triamterene

tenofibrate
flecainide
GEMFIBROZIL*

**HEPARINS:**
dalteparin
ENOXAPARIN*
heparin
HMG CoA REDUCTASE INHIBITORS:
ATORVASTATIN*
CERIVASTATIN*
FLUVASTATIN*
LOVASTATIN*
PRAVASTATIN*
simvastatin

IPRATROPIUM*
isosorbide dinitrate
ISOSORBIDE MONONITRATE*

LEUKOTRIENE INHIBITORS:
montelukast
zafirlukast
zileuton

LIDOCAINE*

METHYLXANTHINES:
aminophylline
dyphylline
enprofylline
oxtriphylline
pent oxyphylline
THEOPHYLLINE*

mexiletine
nedocromil
niacin
nicotinic acid

PHOSPHODIESTERASE INHIBITORS:
amrinone
milrinone

probufol
PROCAINAMIDE*
propafenone
QUINIDINE*

VASODILATORS:
diazoxide
hydralazine
minoxidil
NITROGLYCERIN*
nitroprusside
1. Review of Renal Physiology/Biochemistry (2)

2. Diuretics (2)

   a. Principles and knowledge objectives:

      1) List the major transporters and ion channels involved in renal electrolyte transport. Describe their locations on the nephron and changes that occur when specific diuretic drugs inhibit each one.

      2) Explain the importance of the organic anion transport system and protein binding to the renal action of diuretics. Provide examples of how other drugs or diseases can interfere with the effects of diuretics.

      3) Describe the renal and extrarenal mechanisms by which diuretics are useful in treating hypertension and edema due to cardiac, endocrine, hepatic, pulmonary or renal dysfunction. List appropriate drugs to be used in each condition, including contraindications and limitations. Explain when using combined diuretics may be useful.

      4) Explain the consequences of diuretic therapy on alterations in glucose, lipids, urate, calcium, magnesium and potassium. Where possible, describe the underlying mechanism causing the adverse effect.

      5) Explain the mechanism by which the thiazide and loop diuretics can cause a metabolic alkalosis.

      6) Explain how dopamine and mannitol increase renal blood flow and urine flow. Describe their role in the prevention and treatment of acute renal failure and toxic nephropathy.

      7) Describe the clinical consequences of interactions between diuretics and drugs such as cardiac glycosides, oral hypoglycemics, uricosurics, aminoglycosides, amphotericin B, NSAIDs and ACE inhibitors.
3. **Agents Affecting the Renal Conservation of Water (1)**

   a. **Principles and Knowledge Objectives:**

   1) Describe the roles of vasopressin, aquaporins, V₁ and V₂ receptors, cyclic AMP, and prostaglandins in regulating renal epithelial water permeability. Provide examples by which drugs interact with these components to affect water reabsorption.

   2) Compare and contrast the therapy of central and nephrogenic diabetes insipidus.

   3) Describe the mechanisms by which demeclocycline and lithium carbonate interfere with renal water permeability. Describe the treatment of water intoxication due to the syndrome of inappropriate ADH secretion.

   4) Explain how diuretic therapy can lead to hyponatremia.

   5) Outline the extrarenal uses of vasopressin.

**Drugs to Consider:**
arginine vasopressin
DEMECLOCYCLINE,
DESMOPRESSIN (DDAVP),
HYDROCHLOROTHIAZIDE
lithium carbonate
1. **Drugs for the Treatment of Peptic Ulcer Disease**

   Describe neural, paracrine and endocrine regulation of gastric acid production, H⁺,K⁺-ATPase activity, and concept of acid-peptic aggression vs. mucosal defense.

   Describe the role and mechanism of *H. pylori* in the development of peptic ulcers.

   Describe the role and mechanism of NSAIDS in the development of peptic ulcers.

   a. **Histamine H₂ Antagonists.**

      1) Explain mechanisms by which H₂ antagonists inhibit acid production.
      2) Describe absorption, metabolism and excretion; duration of action.
      3) Explain mechanisms by which certain H₂ antagonists alter responses to other drugs.
      4) Identify adverse effects, especially those related to age or gender, and consequences of cessation of therapy on the course of the disease.

   b. **H⁺, K⁺-ATPase Inhibitors**

      1) Describe the role of H⁺, K⁺-ATPase in gastric acid production.
      2) Explain site and mechanism of H⁺, K⁺-ATPase inhibitor actions.
      3) Consider concept of efficacy to explain potential side effects.
      4) Explain the rationale for their use in peptic ulcer disease and gastroesophageal reflux.

   c. **Prostaglandin Derivatives**
1) Describe the mechanisms of gastric antisecretory and mucosal protective effects.
2) Describe the major side effects associated with misoprostol.
3) Explain the rationale for use of misoprostol in conjunction with anti-inflammatory drugs.

d. Sucralfate

1) Describe the antiulcer actions of sucralfate.
2) Describe side effects and therapeutic limitations.

e. Antacids

1) Explain the mechanism of action of antacids.
2) State their relative rates of onset and duration of action.
3) Explain the rationale for their uses in the treatment of peptic ulcer, gastroesophageal reflux disease, and dyspepsia.
4) Identify the major adverse reactions to major classes of drugs: diarrhea, constipation, acid-base balance, phosphate depletion, acid rebound, milk-alkali syndrome, effects on absorption of other drugs.
5) Provide the rationale for mixtures of antacids.
6) Outline additional concerns for patients with renal impairment.

f. Anticholinergic Drugs

1) Explain the mechanism of action of muscarinic antagonists as gastric antisecretory agents.
2) Relate the therapeutic benefits of muscarinic antagonists to selective effects on subtypes of the muscarinic receptor.
3) Explain the adverse side effects associated with anticholinergic therapy.
4) Describe special concerns about the use of anticholinergic drugs in elderly patients.

g. Antibacterial Drugs

1) Relate peptic ulcer disease to infection with Helicobacter pylori.
2) Describe the role of antibacterial triple therapy with bismuth salts and antibiotics in the management of peptic ulcer disease.

Drugs to Consider:
ALUMINUM HYDROXIDE
2. **Secretory Drugs**

Explain the rational for use of secretory agents in diagnosis of secretory disorders.

Compare the mechanisms of action and relative safety of histamine agonists, cholinergic agonists and gastrin agonists.

**Drug to Consider:**
Pentagastrin

3. **Prokinetic Drugs**

Explain the rationale for use of drugs that increase esophageal clearance, gastric emptying and intestinal transit.

Explain the role of smooth muscle muscarinic M₃ receptors in mediation of prokinetic drug actions.

Describe the expected side effects associated with each class of prokinetic drugs. Consider potential interactions between cisapride and erythromycin.

Compare the prokinetic actions of each class of drugs including consideration of their relative effects at cholinergic, dopamine, 5-hydroxytryptamine (5-HT₄) and motilin receptors.

**Drugs to Consider:**
bethanechol
CISAPRIDE
4. **Laxative Drugs**

Classify laxative drugs as bulk-forming, lubricant, surface active, secretory or osmotic.

Discuss appropriate use of laxatives to treat constipation (include the laxative abuse syndrome).

Compare the mechanisms by which surface active laxatives alter mucosal transport and the mechanisms of action of osmotic laxatives.

Describe the adverse reactions to laxatives including systemic effects and local effects.

Compare various classes of laxatives in terms of time course to onset of desired drug effect.

**Drugs to Consider:**
- bisacodyl
- docusate (dioctyl sodium sulfosuccinate)
- lactulose
- MAGNESIUM HYDROXIDE
- methylcellulose
- mineral oil
- polyethylene glycol

5. **Antidiarrheal Drugs**

Discuss the pathophysiology of secretory diarrhea including alterations in mucosal transport and motility.

Define the therapeutic objectives in treating diarrhea with drugs.

Discuss the antidiarrheal mechanisms of opioids and differences in their pharmacokinetic characteristics.

List nonopioid antidiarrheal drugs and their mechanisms of action.

**Drugs to Consider:**
- atropine
- bismuth subsalicylate
- diphenoxylate
LOPERAMIDE
octreotide

6. **Drugs for the Treatment of Inflammatory Bowel Disease (IBD)**

Discuss the pathophysiology of IBD stressing the postulated role of the immune system.

Define the therapeutic objectives in treating IBD with drugs.

Discuss the role of drug design in localizing drug delivery to the intestinal mucosa.

Discuss the rationale for using specific antibodies as drugs in IBD.

**Drugs to Consider:**
balgalazide
infliximab
mesalamine
sulphasalazine

7. **Drugs for the Treatment of Irritable Bowel Syndrome (IBS)**

Discuss the prevalence and the presenting signs and symptoms of IBS.

Discuss the receptors and neural pathways involved in visceral pain.

Discuss the postulated role of abnormal motility and of visceral hypersensitivity in IBS.

Define the therapeutic objectives in treating IBS with drugs.

**Drugs to Consider:**
5HT-3 antagonists
5HT-4 agonists
dicyclomine
hyoscyamine
opioid agonists
General Comments:

1. The classification of drugs as "prototype" and "secondary" drugs may be misleading, particularly with certain groups of chemotherapeutic agents such as the penicillins and cephalosporins where a number of drugs may be considered to be prototypical for different reasons (e.g., pen G, β-lactamase resistant agents, broad spectrum agents). Moreover, the medical students may confuse "prototype" with "clinically most important". Thus, it is suggested that certain "lead-in" drugs be termed "model drugs" that exemplify the mechanism of action and certain aspects of the pharmacology of a class of chemotherapeutic agents. The most important drugs from the standpoint of current clinical use should be indicated where they are distinct from the model compound. The term "secondary drugs" should probably be reserved for agents not currently considered clinically important.

2. The time devoted to various topics in chemotherapy will vary from institution to institution depending on a number of factors including (a) the amount of time spent in microbiology on basic mechanisms of bacterial cell wall synthesis, mechanisms of action of antibacterial drugs, etc., (b) the coverage of this class of drugs in clinical correlation conference sessions or in lectures given by clinical departments, (c) the expertise of the department, and (d) teaching time available to the department.

3. Information regarding toxicity, antibacterial spectrum, therapeutic uses, and specific pharmacology should be covered as part of the discussion of individual drug classes. Alternatively, it could be done by clinical indications (e.g., TB, broad spectrum, etc.).

4. Antimicrobial drugs should be organized for pedagogical reasons by mechanism of action, i.e., inhibitors of cell wall synthesis, protein synthesis inhibitors, metabolic inhibitors, DNA gyrase inhibitors, DNA damaging agents, etc.
a. Chemotherapy of Microbial Diseases

1) Introduction of chemotherapy (1 hr)

Objectives: concept of selective toxicity, concept of drug target, e.g., DNA, key enzyme steps, cell wall synthesis, protein synthesis, general mechanisms of drug resistance, rationale for drug combinations, rationale for chemoprophylaxis, appropriate and inappropriate use of antimicrobial agents, sources of information about new chemotherapeutic agents

2) Sulfonamides and DNA gyrase inhibitors (1 hr)

Objectives: historical development of antibiotics, mechanism of action, mechanism of resistance, adverse reactions, drug combinations, especially trimethoprim and sulfamethoxazole

Drugs to Consider:
develop the sulfonamides as a class, with description of important differences between them. Concentrate on soluble agents - other agents: CIPROFLOXACIN, NITROFURANTOIN, . DNA gyrase inhibitors norfloxacin, levofloxacin

3) Inhibitors of Cell Wall Synthesis (2 hr)

Objectives: steps of cell wall synthesis and points of attack for drugs, basic chemistry and SAR mechanisms of resistance inhibition of β-lactamases cross resistance, adverse reactions, especially allergic reactions

Drugs to Consider:
model = Penicillin G > 12 penicillins on market; as many as possible should be included; attention should be paid to oral absorption, β-lactamase resistance/inhibitors, penicillin binding proteins, antibacterial spectrum, cephalosporins: >15 on market, concept of first, second, third and fourth generation cephalosporins, as many as possible should be discussed in terms of differences that are pharmacologically and clinically important - other drugs: VANCOMYCIN, carbapenems (imipenem).

4) Inhibitors of protein synthesis

a) Aminoglycosides (1 hr)
Objectives: mechanisms of action; differences between drugs' mechanisms, three major types of drug toxicity: neuromuscular, vestibular oto, renal. Increased ototoxicity and nephrotoxicity in elderly. Pharmacokinetics: blood levels are very important for use of this class of drugs, narrow therapeutic index, combination chemotherapy, drug interactions.

**Drugs to Consider:**
- AMIKACIN
- GENTAMICIN
- neomycin

b) chloramphenicol, macrolides, and tetracyclines. (1 hr)

Objectives: mechanisms of action, antimicrobial spectrum. Toxic effects with special note of hematologic effects of chloramphenicol, adverse effects on newborn, discussion of appropriate use of these agents. Their usefulness is relatively limited (except erythromycin), and they should be used only for specific therapeutic purposes.

**Drugs to Consider:**
- azithromycin
- CIPROFLOXACIN
- CLINDAMYCIN
- DOXYCYCLINE
- ERYTHROMYCIN
- fluoroquinolones
- levofloxacin.
- norfloxacin
- TETRACYCLIN

5) Antimycobacterial Drugs (0.5 hr)


**Drugs to Consider:**
- dapsone.
- ethambutol
ISONIAZID
PYRAZINAMIDE
RIFAMPIN
streptomycin

6) Antifungal Agents (1 hr)

Objectives: . mechanisms of action . topical and systemic uses

Drugs to Consider:

AMPHOTERICIN B
clotrimazole
FLUCYTOSINE
flucytosine
ITRACONAZOLE
Nystatin
terbinafine

7) Antiviral Drugs (1 hr)

Objectives: . mechanisms of action, rationale for new agents. new HIV/AIDS drugs

Drugs to Consider:

ACYCLOVIR
GANCICLOVIR
INDINAVIR
nevirapine
oseltamivir
ribavirin
zanamivir
ZIDOVUDINE (AZT)

8) Antiparasitic Drugs

Time: 2 hour

Objectives: mechanism of action of common drugs . target for anthelmintic treatment is adult non-dividing organisms . role of anchorage and motility in helminth biology and its' importance as a target for anthelmintic drugs. Malaria: disease process, life cycle of organism, importance as a world health problem. schistosomiasis: same as above . drugs of choice for most common parasitic infections of
North America, e.g., trichomonas, toxoplasmosis, entamoeba, histolytica, ascaris, pinworm, hookworm, tapeworm

**Drugs to Consider**

**Antimalarials**
- CHLOROQUINE
- MEFLOQUINE
- quinine
- PRIMAQUINE

**Antiprotozoals**
- METRONIDAZOLE
- pentamidine
- PYRIMETHAMINE
- TRIMETHOPRIM-SULFAMETHOXAZOLE

**Antihelminthics**
- mebendazole
- PRAZIQUANTEL
- pyrantel pamoate
- thiabendazole
- combinations.

9) **Anticancer Drugs (4 hr)**

Objectives: fundamentals of cancer biology, therapeutic modalities; adjuvant chemotherapy, determinants of drug response: tumor determinants, host determinants, leukemias/lymphomas vs. solid tumors, total cell kill concept, apoptosis, selective toxicity: why it is so difficult to achieve cell cycle specificity, combination chemotherapy: rationale and examples, common and peculiar toxicities . mechanisms of drug action, pharmacokinetics, where important: e.g., methotrexate, drug resistance

**Drugs to Consider:**

agents that act on DNA:
- CISPLATIN
- CYCLOPHOSPHAMIDE
- MECHLORETHAMINE
- nitrosoureas (carmustine)
- antimetabolites:
  - 5-FLUOROURACIL
  - 6-Thioguanine
  - fludarabine
  - GEMCITABINE
METHOTREXATE
Natural Products:
bleomycin
DOXORUBICIN
ETOPOSIDE
TOPOTECAN
Antimitotics:
PACLITAXEL
VINBLASTINE
VINCRIStINE
miscellaneous agents worth mentioning:
imatinib mesylate (Gleevec)
interferon
retinoic acid
rituximab
trastuzumab (herceptin)
steroids:
prednisone
antiestrogens:
aromatase inhibitors
flutamide
goserelin
leuprolide
TAMOXIFEN

10) immunomodulators (0.5 hr)

Immunosuppressives: . mechanism of action azathioprine, cyclosporine A, FK506
Note: Immunosuppressive drugs are not covered as a separate topic at represented institutions. Comments about immunosuppressive effects of anticancer drugs are made under individual agents.

Hematopoietic Growth Factors: mechanism of action erythropoietin, rHuGM-CSF (sargramostin)

Chemotherapeutic Drugs to Consider:

Antimicrobial Agents:
Penicillins (Narrow spectrum Penicillinase-resistent (S. aureus):
cloxacillin (oral)
nafcillin (parenteral & oral)
OXACILLIN (parenteral & oral)

Broad spectrum Penicillins (aminopenicillins):
AMOXICILLIN
AMPICILLIN

Primarily antipseudomonal Penicillins:
CARBENCILLIN
TICARCYLLIN

Extended spectrum Penicillins:
Piperacillin

Penicillin plus penicillinase inhibitor:
Amoxicillin plus Clavulanic acid (combination is Augmentin)
Ticacillin plus Clavulanic acid (combination is Timentin)

Cephalosporins (first generation):
Cefadroxil (oral)
Cephalexin (oral)
CEFAZOLIN

Cephalosporins (second generation):
CEFACLOR (oral)
CEFOXITIN (parenteral)

Cephalosporins (third generation):
CEFTRIAXONE

Cephalosporins (fourth generation):
Carbepenem
CEFEPIOME

imipenem

Miscellaneous Cephalosporins
VANCOMYCIN

Inhibitors of Protein Synthesis:
amikacin
azithromycin
chloramphenicol
CLARITHROMYCIN
clindamycin
DOXYCYCLINE
erlythromycin
GENTAMICIN
minocycline
neomycin
TETRACYCLINE

Inhibitors of DNA Synthesis:
SULFAMETHOXAZOLE
SULFASOXAZOLE
TRIMETHOPRIM- SULFAMETHOXAZOLE combination

DNA Gyrase Inhibitors:
CIPROFLOXACIN
Levofloxacain
Norfloxacin

Urinary Tract Antiseptics:
NITROFURANTOIN

DNA Damaging Agent:
METRONIDAZOLE

Antimycobacterial Drugs
dapsone
ethambutol
ISONIAZID
PYRAZINAMIDE
RIFAMPIN
streptomycin

Antifungal Drugs
Polyenes:
AMPHOTERICIN B
Nystatin

Imidazoles:
Clotrimazole
FLUCONAZOLE
ITRACONAZOLE

Miscellaneous:
flucytosine
terbinafine
Antiviral Drugs
Nucleoside Analogues:
ACYCLOVIR
GANCICLOVIR
Ribavirin

Reverse Transcriptase Inhibitor:
Nevirapine
ZIDOVUDINE (AZT)

Protease Inhibitor:
INDINAVIR

Neuroaminidase Inhibitor:
oseltamivir
zanamivir

Antiparasitic Drugs

Antimalarial:
CHLOROQUINE
MEFLOQUINE
PRIMAQUINE
quinine

Antiprotozoal Drugs:
METRONIDAZOLE
pentamidine
PYRIMETHAMINE – sulfonamide combination
TRIMETHOPRIM – SULFAMETHOXAZOLE

Antihelminthic Drugs:
mebendazole
niclosamide
PRAZIQUANTEL
pyrantel Pamoate
thiabendazole

Anticancer Drugs:
alkylating Agents:
CISPLATIN
CYCLOPHOSPHAMIDE
MECHLORETHAMINE
Nitrosoureas (Carmustine)

Antimetabolites:
5-FLUOROURACIL
6-Thioguanine
fludarabine
GEMCITABINE
METHOTREXATE

Natural Products:
bleomycin
DOXORUBICIN
ETOPOSIDE
TOPOTECAN

Antimitotics:
PACLITAXEL
VINBLASTINE
VINCRISTINE

Miscellaneous:
imatinib Mesylate (Gleevec)
interferon
retinoic Acid
rituximab
trastuzumab (Herceptin)

Hormones:
flutamide
goserelin
leuprolide
prednisone
TAMOXIFEN

Immunomodulators

Immunosuppressives:
azathioprine
CYCLOSPORINE A
FK506

Hematopoietic Growth Factors:
erthropoietin
rHuGM-CSF (sargramostin)
### DRUGS ACTING ON THE BLOOD AND BLOOD FORMING ORGANS (2.0)

**Subcommittee:**

<table>
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<th>NAME</th>
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<tbody>
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1. **Drugs for Treating Anemia (1)**

   a. Review erythropoietin and normal control of erythropoiesis including the erythropoietin receptor and the growth factors which act synergistically with erythropoietin on erythroid cell development.

   b. Describe the approved therapeutic indications and pharmacokinetics for recombinant erythropoietin.

   c. Describe the possible etiologies which should be considered if a delayed or diminished response to doses of recombinant erythropoietin within the recommended dose range occurs.

   d. Describe the special relationship of iron stores to the response to recombinant erythropoietin and the recommended approach to iron supplementation, especially in patients on dialysis.

   e. Contrast the pharmacokinetics and therapeutic effects of darbepoetin alpha (novel erythropoiesis stimulating protein, NESP) and epoetin alpha (erythropoietin) in anemic dialysis patients.

   f. Describe the iron absorption and transport pathways and the factors that can lead to abnormal iron balance including genetic hemochromatosis.

   g. State the criteria used for the diagnosis of iron deficiency anemia.

   h. Describe the criteria for oral versus parenteral iron therapy and the associated side effects. What are the predicted rates of response to the two therapies?
i. Describe the risks of acute iron poisoning in children and its treatment.

j. Describe the pharmacologic management of chronic iron overload disease (e.g. secondary to chronic blood transfusion, iron absorption disturbances, etc.).

k. Describe the complications associated with and precautions recommended in the use of Deferoxamine.

l. Describe the sources, transport, metabolism, storage, and excretion of vitamin B-12 and folic acid. State the factors which influence the bioavailability of vitamin B-12 and folic acid.

m. Describe the biochemical systems which are impaired in B-12 and folic acid deficiency and the role of cyanocabalamin and folic acid in correcting the metabolic defect in DNA thymine and methionine synthesis.

n. Describe the appropriate management of the patient with a megaloblastic anemia in regards to both acute and chronic management, vitamin dosage and expected response.

o. Describe the possible metabolic reasons why folic acid will correct the erythropoietic lesion but not the neurologic lesion in Addisonian pernicious anemia.

p. Describe the mechanisms by which various drugs can lead to folate deficiency.

q. What is the rationale for the use of folic acid in elevated serum levels of homocysteine and in spina bifida?

r. Describe the problems associated with using iron, B-12 and folic acid in mixtures of shot-gun preparations.

s. Describe/Diagram the sites of action of the hematopoietic growth factors in the differentiation and maturation of marrow cell lines.

t. Review G-CSF and GM-CSF and their physiological effects on hematopoiesis.

u. Describe the appropriate use of G-CSF in the management of neutropenia.
Drugs to Consider:
darbepoetin alpha (NESP)
DEFEROXAMINE
FILGRASTIM (NEUPOGEN)
FOLIC ACID
IRON (FERROUS SULFATE, iron dextran)
rERYTHROPOIETIN (EPOETIN ALPHA)
sodium ferric gluconate
VITAMIN B-12

2. Anticoagulant, Antithrombotic and Thrombolytic Drugs (1)

a. State the sites of action of heparin in the coagulation process.

b. Describe the relationship between mechanism of action and speed of onset of action of heparin and the oral anticoagulants.

c. Contrast the effects and time course of acetylsalicylic acid, standard non steroidal anti-inflammatory agents (NSAIDs) and cyclooxygenase 2 (COX2) inhibitors on platelet function.

d. Describe the mechanism of action and pharmacokinetics of the following antiplatelet agents: (aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab)

e. Describe the appropriate clinical situations and recommendations for the use of antiplatelet agents.

f. Describe the role of the platelet glycoprotein IIb/ IIIa inhibitors in the management of coronary disease.

g. Describe the adverse effects associated with ticlopidine.

h. Describe the mechanism of action and pharmacokinetics of the following antithrombin agents: Heparin, low molecular weight heparin, hirudin, danaparoid

i. Discuss and contrast the management of heparin therapy using standard versus low molecular weight heparin preparations.

j. Describe the complications associated with heparin therapy, including excessive bleeding and heparin induced thrombocytopenia with associated thrombosis.

k. Discuss the management of heparin toxicity, both the use of protamine to reverse the effects of heparin and the use of hirudin
and danaparoid in the treatment of heparin induced thrombocytopenia.

l. Describe the mechanism of action and pharmacokinetics of the oral anticoagulant warfarin.

m. Describe the interactions of oral anticoagulants with other drugs which bind extensively to plasma protein.

n. Describe the interaction of warfarin with other drugs (i.e. aspirin, corticosteroids, antibiotics) and food sources of vitamin K in the management of the anticoagulated patient.

o. Discuss the approach to the management of the patient on short term and long term oral anticoagulation.

p. Describe the pharmacokinetics of the thrombolytic agents and their use in thrombolytic therapy.

q. Consider the problems associated with thrombolytic therapy e.g. streptokinase in primary post MI.

r. Consider adjuncts to thrombolytic therapy e.g. antithrombin, antiplatelet.

s. Describe the use of desmopressin in the treatment of hemophilia and Von Willebrand’s disease.

**Drugs to Consider:**

ABCIXIMAB
ACETYLSALICYLIC ACID
CLOPIDOGREL
danaparoid sodium
DESMOPRESSIN ACETATE (DDAVP)
dipyridamole
eptifibatide
HEPARIN (standard and low molecular weight)
LEPIRUDIN (rHIRUDIN)
PROTAMINE SULFATE
STREPTOKINASE
TICLOPIDINE
VITAMIN K
WARFARIN SODIUM

**Minimum List of Drugs Affecting Blood:**

ABCIXIMAB
ACETYSALICYLIC ACID
activator (tPA)
CLOPIDOGREL
danaparoid sodium
darbepoetin alpha (NESP)
DEFEROXAMINE
DESMOPRESSIN ACETATE (DDAVP)
dipyridamole
eptifibatide
FILGRASTIM (NEUPOGEN)
FOLIC ACID
HEPARIN
IRON (FERROUS SULFATE, iron dextran)
LEPIRUDIN
PROTAMINE SULFATE
rERYTHROPOIETIN (EPOETIN ALPHA)
sodium ferric gluconate
STREPTOKINASE
TICLOPIDINE
tissue-type plasminogen
VITAMIN B-12
VITAMIN K
WARFARIN SODIUM
1. **Introduction (0.5)**

   a. Prerequisites

   Review:
   
   1) General functions of hormones and their target organs; principle type of hormones (structure-activity relationships, location and type of receptors)
   
   2) Regulation of hormone synthesis/release/disposition: the role of day-night rhythms, patterns of release, binding proteins, modulating factors (neurotransmitters, releasing hormones, nutrients), and measurement in biological fluids
   
   3) Mechanisms of hormone action including: receptors and signal transduction pathways for hormones (the location of receptors, molecular events activated by hormones that interact with intracellular receptors and second messenger systems are commonly linked to extracellular receptors)
   
   4) Etiology of endocrine syndromes including those due to: hormone deficiency/excess, receptor defect, hormone resistance, abnormal hormone dynamics, binding proteins

   b. Objective

   Learn:

   1) Rational basis of endocrine therapy including: indications for hormones/drugs in specific disorders (replacement therapy, diagnosis, medical therapy), route/frequency of administration, site(s)/mechanism(s) of action, adverse effects/contraindications

2. **Hypothalamus, Anterior and Posterior Pituitary (1.5)**
a. General objectives

Review:
1) Hypothalamic neurotransmitters/hormones that regulate hormone secretion from the anterior pituitary; structures and dynamics (feed forward/feed back) of hormones secreted by the anterior pituitary
2) Dynamics of various axes with respect to target gland function, i.e. hypothalamo-pituitary-adrenal axis; hypothalamo-pituitary-thyroid axis; hypothalamo-pituitary-gonadal axis; dynamics of portal system neurosecretion and its significance in the control of the anterior pituitary hormone secretion
3) Know the structures of hormones, i.e., glycoproteins, proteins, polypeptides, amino acid-derived; be cognizant of structural homology among the various families
4) Effects of pharmacologic agents on hypothalamic-pituitary function (e.g. selective serotonin reuptake inhibitors, effects of dopamine agonists and antagonists)

b. Anterior Pituitary

1) Growth hormone/related drugs
   a) Understand the regulation of growth hormone (GH) biosynthesis and secretion including the roles of growth hormone releasing hormone (GH-RH), glucose levels, somatotatin, and dopamine – age; body composition; know the physiological conditions that elicit growth hormone secretion; outline how specific diagnostic maneuvers can elicit GH secretion
   b) Describe the biological actions of growth hormone on peripheral tissues (e.g., protein synthesis, intermediary metabolism). Outline the role(s) of IGFs (somatomedins)
   c) Understand the medical problems related to hypo- or hyper- secretion of GH and the role of releasing/replacement therapy and release inhibiting drugs in the management of these states, respectively
   d) Describe the mechanism of action and the therapeutic indications of the following hormones and GH modulating drugs: sermorelin, bromocriptine, octreotide
   e) Compare the therapeutic doses of GH for children versus adults; consider the rationale and justification for the use in elderly (retard aging) and athletes (enhance muscle strength)
f) List the adverse effects of GH therapy in children and adults

**Drugs to Consider:**
Bromocriptine  
OCTREOTIDE  
SERMORELIN  
Somatrem  
SOMATOMEDINS (IGF-1)  
SOMATROPIN

2) Prolactin/related drugs
a) Understand the regulation of prolactin biosynthesis secretion and release by suckling: effect of dopaminergic and serotonergic agonists and antagonists; describe the biological actions of prolactin on breast development and lactation; learn the interrelationship of the hormones, which are involved in breast development and lactation: growth hormone, estrogen, progesterone, glucocorticoids, TRH, prolactin, oxytocin, and insulin
b) List pharmacological actions that can induce hyperprolactinemia
c) Understand the medical problems related to hypersecretion of prolactin in the female (galactorrhea, amenorrhea, infertility); in the male (hypogonadism, infertility)
d) Describe the mechanism of action of dopaminergic agonists used to treat hyperprolactinemia and the concerns about using these drugs to prevent postpartum lactation

**Drugs to Consider:**  
BROMOCRIPTINE  
Cabergoline  
Pergolide  
PROLACTIN

3) Gonadotropins/related drugs
a) Structure-activity relationships of gonadotropin releasing hormone (GnRH) and synthetic analogs
b) Describe the kinetics of secretion for GnRH and the relationship to the therapeutic uses of synthetic analogs
c) Mode of administration and therapeutic considerations: intermittent (infertility) versus continuous administration
(endometriosis, uterine fibroids, prostate cancer), precocious puberty
d) Adverse effects of GnRH and analogs as therapeutic agents when used to treat infertility, prostatic carcinoma, endometriosis, central precocious puberty
e) Steroidogenic actions/uses (diagnostic/therapeutic) and adverse effects of follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG).

**Drugs to Consider:**
follitropin alfa/beta
GANIRELIX
Gonadorelin
Goserelin
HUMAN CHORIONIC GONADOTROPIN (hCG)
LEUPROLIDE
Menotropins
Nafrelin
UROFOLLITROPIN

4) Adrenocorticotropic Hormone (ACTH)/related drugs
   a) Describe the utility of the rapid ACTH stimulation test in diagnosing pituitary-adrenal disorders; what endpoint is measured?
   b) By what route (s) must cosyntropin be administered
   c) List the possible (rare) side effects of cosyntropin administration

**Drugs to Consider:**
Corticotropin
COSYNTROPIN

c. Posterior Pituitary
Factors that regulate the release of hormones from the posterior pituitary
Structure and dynamics of hormones secreted by the posterior pituitary

1) Vasopressin/related drugs
   a) Structure, pharmacokinetics and actions of vasopressin and analogs, such as desmopressin
   b) Discuss the effects of vasopressin on receptor subtypes and signal transduction systems in vascular smooth muscle and the kidney.
c) Consider drugs that affect vasopressin release/action and their relationship to the therapy of diabetes insipidus (DI) and SIADH; list drugs that can cause diabetes insipidus (nephrogenic and neurogenic) and SIADH.

d) Preparations and routes administration of vasopressin analogs available for treating neurogenic and partial diabetes insipidus, bleeding of esophageal varices and deficient blood clotting factors in hemophilia.

**Drugs to Consider:**
Chlorpropamide  
Demeclocycline  
DESMOPRESSIN  
VASOPRESSIN

2) Oxytocin/related drugs
   a) Structure, pharmacokinetics and actions of oxytocin; roles in parturition and lactation  
   b) Diagnostic and therapeutic uses of oxytocin  
   c) Toxicity and contraindications for oxytocin

**Drug to Consider:**
OXYTOCIN

3. **Adrenal Cortex (1.5)**

   a. Glucocorticoids/related drugs

      1) Know the major steps in the biosynthesis of steroids  
      2) Describe the regulation of corticosteroid synthesis by ACTH and angiotensin  
      3) Describe the actions of corticosteroids on intermediary metabolism, growth and development, electrolyte homeostasis, immune and inflammatory responses; understand the cellular mechanism of action of corticosteroids  
      4) Know the structure-activity relationship of synthetic glucocorticoids, especially those modifications that enhance pharmacodynamics activity and/or determine activity based on route of administration  
      5) Describe the significance of corticosteroid disposition (protein binding, biotransformation, enzyme induction) that may necessitate changes in dosage regimens  
      6) Explain the rationale for corticosteroid use in replacement therapy, as anti-inflammatory and immunosuppressive agents,
and as diagnostic agents in hypothalmo-pituitary adrenocortical disease/dysfunction

7) List the adverse effects/contraindications related to corticosteroid use

8) Explain the rationale for alternate day therapy and the necessity for slow withdrawal following chronic therapy with glucocorticoids

**Drugs to Consider:**
- Aminogluthethimide
- BECLOMETHASONE
- CORTISOL (hydrocortisone)
- DEXAMETHASONE
- KETOCONAZOLE
- METYRAPONE
- Mifepristone
- Mitotane
- PREDNISONE
- triamcinolone

b. Mineralocorticoids/related drugs

1) Review the regulation of aldosterone secretion by angiotensin (I, II, and III)
2) List the analogs used in mineralocorticoid replacement therapy
3) List the adverse effects of excessive mineralocorticoid activity
4) Explain the rationale for spironolactone in treating primary hyperaldosteronism

**Drugs to Consider:**
- ALDOSTERONE
- FLUDROCORTISONE
- SPIRONOLACTONE

4. **Gonads (1.5)**

a. Estrogens/Progestins/related drugs

1) Describe the gametogenic and steroidogenic functions of the ovary and their regulation by gonadotropins
2) Describe the use of drugs such as clomiphene and gonadotropic drugs for the treatment of infertility
3) Describe differences in absorption, distribution, and elimination between synthetic and natural estrogens including those in the environment (e.g., phytoestrogens)
4) Elucidate the effects of estrogen on: cardiovascular function, intermediary metabolism, electrolyte and water balance, cognition, reproductive function, skin, plasma proteins and blood lipids hepatic function; describe the effects of estrogens on laboratory tests, including liver function, clotting factors, thyroid hormone disposition and adrenocortical function

5) State the rationale for the various dosage schedule (e.g., biphasics, triphasics), for oral contraception when combination (estrogen-progestin) therapy is used; list agents used for postcoital contraception

6) List types of hormonal contraceptive agents, other than combination agents, and their routes of administration

7) Describe some of the therapeutic and diagnostic uses of estrogens and progestins other than their utility as oral contraceptives

8) Describe the rationale for use of long-acting progestins for long-term suppression of ovulation

9) List major adverse effects/contraindications for estrogens and progestins alone and in combination; list the most common drug interactions with estrogens and progestins

10) Describe the rationale for the replacement use of estrogens and estrogen/progestin in postmenopausal osteoporosis, cognitive disorders, and cardiovascular disease

11) Describe the use of estrogen receptor antagonists and aromatase inhibitors in breast cancer

12) Define the term “selective estrogen receptor modifier” (SERM); provide examples and outline their therapeutic utility

13) Explain the mechanism of action mifepristone (RU 486) and other abortifacients

14) List the drugs used to treat hirsutism

15) By what mechanisms do drugs produce gynecomastia; list at least one drug for each mechanism you identify

**Drugs to Consider:**
- ANASTROZOLE
- CLOMIPHENE
- conjugated/esterified estrogens
- danazol
- diethylstilbestrol
- ETHINYL ESTRADIOL
- EXEMESTANE
- Levonogestrel
- Mestranol
- Mifepristone
MEDROXYPROGESTERONE
NORETHINDRONE
Phytoestrogens
PROGESTERONE
RALOXIFENE
TAMOXIFEN

b. Androgens/related drugs

1) Know the sources of androgens (ovary, testes, adrenal) and understand their regulation of secretion; define the roles of LH and FSH on gonadal function; define the importance of androgens for sexual differentiation and puberty

2) Describe the effects of androgens on growth and development (anabolic actions vs. androgenic actions); delineate the importance of dihydrotestosterone formation and binding to androgen receptors in the prostate gland and other organs

3) Compare the routes of administration, absorption and relative duration of action of synthetic androgens and testosterone

4) Understand medical problems associated with hypo-(hypogonadism) and hyperfunction (precocious puberty, hyperandrogenism) and rationale for therapy; describe the rationale for the clinical uses of androgens in: replacement therapy, anemia, catabolic states

5) Describe the adverse effects of androgens/anabolic steroids when used in male and female; correlate the hepatotoxicity of certain androgens/anabolic steroids with their chemical structure

6) Relate the mechanism of action of antiandrogens to their potential therapeutic uses: e.g., flutamide, finasteride, spironolactone, leuprolide

Drugs to Consider:
Cyproterone
Danazol
FINASTERIDE
FLUTAMIDE
Leuprolide
OXANDROLONE
Spironolactone
TESTOSTERONE

5. **Thyroid (1.0)**
a. Outline the regulation and the key steps in thyroid hormone synthesis and peripheral conversion; explain the mechanisms by which thyroid hormones regulate cellular function

b. Delineate the relationship between thyroid hormones and the actions of catecholamines; provide the rationale for the use of propranolol in the treatment of hyperthyroidism

c. Describe the signs/symptoms of hypothyroidism (myedema) and the consequences of the disease that can alter drug therapy for other concurrent diseases

d. Provide the pharmacokinetic rationale for selecting the most appropriate form of thyroid hormone as replacement therapy; identify the best index of adequate replacement therapy with thyroid hormone

e. Describe the caution necessary when replacing thyroid hormone in a patient with a history of coronary artery disease

f. Describe the rationale and order of administration of drugs administered to treat thyroid storm

g. Provide the rationale for the uses of drugs/radioiodine in treating hyperthyroidism; explain their mechanism(s) of action; consequences of radioiodine use

h. Provide the pharmacokinetic rationale for selecting the most appropriate antithyroid drug for treating hyperthyroidism (diffuse toxic goiter) in a non-pregnant versus a pregnant female

i. Describe the adverse effects of antithyroid medications and identify those that are potentially life threatening

Drugs to Consider:
Ipodate
LEVOTHYROXINE
Liothyronine
Lithium
METHIMAZOLE
POTASSIUM IODIDE
PROPRANOLOL
RADIOIODINE (¹³¹I)
PROPYLTHIOURACIL

6. Parathyroid/related Drugs (0.5)
a. Understand the regulation of calcium homeostasis and the physiological actions of parathyroid hormone (PTH), calcitonin (CT) and 1,25-dihydroxyvitamin D₃ [1,25-(OH)₂D₃]; understand the role(s) of kidney, liver and GI tract in vitamin D homeostasis

b. Describe the mechanisms regulating synthesis, secretion of PTH and actions and CT their mechanism(s) of action on bone, kidney and intestine

c. Know the available preparations of CT, 1,25-(OH)₂ D₃, and calcium supplements and their clinical uses; compare and contrast the treatment of hypo- and hyper-parathyroidism

d. Know the available preparations of CT and 1,25-(OH)₂D₃ and review the possible adverse effects of CT, 1,25-(OH)₂D₃ and calcium supplement

e. Understand the clinical value of bisphosphonates and CT in the treatment of: hypercalcemia, Paget’s disease, osteoporosis (postmenopausal and glucocorticoid-induced)

f. Describe the chronic toxicity associated with long-term use of sodium fluoride

**Drugs to Consider:**

- ALENDRONATE
- CALCITONIN
- CALCITRIOL
- CALCIUM GLUCONATE
- ETIDRONATE
- Furosemide
- PARATHYROID HORMONE
- Plicamycin
- Prednisone
- sodium fluoride

7. **Pancreas/related Drugs (1.5)**

a. Describe the normal daily patterns insulin secretion and changes that occur in different types of diabetes mellitus

b. Describe the effects of insulin and glucagon on intermediary metabolism and ion transport
c. Describe the pathophysiology of the primary types of diabetes mellitus (bihormonal disease – insulin and glucagon), and their sequelae: diabetic ketoacidosis and nonketotic hyperosmolar coma

d. Describe the pharmacokinetic (onset and duration of action) rationale for the use of insulin preparations in ‘split-mixed’ or continuous s.c. infusion

e. Explain the mechanisms by which oral anti-diabetic agents act and the influence these mechanisms have on selection for therapy in individual patients (e.g., obese)

f. Describe the relative roles of insulin and oral hypoglycemics in the treatment of type I and type II diabetes mellitus

g. List commonly used drugs with which sulfonylurea compounds are known to interact and the postulated mechanisms for these interactions (first vs. second generation)

h. State the nature of the adverse effects of oral hypoglycemics and identify those that may require cessation of therapy or preclude their use

i. Describe the clinical manifestations and management of overdose with insulin and oral hypoglycemic agents, respectively

j. Discuss the use of recombinant DNA insulin preparations and the insulin pumps that are employed in certain patients

**Drugs to Consider:**
ACARBOSE
Chlorpropamide
Diazoxide
Glucagons
GLIPIZIDE
Glyburide
INSULINS (lispro, regular, lente, NPH, ultralente, glargine)
METFORMIN
Nateglinide
PIOGLITAZONE
REPAGLINIDE
Rosiglitazone
tolbutamide

8. **Urogenital System (1.0)**
a. Female Urogenital Tract
   1) Oxytocics (Uterine stimulants)/related drugs

b. Describe the receptors targeted by the oxytocics and the sensitivity of the uterus to the various oxytocics during the three trimesters of pregnancy.

c. State the usual route(s) of administration, onset and duration of action of the various oxytocic agents

d. Describe the clinical use of the individual oxytocics

e. Discuss the utilization of RU486 (mifepristone) versus prostaglandins and oxtocics in therapeutic abortion

f. Describe the potential adverse effects of the oxytocic agents in the mother (uterine, extrauterine) and in the infant

Drugs to Consider:
DINOPROST
Dinoprostone
ERGONOVINE
MIFEPRISTONE
Misoprostol
OXYTOCIN

g. Tocolytics (Uterine relaxants)/related drugs
   1) Describe the mechanism of action of the various tocolytic agents
   2) Identify the potential benefits and risks of administering tocolytic agents to the mother and baby
   c) State the usual route(s) of administration as well as onset and duration of action of the various tocolytic agents

Drugs to Consider:
INDOMETHACIN
magnesium sulfate
RITODRINE
terbutaline

h. Male Urogenital Tract
1) Describe the neuroendocrine factors that regulate functions of the male urogenital tract

2) List the drugs that can be used to treat benign prostatic hyperplasia and impotence; state the usual routes of administration of alprostadil and sildenafil; describe the proposed mechanism of action of the drug listed above and relate the resulting pharmacological effects to their clinical use

3) List the adverse effects and contraindications of the prototype agents in the drug list

Drugs to Consider:
Alprostadil
Doxazosin
saw palmetto
SILDENAFIL
TAMSULOSIN
TERAZOSIN
K. **TOXICOLOGY AND THERAPY OF INTOXICATION (5.0 hr)**

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**Introduction**

A medical pharmacology course should be primarily concerned with three aspects of toxicology: adverse effects of therapeutic agents, acute intoxications, and chronic poisoning/environmental toxicology. The adverse effects of drugs should be taught along with the pharmacology of individual drugs or groups of drugs.

The discussion of acute intoxications should constitute a short, but important, part of the pharmacology course and should deal with the techniques and procedures used in dealing with the effects of exposure to acutely toxic materials. Lectures dealing with chronic intoxications should emphasize environmental toxicology and risk assessment.

**Major recommendations:**

1. **Principles of Toxicology:**
   Many of the mechanisms by which chemicals induce toxic effects are governed by the same principles (e.g. pharmacodynamics, pharmacokinetics) that govern pharmacological effects. The principles section of the pharmacology course could cover both of these topics. The principles of toxicology section can be presented with some additional time to cover bioactivation, cellular defense mechanisms, and threshold concepts. Moreover, these principles should be reinforced and reiterated later in the toxicology section of the course. (1 hr)

2. **Toxicology of Individual Drugs and Drug Groups:**
   The toxicological effects of drugs should be included in the discussion of the pharmacology of the specific drugs and drug groups. A discussion of the toxicology of heroin and other opiates, cocaine, and cardiac glycosides, for example, provides an opportunity to relate principles of toxicology to the therapy of intoxication.
3. **Priority Toxic Chemicals:**
   Rather than extensive discussions of many individual toxicants, priority should be given to select chemicals to include acetaminophen, tricyclic antidepressants, carbon monoxide, cyanide, lead, iron (if not discussed elsewhere), methanol (if not discussed along with ethanol and other alcohols in the CNS section of the course), and organophosphate and carbamate pesticides (if not discussed in the ANS section of the course). This list may be expanded in some schools to satisfy perceived local or regional needs. For example, agricultural chemicals may be given more emphasis in rural areas and air pollutants may be emphasized in urban areas. Finally, the therapeutic use of specific antidotes could be covered along with the relevant priority chemicals or could be discussed in connection with the management of intoxication. (2 hr)

4. **Management of Acute Intoxications:**
   The therapeutic approach to the management of acute intoxication with either drug or non-drug chemicals should be taught. This lecture could effectively present a “decision-tree” approach. If the identity of the poison is known, then the approach would be different than in the case where the identity of the poison is not known. A discussion of the hepatotoxicity of acetaminophen affords an opportunity to relate bioactivation mechanisms, the protective role of glutathione, and therapy with N-acetylcysteine in a case-based setting.

5. **Environmental Toxicology/Risk Assessment:**
   Because chronic, low-dose exposures to chemicals occur more frequently than acute, high-dose exposures, medical students should be provided with information about risk assessment and the hazards associated with chronic exposure to chemicals. Moreover, chronic use of therapeutic agents at moderately high doses, compared to low dose exposure to chemicals in the food, air and water, is now commonplace.

Lectures in this area should deal with the neurotoxic, carcinogenic, mutagenic, and teratogenic potential of chemicals including:

a. Carcinogenic (e.g., the concept of precarcinogen, proximate and ultimate carcinogen).

b. Metabolic transformations of chemical carcinogens.


d. Mutagenicity and relationships with carcinogenicity, Ames test.

e. Smoking and lung cancer (if not covered adequately in pathology) e.g., major carcinogens in cigarette smoke.

f. Chemical prevention of carcinogenicity (e.g. antioxidants).
g. Neurotoxic potential as a common basis for establishing exposure limits.

These lectures provide an excellent opportunity to reinforce fundamental concepts (dose-response, variability of responses in a population, etc.) and to train students to use these concepts in evaluating risk. The reliance on fundamental concepts is important in an area where reliable data for the human population is usually lacking.

6. **Sources of Information:**
Because intoxication associated with diverse types of chemicals may be encountered in clinical practice, medical students should be aware of the information sources available to them. A presentation by the Director of the local or regional poison information center may be effective. Students should also be made aware of available CD-ROM or Internet databases on toxicants. (2 hr for 4, 5 and 6)

7. **Lecture Time:**
In the idealized curriculum, about five lectures should be devoted to toxicology. These lectures may be held in conjunction with discussions in clinical conferences.

**Specific knowledge objectives to be considered:**

1. Describe four basic components in the management of acute poisoning (evaluation of the poisoned individual, supporting care, termination of exposure, and specific drug therapy) and how to decide on their sequence of initiation.

2. Describe a Poison Control Center and list services a physician should expect from an ideal center. Provide information concerning current Internet sources of toxicology databases.

3. Discuss the general principles of risk assessment associated with long-term, low dose exposures. How can fundamental concepts (i.e. dose-response) be used in assessing risk?

Priority toxic chemicals and antidotes which should be discussed

**ACETAMINOPHEN and N-ACETYL-L-CYSTEINE**

**ACTIVATED CHARCOAL**

**AIR POLLUTANTS**

**ALCOHOLS (ETHANOL, METHANOL, ETHYLENE GLYCOL)**

**ARSENIC**

**CARBON MONOXIDE**
CHELATOR THERAPY (2,3-DIMERCAPTOSUCCINIC ACID, DIMERCAPROL, EDETATE)
CYANIDE AND ANTIDOTES
DIG-SPECIFIC ANTIBODY FRAGMENTS
GLUCAGON
HEROIN
IRON AND DEFEROXAMINE
LEAD
MERCURY
METHYLENE BLUE
NALOXONE
SALICYLATES
SODIUM BICARBONATE
TRICYCLIC ANTIDEPRESSANTS
SELECTED PESTICIDES (ANTICHOLINESTERASE, PRALIDOXIME[2-PAM])
1. **Water soluble vitamins** (thiamine, riboflavine, niacin, pyridoxine, cyanocobalamin, folic acid, biotin, carnitine, choline, inositol, pantothenic acid)

For each vitamin:

a. know the trivial name (if any) and active species
b. describe physiological and pharmacological activities
c. know the current RDA (required daily allowance)
d. know the foods rich in the vitamin
e. describe the major deficiency syndrome(s)
f. know any therapeutic use(s)
g. for niacin and pyridoxine identify symptoms of overdoses

2. **Fat soluble vitamins** (vitamins A, D, E and K)

For each vitamin:

a. know the trivial name and the active species
b. describe physiological and pharmacological activities
c. know the current RDA
d. know the foods rich in vitamins
e. describe the major deficiency syndrome(s)
f. describe hypervitaminosis
g. know any therapeutic use(s)
h. for vitamin A analogs tretinoin and isotretinoin, identify medical usefulness
i. for vitamin D identify the metabolic activation and sites of activation.
This chapter was prepared by extensive adaptation of the summary of a workshop held March 1989 in conjunction with the Annual meeting of the American Society for Clinical Pharmacology and Therapeutics. The Subcommittee gratefully acknowledges Dr. David Nierenberg who prepared a draft of the workshop report on the behalf of the Council on Medical Student Education in Clinical Pharmacology, which served as a basis for this report.

The Subcommittee on Clinical Pharmacology sought to identify three general subtopics for the teaching of Clinical Pharmacology to medical students. The Subcommittee recommends a core of factual and conceptual information, i.e., clinical pharmacology "facts" that are distinct from the information taught in basic pharmacology courses. The Subcommittee also recommends clinical pharmacologic skills that students should master in order that they can effectively evaluate and prescribe drugs. Lastly, the Subcommittee recommends the clinical pharmacology attitudes and behaviors which students should develop as they mature to become prescribing physicians.

These facts, skills and attitudes/behaviors should be taught throughout the four years of medical school. Many of the facts and introductory material are initially taught in the 2nd year Medical pharmacology course but the attitude and skills should be taught by example throughout medical school. Because the student’s attitudes may dictate the development of appropriate skills and even facts throughout their medical education, attention to preferred attitudes on therapeutics should begin very early in medical school.

Ideally, many of the clinically-related facts should be taught in the fourth year after the students have learned enough clinical medicine so they can integrate the facts and principles of rational therapeutics into habits for
patient management. However, there are many different and effective ways to teach the material, and different schools have developed their own balance of lectures, seminars, patient-based problem solving, rounds, etc.

1. **Clinical Pharmacologic Facts**
   
a. Principles of clinical pharmacokinetics  
b. Principles of therapeutic drug monitoring  
c. Principles of prevention and management of adverse drug reactions, including drug allergy.  
d. Principles and management of drug-drug interactions.  
e. Principles and prevention of drug-food and drug-botanical interactions.  
f. Pharmacogenetic causes of variable response to drugs.  
g. Sex and gender as causes of variable response to drugs.  
h. Special problems of prescribing to elderly patients.  
i. Special problems of prescribing to pediatric patients.  
j. Special problems of prescribing to pregnant or nursing women.  
k. Special problems of prescribing to patients with underlying diseases such as renal or hepatic disease.  
l. Principles of evaluation and treatment of the poisoned patient.  
m. Rules and regulations affecting drug prescriptions.  
n. The process of new drug development and approval.  
p. Principles of integrating prescribing with the full healthcare team (pharmacists, nurses, patients and their families).  
q. Principles of utilizing modern informatics and databases in safe and effective prescribing.  

2. **Clinical Pharmacologic Skills**
   
a. Pharmacokinetics: Students should be able to quickly and accurately solve the common pharmacokinetics problems presented by patients. They should be adept at computing loading doses and maintenance doses using their knowledge of volume and distribution and clearance when prescribing drugs. They should be able to anticipate interindividual differences or changes in pharmacokinetics parameters due to genetics, sex and cardiac, renal or hepatic function.  

b. Therapeutic drug monitoring: Students become skilled at appropriately ordering the measurement of plasma drug concentrations (including "free" rather than total drug concentrations) when indicated. Ability to interpret drug concentration measurements in the context of the therapeutic window, along with derivation of dosage adjustments to maintain
therapeutic concentrations, should be mastered. They should become skilled at avoiding the overuse and over reliance on this technique, and learn to avoid generating misleading data by ordering drug levels at incorrect times or under inappropriate clinical conditions.

c. Adverse drug reactions: Students should develop reasonable skill at analyzing complicated cases in which patients have several diseases, several symptoms, and are receiving several drugs. Students should practice and sharpen their skills at separating symptoms and signs caused by disease from those caused by the drugs per se. Students should understand how to access the MedWatch voluntary ABR reporting system maintained by the FDA.

d. Drug interactions: Students should become skilled in recognizing and anticipating common drug interactions for the drugs taken by their patients, especially metabolically based interactions due to genetic differences (using knowledge of polymorphisms of cytochrome P450 isozymes, etc). The skill should include a multi-faceted approach to incorporate other healthcare providers and information resources. They should be skilled in using up to date reference sources and electronic databases to screen for potential drug interactions for the drugs they will be prescribing.

e. Special factors in each patient: Students should be able to recognize patient factors (such as age, sex, underlying disease, pregnancy, nursing, etc.) which would require alternate therapeutic plans. In addition, students should have the skills to find available data in these areas in standard reference and electronic data sources.

f. Obtaining and interpreting drug information: Students should be skilled at retrieving and understanding scientific data available from experts, internet sources, books, and other databases. Students should be able to evaluate a new drug's efficacy and toxicity by reviewing primary, peer-reviewed papers. Students should develop a reasonable level of competency in accessing web-based or CD-ROM based information programs that give the latest information about individual drugs, drug classes, drug interactions, drug information for patients, drugs listed by indicators or contraindication, etc.

g. Prevention and management of drug overdoses: Students should be skilled in recognizing presentations of common drug overdose, and in initiating therapy when appropriate. In addition, they
should develop an approach to such problems that can be used in any such patient even before the casual agent has been confirmed. Finally, students also should be skilled in the use of common reference sources for rapidly obtaining accurate information enabling the diagnosis and treatment of toxic emergencies.

h. Substance abuse: Students should become skilled in recognizing the presentations of intoxication, withdrawal, and medical complications of the common drugs of abuse. They should also develop facility with taking a substance abuse history, and should learn techniques for uncovering unsuspected substance abuse problems.

i. Prescribing: Students should master the paradigm for rational therapeutic decision making, that assures selection of appropriate drug therapy only when drug therapy is warranted, at effective individualized and safe dosages, and commit to monitoring therapy with appropriate dosage adjustments and changes or termination of drug therapy. Students should also master the requirements for complete drug prescription. They should be skilled in prescribing complete, accurate, safe and legible written or electronic prescriptions for drugs used in both in-patients and out-patients, including drugs with special restrictions such as those requiring a DEA license. Students should understand the special requirements for prescribing 1) drugs that are investigational, 2) those which are being used for a non-approved indication, and 3) those which are available only from physicians granted an IND.

j. Communications skills: Students should become skilled in talking with their patients to assess and stimulate drug compliance, and to ascertain history (including prescription and nonprescription drugs, topical preparations, dietary supplements, botanicals, etc.). Students should know how to use the various written materials that are available as patient inserts (medication guides).

k. Integrating basic and clinical science: Students should develop the essential skills to enable them to incorporate principles of basic pharmacology into their clinical decision-making patterns, as well as incorporate clinical factors into their approach to evaluating the pharmacology of medications.

l. Recognition of pressures to prescribe irrationally: Students should develop the ability to recognize in themselves tendencies to irrational prescribing, and recognize the forces encouraging
such habits. They should understand the potential for being misled by biased information when they learn about medications from advertisements, detail personnel, colleagues (word of mouth), special sponsored symposia, etc. Although some useful information can be imparted in these ways, students must place the information in context. They should neither blindly accept information from potentially biased sources nor should they refuse to consider the merit of the information. They should also recognize that anecdotal experiences, even their own, can be misleading.

3. **Clinical Pharmacologic Attitudes**:

   a. Balanced approach to drug prescribing: Students should avoid the extremes of therapeutic nihilism and gross over-prescribing. Students should be impressed by the power of drugs to help cure and treat disease, but this should be balanced by respect for the power of drugs to cause serious and even fatal adverse reactions. They should embrace their ethical commitment to monitor the outcome of each prescription in each patient until the intended effect is achieved or a change in therapy is warranted.

   b. Conscious attempt to optimize benefit and minimize risk: Students should recognize that each patient is a special case for drug therapy until proven otherwise. They should also be aware that the best drug for a particular patient may change as the dynamic process of the patient's disease unfolds.

   Students should recognize that treatment of any disease or syndrome can often involve several or many combinations of drug choices and treatment regimens. The best choice for a given patient must be sought in a specific effort to maximize the chance of a therapeutic outcome, and minimize the chances of drug-induced toxicity or failure. Those factors which make each patient unique should be consciously sought and considered. This attitude is essentially the opposite of the "cookbook" approach to drug therapy.

   c. Balanced approach to the introduction of new drugs: Students should not refuse to prescribe a new drug product just because it is new, nor should they enthusiastically embrace all new drugs as being the latest and the best. Rather, students should understand that the place of a new drug in the current pharmacopeia may not initially be clear, and that subsequent data may radically change the manner in which the drug is prescribed. Students should be willing to take responsibility for developing their own
approach to learning about new drugs as they are approved by the FDA and marketed.

d. Importance of the therapeutic contract: Students should understand that at the heart of drug prescribing is a contract between the physician and the patient. Communication is essential so that the physician can learn enough information to prescribe optimally, and then again to ensure optimal compliance. In addition, the physician must understand that the contract requires him or her to follow the patient over time to see whether the therapeutic trial results in beneficial or unwanted effects.

e. Acceptance of the need to prescribe as a team leader with responsibility to the patient to utilize all resources available to maximize the benefits of therapy. This requires the student to accept the fact that they cannot memorize all of the facts required for optimal prescribing and must rely on computerized databases, nurses, pharmacists, the patient and the patient’s family as members of the therapeutic team.

**Recommendations:**

Some schools have chosen to provide the bulk of this teaching in a fourth year course; others have incorporated the teaching of clinical pharmacology in the second year Medical Pharmacology course (Peck, CC and Halkin, H, J. Med. Ed. 56:1024-6, 1981). Much of the material of clinical pharmacology cannot be taught effectively during the second year because the students have usually not had an adequate clinical experience to fully integrate and appreciate the material or principles involved. Therefore, a formal course, problem solving instruction and/or small group discussions are often incorporated in the third and fourth years to reinforce the principles and expand upon the database of clinical pharmacology (Cantilena and Woosley, Clin. Pharm. Ther. 60:1-7, 1996).

Most courses in the fourth year require 20-25 hours focusing on general principles and core topics with commonly used drugs. Some schools have devoted over 70 hours to courses that include, not only core material, but also detailed discussion of a variety of therapeutic topics. An innovative fourth year course at Georgetown University was recently described (Knollman, B. et al, Naunyn-Schmeideberg’s Archives of Pharmacology, March, 2002).
HERBAL PRODUCTS (1 hr)

1. Emphasize that the current regulations for herbal products are different from those for OTC and prescription drugs as to claims, content, efficacy and toxicity and refer to the “Dietary Supplement and Health Education Act of 1994”.

2. Describe problems, that may be encountered when offering an entire herb or extract versus a specific active ingredient as to purity and reproducible potency of the active substance.

3. Indicate the reasons why therapeutic uses of herbal products should rely only on scientific evidence and not anecdotal stories.

4. Discuss some specific herbal products and some of their purported medical uses citing available pharmacological evidence as well as their known toxicities.

5. Discuss precautions for the use of herbal products in some diseases, certain age and patient groups and their interactions with OTC and prescription drugs.

6. Emphasize that the physician must ask the patient about the use of herbal products when taking a complete history.

Herbal Medications to Consider:

Aloe (*aloe vera*)
Echinacea (*echinacea purpurea*)
German Chamomile
Black Cohosh (*cimicifuga racemosa*)
Gingko (*ginkgo biloba*)
Ginseng (panax ginseng and quinquefoliam)
St. John's Wort (*hypericum perforatum*)
Saw Palmetto (*seroona repens or sabal serrulata*)
Ephedra (*ma huang*)
Kava Kava (*piper methysticum*).
Autacoids and Nonsteroidal Antiflammatory Drug List

Histamine/Antihistamines

- astemizole
- CROMOLYN SODIUM
- HISTAMINE
- promethazine
- chlorpheniramine
- DIPHENHYDRAMINE
- LORATADINE
- RANITIDINE
- CIMETIDINE
- famotidine
- nizatidine
- TERFENADINE

Drugs for Motion Sickness

- DIMENHYDRINATE
- meclizine
- promethazine
- SCOPOLAMINE

Eicosanoids

- alprostadil (PGE1)
- carboprost (15-methyl-PGF2)
- caverject (PGE1)
Antipyrretics and Analgesics

- ACETAMINOPHEN
- ARSPRIN and related salicylates
- non-steroidal drugs other than aspirin (see below)
- combinations - acetaminophen and ASA with opioids and/or caffeine
- diflunisal

Nonsteroidal Anti-inflammatory Drugs

- ASPIRIN
- IBUPROFEN
- KETOPROFEN
- meclofenamate
- phenylbutazone
- PIROXICAM
- NAPROXEN
- sulindac

Disease Modifying Antirheumatic Drugs (DMARDS)

- auranofin
- AUROTHIIOGLUCOSE
- azathioprine
- chloroquine
- CYCLOPHOSPHAMIDE
- cyclosporine
- D-penicillamine
- sulfasalazine

Antigout Drugs

- ALLOPURINOL
- COLCHICINE
- probenecid
- SULFINPYRAZONE
# Autonomic Nervous System & Neuromuscular Junction

**PRIMARY DRUGS** - All capital letters  
**SECONDARY DRUGS** - Small letters

<table>
<thead>
<tr>
<th>Primary Drug</th>
<th>Secondary Drug</th>
<th>Drug</th>
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<tbody>
<tr>
<td>ACETYLCHOLINE (ACH)</td>
<td>ALBUTEROL</td>
<td>AMPHETAMINE</td>
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<tr>
<td>ATENOLOL</td>
<td>atracurium</td>
<td>ATROPINE BETHANECHOL</td>
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<tr>
<td>black widow spider venom</td>
<td>botulinum toxin</td>
<td>chlorpyrifos</td>
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<td>CLONIDINE</td>
<td>COCAINE</td>
<td>DOBUTAMINE</td>
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<td>DOPAMINE</td>
<td>Echothiophate</td>
<td>EDROPHONIUM</td>
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<td>ephedrine</td>
<td>EPINEPHRINE</td>
<td>esmalol</td>
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<td>guanethidine</td>
<td>hemicholinium</td>
<td>hexamethonium</td>
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<td>ISOPROTERENOL</td>
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<td>MUSCARINE</td>
<td>NEOSTIGMINE</td>
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<tr>
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<td>PHYSOSTIGMINE</td>
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<td>pralidoxime</td>
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<td>pseudoephedrine</td>
<td>pyridostigmine</td>
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<td>RESERPINE</td>
<td>ritodrine</td>
<td>salmeterol</td>
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<td>SCOPOLAMINE</td>
<td>soman</td>
<td>SUCCINYLCHOLINE</td>
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<td>TERBUTALINE</td>
<td>terazosin</td>
<td>timolol</td>
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<td>trimethaphan</td>
<td>TUBOCURARINE</td>
<td>tyramine</td>
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<tr>
<td>PRIMARY DRUGS</td>
<td>SECONDARY DRUGS</td>
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<tr>
<td>ACETYLSALICYLIC ACID</td>
<td>COBALAMIN (cyanocobalamin,hydroxocobalamin)</td>
<td>cyclosporine</td>
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<tr>
<td>DEFEROXAMINE</td>
<td>desmopressin acetate (DDAVP)</td>
<td>ERYTHROPOIETIN(Epo)</td>
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<tr>
<td>FOLIC ACID</td>
<td>GM-CSF</td>
<td>G-CSF</td>
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<tr>
<td>HEPARIN</td>
<td>IgG</td>
<td>IRON(FerroUS SULFATE, iron dextran)</td>
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<tr>
<td>leucovorin</td>
<td>PREDNISONE</td>
<td>protamine sulfate</td>
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<tr>
<td>STREPTOKINASE</td>
<td>TISSUE PLASMINOGEN ACTIVATOR(tPA)</td>
<td>thrombopoietin</td>
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<tr>
<td>UROKINASE(scuPA)</td>
<td>VITAMIN K</td>
<td>WARFARIN SODIUM</td>
</tr>
</tbody>
</table>
Cardiovascular and Respiratory Drug List

PRIMARY DRUGS - All capital letters
SECONDARY DRUGS - Small letters

[Antiarrhythmic Drugs] - [Inotropic Agents] - [Antihypertensives and Related Drugs]
[Antianginal Drugs] - [Antihyperlipidemic Drugs] - [Respiratory Drugs]

Antiarrhythmic Drugs

• adenosine
• digitoxin
• LIDOCAINE
• NIFEDIPINE
• QUINIDINE

• amiodarone
• DIGOXIN
• propafenone
• procainamide
• d-SOTOLOL

• bretylium
• disopyramide
• mexiletine
• PROPRANOLOL
• VERAPAMIL

Inotropic Agents

• DIGOXIN
• dobutamine
• dopamine

Antihypertensives and Related Drugs

• ANGIOTENSIN (I & 11)
• CLONIDINE

• atenolol
• diazoxide

• CAPTOPRIL
• DILTIAZEM
- ENALAPRIL
- guanabenz
- indapamide
- metazolone
- minoxidil
- nitroprusside
- PROPRANOLOL
- spironolactone

- esmolol
- HYDRAZINE
- labetolol
- methylldopa
- NIFEDIPINE
- pindolol
- quinapril
- triamterene

- FUROSEMIDE
- HYDRAZINE
- losartan
- METOPROLOL
- NITROGLYCERIN (i.v.)
- PRAZOSIN
- reserpin
- VERAPAMIL

### Antianginal Drugs

- DILTIAZEM
- dipyridamole
- isosorbid dinitrate
- NIFEDIPINE
- NITROGLYCERIN
- PROPRANOLOL
- timolol

### Antihyperlipidemic Drugs

- CHOLESTYRAMINE
- CLOFIBRATE
- colestipol
- GEMFIBROZIL
- LOVASTATIN
- NICOTINIC ACID
- probucol

### Respiratory Drugs

- ALBUTEROL
- beclomethasone
- CROMOLYN SODIUM
• EPINEPHRINE
• flunisolide
• IPRATROPIUM BROMIDE
• isoproterenol sulfate
• metaproterenol
• nedocromil
• oxymetazoline
• phenylephrine
• pseudoephedrine
• salmeterol
• TERBUTALINE
• THEOPHYLLINE
Chemotherapy Drug List

PRIMARY DRUGS - All capital letters
SECONDARY DRUGS - Small letters


Antimicrobial Agents

Penicillins

Narrow spectrum Penase-sensitive

- Pen G
- PEN V (or Penicillin V with K)

Narrow spectrum Penase-resistant (S. aureus)

- NAFCILLIN (parenteral & oral)
- OXACILLIN (parenteral & oral)
- cloxacillin (oral)

Broad spectrum (aminopenicillins)

- AMOXICILLIN
- AMPICILLIN
Primarily antipseudomonal

- TICARCILLIN
- CARBENICILLIN

Extended spectrum

- PIPERACILLIN

Amidopenicillins

- Mecilliman

Penicillin plus penicillinase inhibitor

- Amoxicillin plus clavulanic acid (combination is Augmentin)
- tricardillin plus clavulanic acid (combination is Timentin)

Cephalosporins

First generation

- CEFADROXIL (oral)
- CEPHALOTHIN (parenteral)
- CEPHALEXIN (oral)

Second generation

- CEFOXITIN (parenteral)
- CEFACLOR (oral)

Third generation

- CEFTRIAXONE
- CEFTAZIDIME

Vancomycin; Teicoplanin

Inhibitors of Protein Synthesis
Aminoglycosides
- GENTAMICIN
- TOBRAMYCIN
- AMIKACIN
- NETILMICIN

CHLORAMPHENICOL
ERYTHROMYCIN
CLINDAMYCIN

Tetracyclines
Short acting
- TETRACYCLINE
- CHLORTETRACYCLINE
- OXYTETRACYCLINE

Long acting
- DOXYCYCLINE
- MINOCYCLINE

Antimetabolites
Inhibitors of DNA synthesis
- Norfloxacin
- Ciprofloxacin

Sulfonamides
Best urine solubility
- SULFASOXAZOLE
- SULFACYTINE
- SODIUM SULFACETAMIDE (ophthalmic use)

With Trimethoprim
• SULFAMETHOXAZOLE

Topical (burns)

• SILVER SULFADIAZINE

TRIMETHOPRIM

• Use as TRIMETHOPRIM - SULFAMETHOXAZOLE combo.

Pyrimethamine

• Use as PYRIMETHAMINE - SULFADOXINE combo. (Fansidar) for malaria

Urinary Tract Antiseptics

• NALIDIXIC ACID   • CIPROFLOXACIN   • NITROFURANTOIN

Cationic Surfactants

• POLYMIXIN B

Drugs for Anaerobic Bacteria Only

• Metronidazole

Antimycobacterial Drugs

• ISONIAZID   • ETHAMBUTOL   • RIFAMPIN
• STREPTOMYCIN   • DAPSONE
Antifungal Drugs

Polyenes
- AMPHOTERICIN B
- NYSTATIN

Imidazoles
- KETOCONAZOLE (oral)
- MICONAZOLE (topical)
- FLUCYTOSINE
- FLUCONAZOLE
- Griseofulvin
- Itraconazole

Antiviral Drugs
- AMANTIDINE (Influenza prophylaxis only)
- VIDARABINE
- ZIDOVUDINE
- GANCICLOVIR
- ACYCLOVIR
- ribavirin
- dideoxyinosine

Antiparasitic Drugs

Antimalarial
- CHLOROQUINE
- MEFLOQUINE
- PRIMAQUINE
- PYRIMETHAMINE-SULFASOXINE (Fansidar)
- Quinine

Antiprotozoal Drugs
Amebiasis and Trichomonas

- METRONIDAZOLE

Pneumocystis

- TRIMETHOPRIM - SUFAMETHOXAZOLE
- pentamidine

Toxoplasmosis

- PYRIMETHAMINE - sulfonamides combo

Antihelminthic Drugs

Flatworms

- PRAZIQUANTEL

Fluke and Tapeworm Infections

Schistosomiasis

Fascioliasis (liver, intestinal and lung flukes)
Tapeworms

Filariasis

- Thiabendazole

Intestinal Roundworms

Ascaris

- mebendazole
Enterobius (Pinworm)

Trichuris (Whipworm)

Hookworm

- PYRANTEL PAMOATE

Anticancer Drugs and Immunosuppressives


Alkyating Agents

- MECHLORETHAMINE
- Nitrosoureas (carmustine, lomustine)

Antimetabolites

- METHOTREXATE
- Cytosine arabinoside
- 6-MERCAPTOPURINE
- 5-Fluorouracil

Natural Products

- Dactinomycin
- BLEOMYCIN
- DAUNORUBICIN
- mitomycin C
- DOXORUBICIN
- ETOPOSIDE (VP-16)

Antimitotics

- VINCristINE
- VINBLASTINE
- palcitaxel

Miscellaneous

- HYDROXYUREA
- CISPLATIN
- asparaginase
- Interferon
- Amsacrine

**Hormones**

- Estrogens
- Anti-estrogen (TAMOXIFEN)
- flutamide
- leuprolide
- PREDNISONE
- goserelin

**Immunosuppressives**

- azathioprine
- CYCLOSPORIN A
- FK506
Endogenous Agents

- ACETYLCHOLINE (ACH)
- ADENOSINE TRIPHOSPHATE (ATP)
- ASPARTATE (Asp)
- Beta-Amyloid
- BRADYKININ
- DOPAMINE (DA)
- Beta-endorphin
- NOREPINEPHRINE
dynorphins
- Beta-endorphin
- met-enkephalin
- leu-enkephalin
- 5-HYDROXYTRYPTAMINE (5HT)
- GAMMA-AMINOBUTYRIC ACID (GABA)
- GLUTAMATE (glu)
glycine
- HISTAMINE
- Nerve Growth Factor (and other growth factors)
- substance P

Inhalation and Intravenous Anesthesia
- ALFENTANIL
- HALOTHANE
- Methohexital
- MORPHINE
- SUFENTANIL
- ENFLURANE
- ISOFLURANE
- Methoxyflurane
- NITROUS OXIDE (N20)
- Etomidate fentanyl
- KETAMINE
- MIDAZOLAM
- PROPOFOL

**Local Anesthetics**

- BENZOCAINE
- Bupivacaine
- cocaine
- LIDOCAINE
- PROCAINE
- tetracaine

**Opioids**

**Agonists**

- CODEINE
- heroin
- METHADONE
- D-PROPOXYPHENE
- DIPHENOXYLATE
- Loperamide
- MORPHINE
- combinations - opioids plus acetaminophen and ASA
- fentanyl
- MEPERIDINE
- oxycodone

**Agonist/Antagonists and Antagonists**

- BUPRENORPHINE
- BUTORPHANOL
- l-alpha-acetyl-methadol
Antitussives, Expectorants and Mucolytics

- acetylcysteine
- ammonium chloride
- CODEINE
- DEXTROMETHORPHAN
- GUANIFENESIN
- HYDROCODONE

Drugs for Motor Disorders/Muscle Relaxants

- AMANTADINE
- BENZTROPINE
- cyclobenzaprine
- LEVODOPA (L-DOPA)
- TRIHEXYPHENIDYL
- BACLOFEN
- BROMOCRIPTINE
- CARBIDOPA
- DANTROLENE
- DOPAMINE
- Pergolide
- SELEGILINE

Antiepileptics

- acetazolamide
- DIAZEPAM
- Lamotrigine
- primidone
- carbamazepine
- ETHOSUXIMIDE
- PHENOBARBITAL
- VALPROIC ACID
- clonazepam
- Gabapentin
- PHENYTOIN
- vigabatrin

Hallucinogens
• atropine
• scopolamine
• LYSERGIC ACID DIETHYLAMIDE (LSD)

• MARIJUANA
• MDMA
• MESCALINE

• PHENCYCLIDINE (PCP)
• dronabinol (delta-9 THC)

Mood Disorders

Antidepressants

• AMITRIPTYLINE
• clomipramine
• desipramine
• doxepin
• FLUOXETINE
• IMIPRAMINE
• maprotiline
• NORTRIPTYLINE
• PAROXETINE
• phenelzine
• SERTRALINE
• trazodone
• TRANYLCYPROMINE

Antimanic drugs

• LITHIUM CARBONATE
• carbamazepine
• Valproic acid

Antipsychotics

• CHLORPROMAZINE (CPZ)
• CLOZAPINE
• FLUPHENAZINE
• HALOPERIDOL
• RISPERIDONE
• THIORIDAZINE
• trifluoperazine
• thiothixene

Sedative-Hypnotics
• alprazolam  • chloral hydrate  • diphenhydramine  
• FLURAZEPAM  • lorazepam  • oxazepam  
• paraldehyde  • pentobarbital  • TEMAZEPAM  
• TRIAZOLAM  • ZOLPIDEM

**Amphetamines, Anorexogenics and CNS Stimulants**

• AMPHETAMINE  • CAFFEINE  • COCAINE  
• EPHEDRINE  • fenfluramine  • METHAMPHETAMINE  
• METHYLPHENIDATE  • phentermine

**Anxiolytics**

**Benzodiazepines**

• ALPRAZOLAM  • chlorazepate  • CHLORDIAZEPOXIDE  
• DIAZEPAM  • FLUMAZENIL  (antagonist)  • LORAZEPAM  
• OXAZEPAM

**Non-Benzodiazepine**

• BUSPIRONE

**Ethanol and Alcoholism**
Drugs of Abuse and Dependence

- AMPHETAMINES/METHAMPHETAMINE
- BUFOTENIN
- COCAINE
- DIAZEPAM
- ETHANOL
- Glutethimide
- HEROIN
- LSD
- Organic solvents
- MARIJUANA/THC
- NICOTINE
- PENTOBARBITAL
- PHENCYCLIDINE

Drugs for Migraine

- butorphanol
- CAFFEINE
- calcium channel blockers
- CLONIDINE
- ERGOTAMINE
- 5-Hydroxytryptamine (5-HT)
- METHYSERGIDE
- norepinephrine (NE)
- PROPRANOLOL
- PROSTAGLANDINS (carboprost, tromethamine, dinoprostone, dinoprost)
## Diuretics and Renal Drug List

<table>
<thead>
<tr>
<th>PRIMARY DRUGS</th>
<th>SECONDARY DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetazolamide</td>
<td>AMILORIDE</td>
</tr>
<tr>
<td>chlorthalidone</td>
<td>demeclocycline</td>
</tr>
<tr>
<td>dopamine</td>
<td>ethacrynic acid</td>
</tr>
<tr>
<td>HYDROCHLOROTHIAZIDE</td>
<td>mannitol</td>
</tr>
<tr>
<td>spironolactone</td>
<td>TRIAMTERENE</td>
</tr>
<tr>
<td></td>
<td>bumetanide</td>
</tr>
<tr>
<td></td>
<td>DESMOPRESSIN ACETATE (DDAVP)</td>
</tr>
<tr>
<td></td>
<td>FUROSEMIDE</td>
</tr>
<tr>
<td></td>
<td>POTASSIUM CHLORIDE (e.g. Slow K)</td>
</tr>
</tbody>
</table>
Endocrine Drug List

[Primary Drugs - All capital letters]

[Secondary Drugs - Small letters]


**Pituitary-Hypothalamic Drugs**

- arginine vasopressin
- corticotropin releasing hormone (CRH)
- GONADOTROPIN RELEASING HORMONE
- hCG
- OXYTOCIN
- OCTREOTIDE (synthetic somatostatin octapeptide)
- BROMOCRIPTINE
- DESMOPRESSIN ACETATE
- cortisol (ACTH)
- gonadorelin
- GROWTH HORMONE
- hMG
- Prolactin
- growth hormone releasing hormone
- levodopa
- LEUPROLIDE

**Adrenocorticoids**

- aldosterone
- beclomethasone
- aminoglutethimide
- betamethasone
- angiotensin (I, II & III)
- DEXAMETHASONE
• FLUDROCORTISONE  • flucinonide  • HYDROCORTISONE (cortisol)
• ketoconazole  • METYRAPONE
• PREDNISONE
• triamcinolone

**Sex Hormones**

• CLOMIPHENE  • CONJUGATED ESTROGENS (premarin, estrone, equilin)
• danazol  • cyproterone acetate
• ESTRADIOL (in salts-benzoate, valerate, cypionate)  • DESOGESTROL
• FINASTERIDE  • ETHINYL ESTRADIOL
• ketoconazole  • ethynodiol
• methyltestosterone  • FLUTAMIDE
• methyltestosterone  • megestrol acetate
• methyltestosterone  • mestranol
• OXANDROLONE  • NORGESTREL
• RU-486, mifepristone  • TAMOXIFEN TESTOSTERONE-salts (propionate, heptanoate, cypionate)

**Thyroid/Parathyroid Drugs**

• alendronate  • calcium carbonate and  • calcitonin
other salts

- calcitriol (1,25 dihydroxy Vitamin D3)
- liothyronine sodium (T3)
- parathyroid hormone
- radioactive iodide

etidronate disodium, pamidronate, fluoride

methimazole

POTASSIUM IODIDE

thyrotropin stimulating hormone (TRH)

LEVOTHYROXINE SODIUM

mithramycin

PROPYLTHIOURACIL

triiodothyronine (T3)

Insulins/Oral Hypoglycemic Drugs

- acarbose
- GLIPIZIDE
- humulins (L,N,R)
- METFORMIN
- tolbutamide

- ACETOHEXAMIDE
- glucagon
- insulin zinc (lente, semi-lente)
- somatostatin

EXTENDED ZINC INSULIN (ultra-lente)

GLYBURIDE

LEU PRO INSULIN (fast acting)

tolazamide

Uterine Drugs

- carboprost
- EICOSANOIDs
- NAPROXEN
- terbutaline

- DINOPROST
- ERGONOVINE MALEATE
- OXYTOCIN

- dinoprostone
- MAGNESIUM SULFATE
- ritodrine
Gastrointestinal Drug List

PRIMARY DRUGS - All capital letters
SECONDARY DRUGS - Small letters


Gastric Antacid/Secretory/Antisecretory Drugs

- ALUMINUM HYDROXIDE
- CIMETIDINE
- METOCLOPRAMIDE
- RANITIDINE
- ATROPINE
- famotidine
- MISOPROSTOL
- SUCRALFATE
- calcium carbonate
- MAGNESIUM HYDROXIDE
- OMEPRAZOLE

Laxatives and Antidiarrheal Drugs

- bisacodyl
- lactulose
- methylcellulose
- bismuth subsalicylate
- LOPERAMIDE
- phenolphthalein
- diphenoxylate docusate (dioctyl sodium sulfosuccinate)
- MAGNESIUM HYDROXIDE

Therapy of H. pylori infection
• bismuth subsalicylate  • clarithromycin  • amoxicillin
• tetracycline  • metronidazole

**Anti-inflammatory Drugs**

• mesalamine  • sulfasalazine  • prednisone
Toxic Chemical and Antidotes Drug List

- ACETAMINOPHEN
- N-ACETYL-L-CYSTEINE
- ACTIVATED CHARCOAL
- amyl nitrite
- arsenic
- CARBON MONOXIDE
- cyanide
- DEFEROXAMINE
- DIG-SPECIFIC ANTIBODY FRAGMENTS
- dimercaprol
- 2,3-DIMERCAPTOSUCCINIC ACID
- edetate
- ETHANOL
- ethylene glycol
- GLUCAGON
- IPECAC
- IRON
- LEAD
- methanol
- methylene blue
- NALOXONE
- organophosphates
- pralidoxime
- SALICYLATES
- SODIUM BICARBONATE
- sodium nitrite
- sodium thiosulfate
- TRICYCLIC ANTIDEPRESSANTS
### Vitamins Drug List

- **ASCORBIC ACID**
- **CYANOCOBALAMIN**
- **FOLIC ACID**
- **NICOTINAMIDE**
- **NICOTINIC ACID**
- **VITAMIN A**
- **VITAMIN D**
- **vitamin E**
- **VITAMIN K**
- **+TRETINOIN**