Introduction To Pharmacology

(Lecture)

OBJECTIVES

- Describe how the size, shape and chemical nature of a drug affects its pharmacodynamic and pharmacokinetic properties.
- Explain how the presence of an asymmetric carbon affects a drug's pharmacologic action.
- Describe important differences between an agonist and a competitive pharmacologic antagonist that bind to the same receptor.
- Compare and contrast the common routes of drug administration.
- Name and define the two major processes that allow a drug to travel from its site of administration to its site of action.
- Explain why a hydrophobic drug is more likely than a hydrophilic drug to rely upon metabolism for elimination.
- Outline the system of drug regulation and the process for approval of new drugs in the US.
- Explain the difference between a generic and proprietary drug.

KEY WORDS

absorption
agonist
blood-brain barrier
DEA
distribution
drug metabolism
elimination
enantiomer
FDA
first pass effect
formulation
generic drug
hydrophilic
hydrophobic
lipophilic
OTC drug
parenteral administration
pharmacodynamics
pharmacokinetics
pharmacologic antagonist
proprietary drug
racemic mixture
receptor
schedule of controlled drugs
selectivity
teratogen
toxicology

REQUIRED READING

Chapter 1, *Basic and Clinical Pharmacology,* 9th edition. In Chapter 1, the sections that are most important include "The Nature of Drugs", "Drug-Body Interactions", "Pharmacodynamic Principles", and "Pharmacokinetic Principles". The topics of drug permeation and ionization of weak acids and weak bases, which are addressed in Chapter 1 of the textbook, will be covered by Dr. Fulton. Dr. Fulton also will expand on drug reactivity and drug-receptor bonds.

Chapter 5, *Basic and Clinical Pharmacology,* 9th edition. Read the first section on p. 64, and the section entitled "The Food & Drug Administration" on pp. 69-71. Look over Figure 5-1 on p. 65 and read through Table 5-4 on p. 70.

Chapter 66, *Basic and Clinical Pharmacology,* 9th edition. Read the sections entitled "Legal Factors (USA)", "Who May Prescribe", and "Socioeconomic Factors" on pp. 1096-1100.

RECOMMENDED READING

Prilosec, Nexium and Stereoisomers. Med Lett Drugs Ther. 2003 Jun 23;45(1159):51-2. Available on iROCKET.

I. OVERVIEW

In the Prologue Block, the basic principles of pharmacology are covered in 5 lectures and 3 small group exercises. This lecture presents an overview of medical pharmacology while the subsequent lectures delve more deeply into the two major divisions of pharmacology – pharmacodynamics and pharmacokinetics. In addition, Dr. Fulton will address principles of drug action in her sessions.

The purpose of this syllabus section is to outline major topics, guide your study of the assigned reading in the textbook, and present information that is not covered in the assigned reading.

II. GENERAL DEFINITIONS

A. Pharmacology is the study of the interaction of chemicals with living systems.

B. Drugs are chemicals that act on living systems at the chemical (molecular) level.

C. Medical pharmacology is the study of drugs used for the diagnosis, prevention, and treatment of disease.

D. Toxicology is the study of the untoward effects of chemical agents on living systems. It is usually considered an area of pharmacology.

E. Pharmacodynamic properties of a drug describe the action of the drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.

F. Pharmacokinetic properties describe the action of the body on the drug, including absorption, distribution, metabolism, and excretion. Elimination of a drug may be achieved by metabolism or by excretion.

III. THE NATURE OF DRUGS

A. Size. The great majority of drugs lie in the range from molecular weight 100 to 1,000. Drugs in this range are large enough to allow selectivity of action and small enough to allow adequate movement within the various compartments in the body.

B. Chemistry and reactivity. Drugs may be small, simple molecules (amino acids, simple amines, organic acids, alcohols, esters, ions, etc.), carbohydrates, lipids, or even proteins. Binding of drugs to their **receptors**,

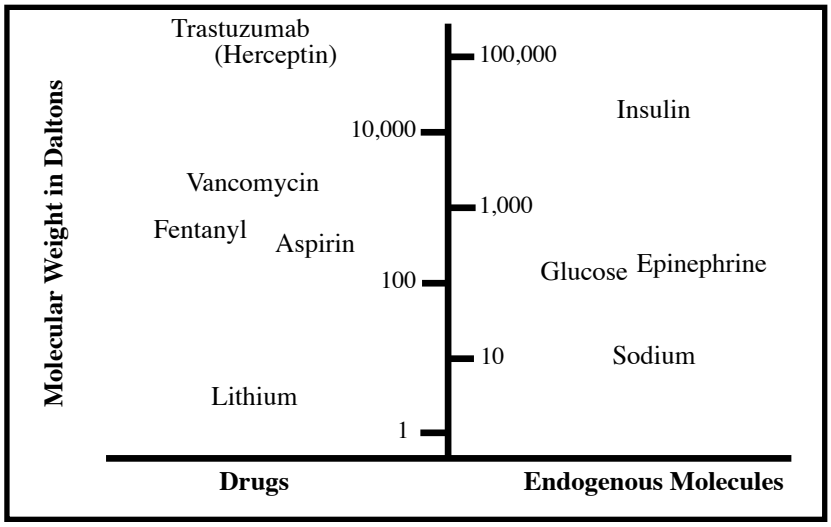

Figure 1. *Molecular weights of several endogenous molecules and drugs. Lithium is used to treat people with psychiatric disorders, fenanyl is a opioid analgesic and trastuzumab is an antibody used to treat women with breast cancer.*

the specific molecules in a biologic system that mediate drug effects, is usually by noncovalent bonds (hydrogen bonds, van de Waals attractions, and ionic bonds), and less commonly by covalent bonds. Weaker, noncovalent bonds require a better fit of the drug to the receptor binding site and, usually, a reversible type of action. Very strong bonding, eg, covalent bonds, usually involves less selectivity and an irreversible interaction.

C. Shape. The overall shape of a drug molecule is important for the fit of the drug to its receptor. Between a quarter and a half of all drugs in use exist as stereoisomers. In most cases the stereoisomers are chiral **enantiomers**. Enantiomers are mirrored image twin molecules that result from the presence of an asymmetric carbon, or in a few cases, other asymmetric atoms in their structures. Chiral enantiomers often differ in their ability to bind to and alter the function of receptors. They also can differ in their rates of elimination and in their toxicity. Most chiral drugs are still provided as

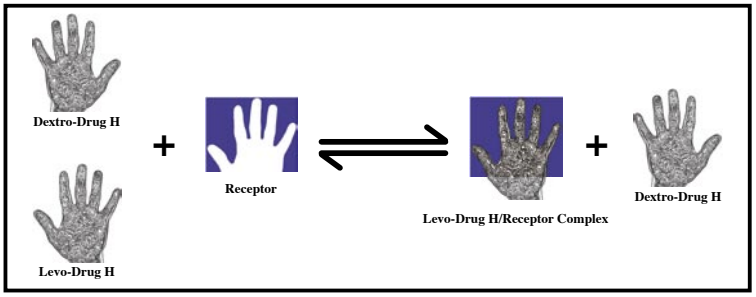

Figure 2. *The two hands represent the enantiomers of Drug H. The shape of the Levo enantiomer allows it to bind tightly to the drug-binding site in the receptor. Note that this binding is reversible.*

racemic mixtures (mixtures of isomers) because it is expensive to separate the stereoisomers. In the past, little was known about the relative activity of stereoisomers. However, the Food and Drug Administration (FDA) now requires information about the structure and activity of each isomer present in a racemic mixture of a new medication.

Is it clinically beneficial to separate stereoisomers? There are not a lot of clinical data to help answer this question. However, for most of the drugs that have been investigated, it appears that purified stereoisomers have only modest or no benefit over racemic mixtures. This question is important because in recent years, several drug companies have marketed a stereoisomer of a racemic mixture just as the patent on the racemic mixture expired. The steroisomer is a "new drug" and enjoys more years of patent protection, which generally means that it is more expensive than the older racemic mixture. For more information on this topic, see the Medical Letter article entitled Prilosec, Nexium and Stereoisomers, available on iROCKET.

IV. INTRODUCTION TO PHARMACODYNAMICS

A. Concentration-Response. A fundamental principle of pharmacology is that a relationship exists between the concentration of a drug at its site of action and its beneficial or toxic action. The reliance of pharmacodynamic effects upon drug concentration provides the key link between pharmacokinetics and pharmacodynamics for **it is the action of the body upon a drug that determines its concentration at its site of action**.

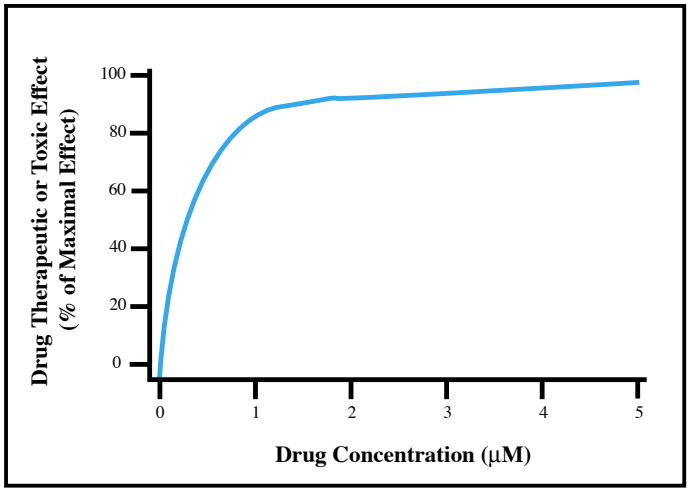

Figure 3. *The therapeutic and toxic effects of drugs are determined by their concentration in the vicinity of drug receptors. At high concentrations, effects plateau and further increases in drug concentration do not produce greater effects.*

B. Properties of Drug Receptors. Most receptors are proteins (eg, enzymes, hormone and neurotransmitter receptors); in addition, some DNA and RNA molecules serve as drug binding targets. A successful receptor must distinguish between different ligands. That is, it must bind selectively to certain ligands. In many cases, drugs bind to a site on a protein that normally binds to an endogenous small molecule or protein.

C. Types of Drug-Receptor Interactions. When a drug activates a receptor that it binds to, the drug is an **agonist**. Most agonists mimic the effects of small molecules or proteins that serve as endogenous regulators of the receptor to which the drug binds. **Pharmacologic antagonists** have the

Drug	Clinical Use	Drug Receptor	Type of Molecule
Albutolol	Asthma	Neurotransmitter receptor	Protein on cell surfaces
Penicillin	Infection	Bacterial enzyme	Secreted bacterial protein
Digoxin	Congestive heart failure	Na,K-ATPase	Protein transporter on cell surfaces
Lidocaine	Local anesthesia	Voltage-gated sodium channels	Protein ion channel on cell surfaces
Cyclophosphamide	Cancer	DNA	Nucleic acid

Table 1. *Examples of different types of endogenous molecules that serve as receptors, or targets, of drugs.*

opposite effect. That is, they prevent the effect of endogenous agonists on the function of the receptor. Most of the time, a pharmacologic antagonist binds to the same site as an agonist and competes with the agonist for binding to a critical site on the receptor. Pharmacologic antagonists have two important properties.

1. In the absence of an agonist, they do not elicit a biologic response.

2. The effects of a competitive pharmacologic antagonist can be overcome by adding more agonist.

D. Graphical Representation of Concentration-Effect Relationships.

The relationship between drug concentration and receptor binding, and drug concentration and pharmacodynamic effect can best be understood through the use of graphical representations such as shown in Figure 3. In the "Drug-Receptor Interactions" session later in Prologue, you will learn to construct concentration-response graphs and use these graphs to make inferences about the pharmacodynamic effects of drugs.

V. INTRODUCTION TO PHARMACOKINETICS

Pharmacokinetics concerns the effects of the body on the administered drug. It can be pictured as the processes of **absorption**, **distribution**, and **elimination**. Elimination includes both **metabolism** and **excretion**. All of these processes

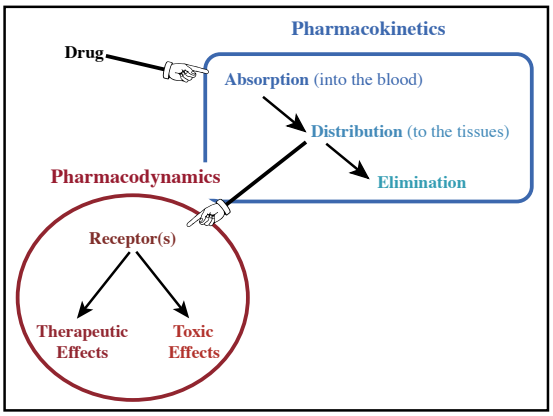

Figure 4. *Drugs are absorbed from their sites of administration into the blood, distributed via the blood to the tissues and then eliminated. The concentrations of drugs at their sites of interaction with receptors is determined by these pharmacokinetic properties. Concentration-dependent interaction with receptors produces therapeutic and toxic effects.*

involve movement of drug molecules through various body compartments and across the barriers separating those compartments.

A. Absorption of Drugs. Drugs usually enter the body at sites remote from the target tissue and are carried by the circulation to the intended site of action. Before a drug can enter the bloodstream, it must be absorbed from its site of administration. The rate and efficiency of absorption differs depending on the route of administration. Common routes of administration of drugs and some of their features include:

1. **Oral** (swallowed). Maximum convenience but may be slower and less complete than parenteral (non-oral) routes. Dissolution of solid formulations (eg, tablets) must occur first. The drug must survive exposure to stomach acid. This route of administration is subject to the first pass effect (metabolism of a significant amount of drug in the gut wall and the liver, before it reaches the systemic circulation).

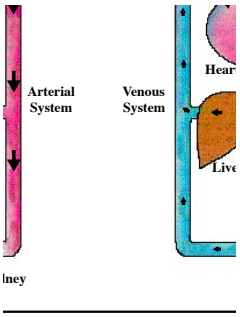

Figure 5. *In this figure, the size of the "drug" arrows represents the drug concentration in that part of the body. The drug represented in (A) does not undergo first pass metabolism whereas the drug represented in (B) undergoes significant first pass metabolism.*

2. **Sublingual** (under the tongue). Permits direct absorption into the systemic venous circulation thus avoiding the first pass effect. May be fast or slow depending on the physical formulation of the product. Nitroglycerin is administered by this route in the treatment of angina.

3. **Rectal** (suppository). Same advantage as sublingual route; larger amounts are feasible. Useful for patients who cannot take oral medications (eg, because of nausea and vomiting).

4. **Intramuscular**. Absorption is sometimes faster and more complete than after oral administration. Large volumes (eg, 5 - 10 mL) may be given. Requires an injection. Generally more painful than subcutaneous injection. Vaccines are usually administered by this route.

5. **Subcutaneous**. Slower absorption than intramuscular. Large volumes are not feasible. Requires an injection. Insulin is administered by this route.

6. **Inhalation**. For respiratory diseases, this route deposits drug close to the target organ; when used for systemic administration (e.g., nicotine

in cigarettes, inhaled general anesthetics) it provides rapid absorption because of the large surface area available in the lungs.

7. **Topical**. Application to the skin or mucous membrane of the nose, throat, airway, or vagina for a local effect. It is important to note that topical drug administration can result in significant absorption of drug into the systemic circulation. Drugs used to treat asthma are usually administered this way.

8. **Transdermal**. application to the skin for **systemic** effect. Transdermal preparations generally are patches that stick to the skin and are worn for a number of hours or even days. To be effective by the transdermal route, drugs need to be quite lipophilic. Nicotine is available as a transdermal patch for those who are trying to stop cigarette smoking.

9. **Intravenous.** Instantaneous and complete absorption (by definition, 100%); potentially more dangerous because the systemic circulation is transiently exposed to high drug concentrations.

B. Distribution of Drugs. The distribution of drugs from the site of absorption, through the bloodstream and to the target tissue depends upon:

1. The **blood flow** to the tissue is important in the rate of uptake of a drug. Tissues that receive a high degree of blood flow (eg, brain, kidney) have a fast rate of uptake whereas tissues with a low degree of blood flow (eg, adipose tissue) accumulate drug more slowly.

2. **Solubility** of the drug in the tissue. Some tissues, eg, **brain**, have a high lipid content and dissolve a higher concentration of lipophilic agents.

3. **Binding** of the drug to macromolecules in the blood or tissue limits their distribution.

4. The **ability to cross special barriers.** Many drugs are poorly distributed to the brain and the testis because these tissues contain specialized capillaries (the smallest type of blood vessel). The endothelial cells that line these capillaries form a **blood-brain barrier** and a blood-testis barrier by preventing the movement of hydrophilic molecules out of the blood and into the tissue, and by actively pumping lipophilic molecules out of the endothelial cell and into the blood.

   Of special concern is the ability of drugs to distribute to breast milk in lactating women, and the ability of drugs to cross the **placenta** (the specialized tissue connecting a pregnant woman and her fetus) and affect the developing fetus. A number of drugs are known to be **teratogens** (drugs that cause abnormal fetal development) and should be avoided in pregnancy. Women taking drugs that are considered unsafe for infants and that achieve appreciably high concentrations in breast milk should not breast-feed their infants. Information about the safety of drugs in

pregnancy and breast-feeding is available in many textbooks, guidebooks and electronic drug databases.

C. Elimination of Drugs. The rate of elimination (disappearance of active drug molecules from the bloodstream or body) is almost always related to termination of pharmacodynamic effect. Therefore, knowledge of plasma concentrations of a drug is important in describing the intensity and duration of a drug's effect. There are two major routes of elimination:

1. Excretion. The most common route for drug excretion is through the kidney and out of the body in the urine. To be excreted by the kidney, drugs need to be reasonably hydrophilic so that they will remain in the fluid that becomes the urine. Patients with impaired kidney function usually have a reduced ability to eliminate hydrophilic drugs. To avoid excessively high drug concentrations in these patients, you will need to reduce their dosages or give dosages less frequently. A few drugs enter the bile duct and are excreted in the feces.

2. Metabolism. The action of many drugs, especially lipophilic compounds, is terminated by enzymatic conversion, or metabolism, to biologically inactive derivatives. In most cases, the enzymatic conversion forms a more hydrophilic compound that can be more readily excreted in the urine. Most of the enzymes that catalyze drug-metabolizing reactions are located in the gastrointestinal tract and the liver. Some drugs inhibit drug-metabolizing enzymes and thus cause drug-drug interactions when co-administered with drugs that depend upon metabolism for elimination.

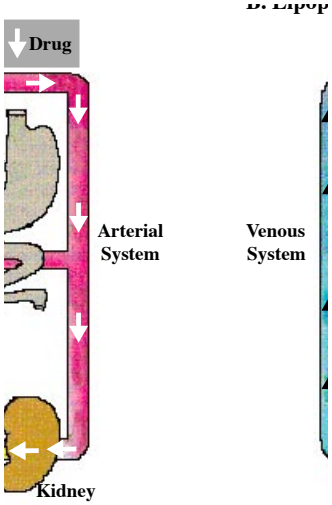

Figure 6. *Hydrophilic drugs (A) are usually eliminated by renal excretion. They remain in the fluid that becomes urine because they cannot easily cross the membranes of cells that line the tubules in the kidney. Lipophilic drugs can cross the membranes of cells that line the tubules in the kidney. They slip back into the blood and recirculate. They usual require metabolism, a process that makes them more hydrophilic and usually also destroys their pharmacologic activity, for elimination.*

D. Pharmacokinetic Calculations. Models of drug distribution and elimination plus actual data based on clinical trials in which drugs were administered to healthy volunteers and patients allow the measurement of pharmacokinetic parameters. These parameters are used to calculate appropriate dosages. In subsequent lectures and a small group exercise, you will learn about these pharmacokinetic parameters and begin to use them to calculate drug dosages.

VI. INTRODUCTION TO DRUG REGULATION IN THE US

A. Regulatory Oversight. It is interesting to note that prior to 1906, there was no federal regulation of the sale of drugs in the US. Such regulation was left to the states, which, until late in the 1800s, mostly chose not to have controls. As a result, basically anyone could sell anything, including products containing cocaine or opioids (eg, morphine) and could freely advertise outrageous claims of benefit and safety. In spite of strong resistance by pharmaceutical companies, the federal government in 1906 initiated the first in a series of progressively stronger laws intended to ensure the effectiveness and safety of drugs sold in the US. (See Table 5-4 in the *Basic and Clinical Pharmacology* textbook for a list of the major laws affecting drug regulation.)

Today, the **Food and Drug Administration** (**FDA**) is responsible for approval of new drugs and oversight of the marketing and sale of drugs already on the market. This includes both **prescription** drugs and **over-the-counter** (**OTC**) drugs (drugs that do not require a prescription). However, you should note that the FDA **does not** have much authority over "dietary supplements", which include vitamins, amino acids, mineral and herbal medication, even though most of these products have significant pharmacologic activity. The **Drug Enforcement Agency** (**DEA**) also has jurisdiction over drugs. The DEA classifies drugs into one of 5 "schedules" on the basis of their potential for abuse (habitual use of a drug not needed for a therapeutic effect). There are special restrictions upon the prescription of drugs assigned to Schedules I-IV; most drugs are assigned to Schedule V and lack special DEA restrictions. You will learn more about scheduling of drugs in the Brain, Mind and Behavior (BMB) block and can see examples of scheduled drugs on the inside of the front cover of your *Basic and Clinical Pharmacology* textbook. The states also participate in the process of drug regulation primarily by controlling the licensing of health professionals who can write drug prescriptions. In California, physicians, dentists, podiatrists and veterinarians write prescriptions. In addition, nurse practitioners, physician's assistants, optometrists and pharmacists have limited prescribing authority.

B. The Drug Approval Process. The approval process for new drugs, especially drugs that are the first in a wholly new chemical class (as opposed to "me-too" drugs that are only slightly different from a previously-approved drug), is complex, time-consuming and expensive (to the tune of $100-$500 million dollars per new drug). Once a promising new candidate is identified, it is tested in *in vitro* systems and experimental animals (see Figure 5-1 on p. 65 of the textbook). Drugs that still look promising after these **preclinical studies** are approved by the FDA for testing in **clinical trials** first in

healthy people and then in people with the target disease. These clinical trials are used to evaluate safety and effectiveness. If the FDA decides that the drug still looks good after three phases of clinical trials, the manufacturer receives approval to market the drug. It is important that the manufacturer and the FDA continue post-marketing surveillance of new drugs because of

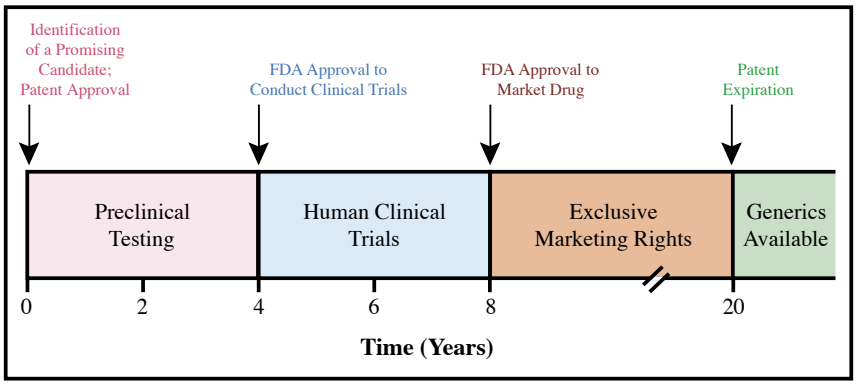

Figure 7. *Stages of the drug approval process and approximate time for each stage.*

the risk of toxicity that occurs rarely enough so it is not detected in the initial small clinical trials.

C. Patent Protection and Generic Drugs. A company usually patents new chemicals early in the drug discovery process. US patents provide 20 years of protection. However, the drug approval process takes 6-8 years or even longer so the actual time after FDA approval that a drug is marketed with exclusive rights is much less than 20 years. The government recognizes this problem and has given the FDA the ability to provide "extensions" so that a drug can have at least 5 years of patent protection after FDA approval but no more than 14 years. Economically, this is important because once a patent expires, other companies can sell a **generic drug**, which is an exact copy of a proprietary drug. The process for approval by the FDA of a generic drug is much less cumbersome and expensive than the process for approval of a new drug. Basically, the maker of a generic product just needs to show that their drug has the same pharmacokinetic properties as the proprietary drug. Generic products usually cost significantly less than trade-named products; in some cases, the difference in price can be as much as 50-fold! Since pharmaceutics consume over 10% of all medical costs in the US and is the sector that is growing most rapidly, the government, consumers and administrators of managed care organization are anxious to promote the use of generic products in an effort to control pharmaceutical costs.

D. Nomenclature. Every drug has at least three names - a chemical name (e.g. 6-dimethylamino-4,4-diphenyl-3-heptanone hydrochloride), a generic name (e.g., methadone hydrochloride) and a proprietary (or **trade**) name

(e.g., Dolophine). Chemical and generic names are written in lower case whereas trade names are capitalized. In Essential Core and USMLE exams, generic drug names are used. However, you will soon find that by health professionals and patients mostly use proprietary names so eventually you will become familiar with both types of names. One reason for the popularity of proprietary names is that they are quite "catchy". After all, pharmaceutical companies put great effort into designing memorable names for their drugs and prominently displaying those names on everything imaginable —from pens to billboards. You can find proprietary names in the list of drugs at the back of each chapter and in the index in your *Basic and Clinical Pharmacology* textbook. When you are working in clinical situations, you will find it handy to have a copy of Epocrates (freely down-loadable; see iRocket for a link), if you have a handheld computer. Alternatively, the *Tarascon Pocket Pharmacopoeia*, a tiny handbook available for about $8 in the bookstore, has proprietary names as well as a wealth of practical prescribing information.

VII. SUMMARY

A. Most drugs have molecular weights in the range of 100-300 Daltons, and bind reversibly to their receptors.

B. Nearly all drug effects are concentration-dependent.

C. Most drug receptors are proteins.

D. The three main processes of pharmacokinetics are absorption of drug into the blood, distribution to the tissues and elimination by excretion or metabolism.

E. Lipophilic drugs usually are widely distributed and require metabolism for elimination.

F. Drugs are strictly regulated by the FDA and DEA.

G. The introduction of generic drugs almost always results in a dramatic lowering of the price of a drug.