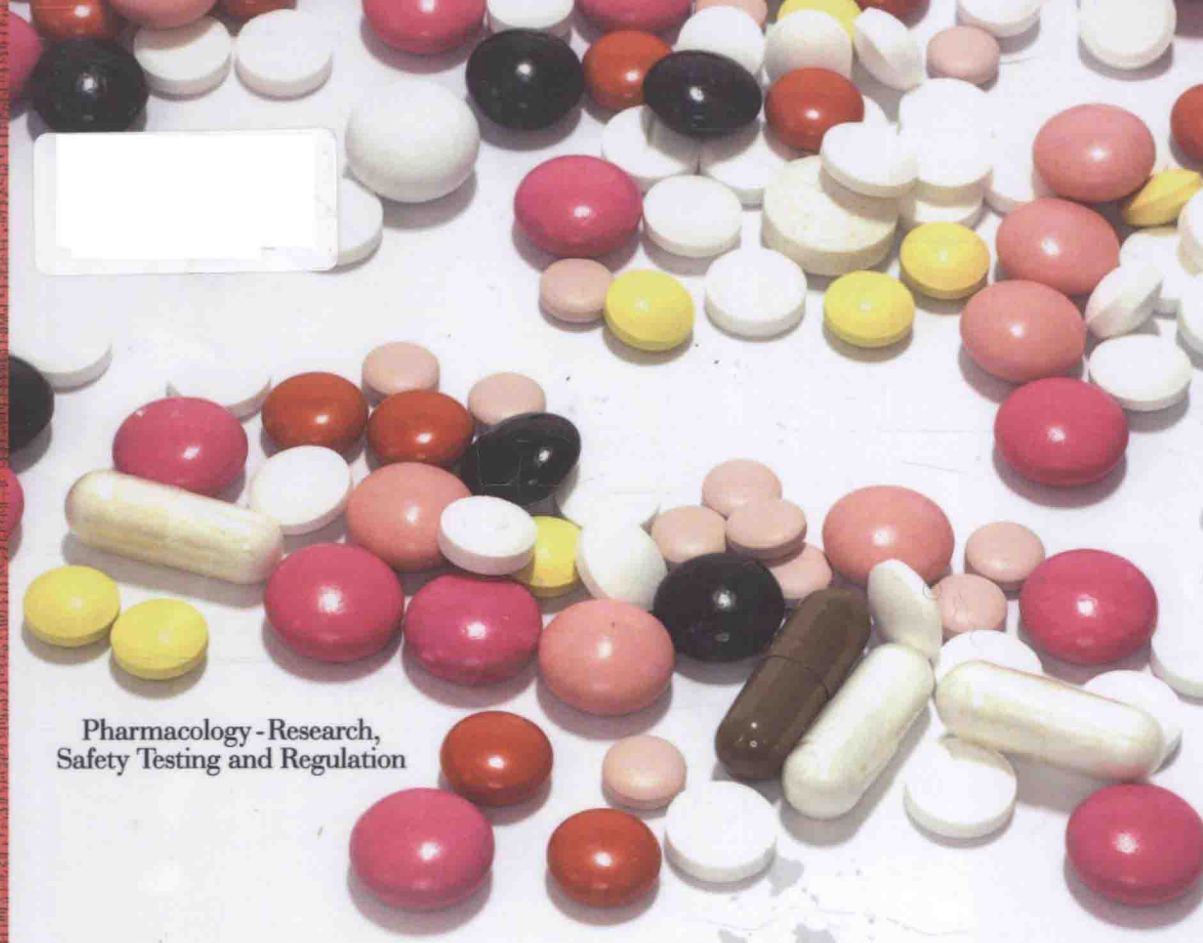

Nova Biomedical

Pharmacology - Research, Safety Testing and Regulation

Rafik Karaman
Editor

Commonly Used Drugs

Uses, Side Effects, Bioavailability and Approaches to Improve It

NOVA

PHARMACOLOGY - RESEARCH, SAFETY TESTING AND REGULATION

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Preface

Pharmacology is the science of medicine used in animals and humans. Many prescribed drugs are dispensed by pharmacists on a daily basis, and this is considered one of the most dangerous and important activities practiced by pharmacists. Comprehensive knowledge and critical understanding of the pharmacology principles which include the pharmacokinetics and pharmacodynamics of drugs is the solid basis for a safe and effective therapeutic practice.

The focus of this book is on providing comprehensive, authoritative, and readable chapters on classes of commonly used drugs for medical and pharmacy students, nurses, junior doctors, pharmacists and other allied professionals in the health sciences.

This book is a collaborative effort by the editor and some of his colleagues and graduate students as coauthors. The book is mainly devoted on describing the pharmacology, pharmacokinetics, uses, side effects and ways to improve the bioavailability for some of the most commonly used drugs.

The first chapter introduces a comprehensive overview on the definition of drugs, approaches of drugs classification and some important aspects of drugs design and development, drug effectiveness and safety, and drug errors.

The second chapter describes the three antibiotic classes, their mechanism of action, clinical uses, side effects, and their resistance by different bacteria. These described antibiotics include vancomycin, penicillins, cephalosporins, carbapenems tetracyclines, aminoglycosides, macrolides, chloramphenicol, fluoroquinolones and sulfonamides.

The third chapter discusses the current used medicines for treating pain. These medications include the non-steroidal anti-inflammatories (NSAIDs), acetaminophen and opiates and their combination.

The fourth chapter describes a number of drugs used to lower lipid levels in the blood such as statins, their adverse effects and methods to improve their bioavailability.

The fifth chapter is devoted to the description of the pathogenesis and types of diabetes and the current used drugs to treat this disease. In addition, a detailed description of the pharmacokinetic properties, mechanism of action, side effects of known anti-hyperglycemic agents is presented.

The sixth chapter describes the two different classes of anti-hemorrhagic agents (hemostatic agents): the first class includes systemic drugs such as tranexamic acid, ω-aminocaproic acid, anti-inhibitor coagulant complex-heat treated, anti-hemophilic factor, factor IX, carbazochrome, fibrinogen concentrate, oprelvekin and phylloquinone, and the

second class of hemostatic agent is the local acting agents such as cellulose, collagen, gelatin, thrombin and thrombin combination products.

The seventh chapter is devoted to osteoporosis (a progressive bone disease) and the various therapies available for treating this disease such as bisphosphonates, raloxifene, calcitonin, teriparatide and denosumab.

The last chapter is devoted to the description of two different autoimmune diseases; multiple sclerosis (MS) and psoriasis. Up to date there is no known cure for MS and psoriasis. The available treatments approved by the FDA are mainly considered symptom relieving drugs and their major therapeutic action is only to slow the disease progression, and they lack the ability to eliminate the disease completely. A great devotion in this chapter was given to discuss several aspects regarding fumarate acid esters including; pharmacokinetics, mode of action, recommendations and specifically their potential as an effective treatment for psoriasis and MS.

I want to express my sincere gratitude to all coauthors for their great efforts and cooperation. It has been a pleasure for me to be in the center of composing this nice piece of pharmacology book. I hope that this book will provide a succinct review of pharmacology with over 750 references. It is especially helpful to undergraduate and graduate students preparing for variety types of examinations.

Rafik Karaman, Ph.D.
Editor

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Chapter 1

Drug Overview

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Abstract

A drug is a chemical substance with known biological effects on humans or other animals. In the pharmacology field, a drug is defined as a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being. Drugs usually affect either normal or abnormal physiological processes. Drugs may be used for a limited duration, or on a regular basis for chronic disorders. The way drugs are classified or grouped are confusing. Therefore, a new approach of drugs classification is presented in this chapter along with general information on drugs which includes definition, drugs and diseases types, drugs administration, drugs interactions and drug names. In addition, the chapter describes some important aspects of drugs design and development, drug effectiveness and safety, and drug errors.

Keywords: Drugs, Disease, Drug classification, Drug administration, OTC drugs, Prescription drugs, Drug interactions, Drug safety

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADME	Absorption, Distribution, Metabolism and Excretion
AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredients
BCS	Biopharmaceutical Classification System
BP	Blood Pressure

BTC	Behind-the-Counter
CNS	Central Nervous System
CoA	Coenzyme A
COMT	Catechol O-Methyltransfarase
Cox-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
DDT	Dichlorodiphenyltrichloroethane
DMARDs	Disease- Modifying Antirheumatic Drugs
DNA	Deoxyribonucleic Acid
DPP-IV	Dipeptidyl Peptidase-IV
FDA	Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
GIT	Gastrointestinal Tract
HCl	Hydrochloric Acid
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme A
I.V	Intravenous Injection
IM	Intramuscular Injection
INR	*International Normalized Ratio*
IRB	Institutional Research Board
K_{cal}	Kilocalorie
LSD	Lysergic Acid Diethylamide
MAO	Monoamine Oxidases
MAOIs	Monoamino Oxidase Inhibitors
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OMAs	Organic Medicinal Agents
OTC	Over-the-Counter
POM	Prescription Only Medicines
R&D	Research and Development
RNA	Deoxyribonucleic acid
R_x	Medical Prescriptions
SAM	S-Adenosylmethionine
SAR	Structure Activity Relationships
Sc	Subcutaneous
SNRI	Serotonin Nonselective Reuptake Inhibitor
SSRIs	Selective Serotonin Reuptake Inhibitors
T_3	Triiodothyronine
T_4	Thyroxine
TCA	Tricyclic Antidepressant
TNF	Tumor Necrosis Factor

Drugs Definition

A drug is a chemical substance that has known biological effects on humans or other animals, used in the treatment, cure, mitigation, prevention, or diagnosis of disease or used to

enhance physical or mental well-being. Drugs may be used for a limited duration, or on a regular basis for chronic disorders. Drugs are generally taken to cure and/or relieve any symptoms of an illness or medical condition, or may be used as prophylactic medicines. A drug usually interacts with either normal or abnormal physiological process in a biological system, and produces a desired and positive biological action. If the drug's effect helps the body, the drug is called a medicine, whereas, if its effect causes harm to the body, the drug is classified as a poison [1-3]. The drugs can treat different types of diseases such as infectious diseases, non-infectious diseases, and non-diseases (alleviation of pain, prevention of pregnancy and anesthesia).

Disease Classification

There are three various ways of expressing human ill-health: disease, illness and sickness. Disease is abnormal pathophysiological conditions affects either part or all or the body organisms and associated with a group of signs, symptoms and laboratory findings linked by a common pathophysiologic sequence.

Disease may be caused due to external sources, such as infectious diseases such as bacteria (pneumonia, salmonella), viruses (common cold, AIDS), fungi (thrush, athletes foot) and parasites (malaria) or it may be caused due to internal dysfunctions, such as autoimmune diseases or non-infectious diseases such as disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc. (e.g., diabetes, heart disease, cancer, hemophilia, asthma, mental illness, stomach ulcers, arthritis). Diseases are most likely affect people physically, and/or emotionally.

Diseases could be acute (short e.g., common cold, respiratory infections) or chronic (lasts for a long time, above six months e.g., diabetes, asthma, arthritis, cancer). Illness is a condition of being unhealthy in the body or mind or it is the subjective state of the individual who feels aware of not being well. The ill individual may or may not be suffering from disease (illness can include lethargy, depression, anorexia, sleepiness, hyperalgesia and inability to concentrate). Sickness is the social role assumed by an individual suffering from an illness.

Other terms for ill-health are syndrome and conditions; when the signs and symptoms have not yet clearly been placed in a common pathophysiologic sequence the disease is referred to as a syndrome. Diseases of a chronic nature are sometimes called conditions, especially if they are present since birth [4-5]. Thus; a disease is a condition of impaired health resulting from a disturbance in the structure or function of the body.

Diseases may be classified into the following major categories:

- *Infectious diseases*: also known as transmissible or communicable diseases. They are caused by microorganisms, viruses, rickettsia, bacteria, fungi, protozoa and worms. They are contagious illnesses that can be transmitted between people or animals in a variety of ways. All communicable diseases are transmitted *via* some form of infectious pathogen. A communicable disease that passes through sexual contact is

called a sexually transmitted disease. Antibiotics, antivirals, antifungals, antiprotozoal and anthelminthic agents are the drugs used to treat infectious diseases.

- *Non-communicable diseases*: non-infectious and non-transmissible. They are not mainly caused by an acute infection and result in long-term health consequences and often create a need for long-term treatment and care. They are chronic and considered as the number one cause of death and disability in the world. These include chronic lung disease, autoimmune disease, heart disease, stroke, cancers, asthma, diabetes, chronic kidney disease, osteoporosis, Alzheimer's disease, injuries and mental health disorders and more.
- *Allergic diseases*: are caused by antigens and foreign substances.
- *Metabolic disorders*: are caused by defects in the body's ability to carry out normal reactions, these may be hereditary, deficiency, and congenital defects.
- *Cancer:* is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. The majority of cancers are due to environmental factors and the remaining are due to inherited genetics.
- *Toxic diseases*: are caused by the consumption of substances, which are harmful to the human body (caused by poisons).
- *Psychosomatic and mental diseases*: psychosomatic disorders are diseases which involve both mind (psyche) and body (soma). These may include affective emotional instability, behavioral dysregulation, and/or cognitive dysfunction or impairment. These include major depression, generalized anxiety disorder, schizophrenia, and attention deficit hyperactivity disorder (ADHD). These diseases affected the ability of a person to work or study and harm his life including interpersonal relationships.
- *Miscellaneous diseases*: Among this class are foodborne illness or food poisoning, airborne diseases, lifestyle diseases (any disease that appears to increase in frequency as countries become more industrialized and people live longer, especially if the risk factors include behavioral choices like a sedentary lifestyle or a diet high in unhealthful foods such as refined carbohydrates, trans fats, or alcoholic beverages) and organic diseases (caused by a physical or physiological change to some tissue or organ of the body, excluding infections and mental disorders).

The general classification of diseases which is most widely used, is that based on pathogenesis or disease mechanisms. Most diseases can be assigned in the following classification:

(i) Congenital diseases: also referred as birth defects; the conditions existing at birth and often before birth, involve defects in or damage to a developing fetus. They may be genetic (inherited or sporadic mutations, inheritance of abnormal genes from the parents) and non-genetic (environmental or accidental). The causes also include fetal alcohol exposure, toxic substances (drugs and/or environmental toxin during pregnancy), infections, lack of nutrients (folic acid), radiation and physical restraint [5]. Congenital anomalies and preterm birth are important causes of childhood death, chronic illness, and disability in many countries.

(ii) Acquired diseases: the medical condition which develops after birth. For example, inflammatory, hemodynamic, growth disorders, injury and disordered repair, disordered immunity, metabolic and degenerative disorders [5].

Drugs Classification

There are different ways to group or classify drugs; therefore, different classification systems for therapeutic agents exist. A drug may be classified by its chemical structure; by the way it is used to treat a particular condition, by its source or by its mechanism of action. Each drug can be classified into one or more drug classes [3, 6].

Drug can be classified by the following ways:

1. By its pharmacological effect; drugs are classified by their biological effect they have, e.g., anti-inflammatory, analgesics, antiviral, anticancer, antianxiety, anti-depressants, antipsychotics, antihypertensive, antibacterial agents, antiarrhythmic, diuretics and others [7-9].
2. By its chemical structure; drugs are grouped together by their chemical structures based on a common skeleton they have. Some examples include sulfonamides, sulfonylurea, tricyclic antidepressants, β-lactams (penicillins), barbiturates, opiates, steroids, catechol amines, aminoglycosides and others. All drugs of a certain chemical group have the same uses, or act on the same site of action [9].
3. By its target system; drugs in this class are classified according to a certain target or target organ system in the body where they affect. Examples for such class include drugs acting on the cardiovascular system, drugs acting on the nervous system, drugs acting on the gastrointestinal system and drugs acting on the musculoskeletal system [9].
4. By its site of action; drugs are classified according to the drug targets (receptors, enzymes, cell lipids, pieces of DNA or RNA and carbohydrates) where they interact. Most of drugs interact with enzymes or receptors to give their biological action and others interact with other drug targets such as, drugs inhibit the enzyme acetylcholinesterases. This classification is specific as most of drugs targets have been identified. The drugs in this group have a common mechanism of action [9].
5. By its mechanism of action; there are a difference between actions of drugs and their effects. Drugs are classified by a specific biochemical interaction through which a drug substance produces its pharmacological effect. Drugs are divided into six classes according to their biochemical mechanism of action: (i) signal-transduction systems, (ii) other components of plasmatic membranes, (iii) intracellularly, (iv) a gene therapy, (v) extracellularly and (vi) invasive agents [9-11]. A mechanism of action usually includes the specific molecular targets to which the drug binds or interacts. For example; the mechanism of action of non-steroidal anti-informatory (NSAIDs) drugs is by inhibiting cyclooxygenase enzyme and thus stopping the production of prostaglandins and thromboxane and as a result reducing the pain and inflammation. One major problem of pharmacology is that there is no such a drug

which produces only a single effect. The primary effect is the desired therapeutic effect. Secondary effects are all other effects beside the desired effect which may be either beneficial or harmful. Drugs are chosen to exploit differences between normal metabolic processes and any abnormalities which may be present. Since the differences may not be great, drugs may be nonspecific in action and alter normal functions as well as the undesirable ones which lead to unwanted side effects. The mechanisms of action of some drugs are still unknown. Many drugs have multiple mechanisms of action thus; it is sometimes difficult to agree on how to classify a particular drug.

6. By its physicochemical properties; this classification is also know the biopharmaceutical classification system (BCS). It is the measures of permeability, solubility and dissolution of the drugs. The system is designed mainly for oral drug delivery as most of the drugs are administered orally. BCS is a tool in a drug product development used by the industry. The primary purpose of the BCS is to help in qualifying drug products for a waiver of *in vivo* bioequivalence studies. The aim of the BCS is the measurement of the permeability and solubility of the drug *in vitro* and thus prediction of its performance *in vivo*. The information will help in the drug's formulation. The BCS places a given active pharmaceutical ingredients (API) in one of four categories depending on its permeability and solubility [12]:

Class I: high permeability, high solubility; a drug substance is considered "highly soluble" when the highest dose strength is soluble in less than 250 ml water over a pH range of 1–7.5 and 37 °C. A drug substance is considered "highly permeable" when the extent of the absorption (parent drug plus metabolites) is more than 90% of the administered dose. Those compounds are well absorbed and their absorption rate is usually higher than their excretion. Examples include metoprolol, amiloride, chloroquine, cyclophosphamide, diazepam, digoxin, doxycycline, fluconazole and etc.

Class II: high Permeability, low Solubility; drug's absorption in this class is generally slower than those in Class I. The dissolution-rate of these drugs is limited. However, specific techniques may be considered to enhance their dissolution rate. The bioavailability of those products is limited. Examples for this class include glibenclamide, bicalutamide, ezetimibe, carbamazepine, dapsone, ibuprofen, nifedipine, sulfamethoxazole, trimethoprim and etc.

Class III: Low Permeability, High Solubility; drugs in this class are quite soluble and generally have rapid dissolution rates; however, their absorption is limited due to their low permeation. The formulation method to be used should change the permeability or gastro-intestinal duration time and thus enhance intestinal absorption. Examples include cimetidine, abacavir, acetaminophen, acyclovir, allopurinol, atenolol, captopril, codeine phosphate, metformin, promethazine, sodium cloxacillin, ibuprofen and etc.

Class IV: Low Permeability, Low Solubility; drugs in this class have significant problems due to their low solubility and low permeability. Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. Techniques can be considered regarding selection of excipients designed to enhance their dissolution rates and absorption. Examples include hydrochlorothiazide, furosemide, ritonavir, acetazolamide and etc.

7. By its source or origin; drugs can be classified according to their origin:

(i) *Natural compounds*: materials obtained from either plant or animal, such as vitamins, hormones, amino acids, antibiotics, alkaloids and glycoside. Natural products (secondary metabolites) have been the most successful source of potential drug leads.
(ii) *Synthesis compounds*: they are chemically produced in a laboratory, either pure synthesis or synthesis of organic compounds whose structures are closely related to those of naturally occurring compounds.
(iii) *Semi-synthesis compounds*: some compounds either cannot be purely synthesized or cannot be isolated from natural sources in low cost. Therefore, the natural intermediate of such drugs could be used for the synthesis of the desired product such as semisynthetic penicillins [13].

8. By its activity: drug activity can be classified as structurally non-specific drugs or structurally specific drugs. The actions of structurally non-specific drugs result from accumulation of a drug in some vital part of a cell with lipid characteristics such as general anesthetics, hypnotics, some bactericidal and insecticides. The structurally non-specific drug depends on physical properties like solubility, partition coefficients and vapor pressure and not on the presence or absence of some chemical groups [14]. Structurally specific drug is dependent upon the interaction of the drug with a cellular receptor. It is dependent upon factors such as the presence or absence of certain functional groups, intramolecular distance, and shape of the molecules. The drug activity is not easily correlated with any physical property and small changes in the structure often lead to changes in activity.
9. By its route of administration: route of administration is the path by which a drug or other substance is taken into the body. Route of administration are generally classified by the location at which the drug is applied or where the target of action is. Each route of administration has specific purposes, advantages, and disadvantages [15-17]. Drugs are introduced into the body by several routes: *(a) Gastrointestinal/enteral:* administration through the gastrointestinal tract (GIT) is termed enteral or enteric administration (meaning 'through the intestines'). Usually includes oral and rectal administration. Sublingual (under the tongue) and buccal are sometime classified as enteral. Enteral administration can be used for systemic administration such as tablets and capsules, as well as local (topical), such as enema. Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. The oral route is the most often used and most convenient because it is the safest and least expensive. Some drugs are placed under the tongue (taken sublingually) or between the gums and teeth (buccal). Nitroglycerin (used to treat angina) is given sublingually, has a rapid absorption and an immediate effect. Many drugs that are administered orally can also be administered rectally as a suppository. A suppository is prescribed for people who cannot swallow (pediatrics, elderly). Other routes of administration are used when the oral route cannot be used. For example, when a person cannot take anything by mouth or a drug must be administered rapidly or in a precise or very high dose, or a drug is poorly or erratically absorbed from the digestive tract. *b) Central nervous system:* this includes epidural (injection or infusion into the epidural space), intracerebral (into the cerebrum) direct injection into the brain (e.g., treatment of brain malignancies and

intracerebroventricular (into the cerebral ventricles) and *(c) Other locations:* this includes; intravenous, intramuscular, intravaginal, intrauterine, epicutaneous or topical (application to the skin). *Topical:* local effect, substance is applied directly where its action is desired to a specific location. Examples, epicutaneous, inhalational, enema, ophthalmic drugs/ eye drops (onto the conjunctiva), and otic drugs (ear drops). *Enteral:* administration involves any part of the GIT. The desired effect is systemic; drug is given via the digestive tract. The drug may be introduced orally by mouth or by gastric feeding tube, duodenal feeding tube, or gastrostomy. *Parenteral:* desired effect is systemic; substance is given by routes other than the digestive tract. Examples: intravenous, intra-arterial, intra-muscular, intracerebral, intracerebroventricular and subcutaneous (hypodermoclysis).

10. By its safety during pregnancy: many drugs are used in pregnancies. The most commonly used drugs include antiemetics, antacids, antihistamines, analgesics, antimicrobials, diuretics, hypnotics, tranquilizers, and social and illicit drugs. Medications taken by the pregnant woman can cross the placenta and enter the developing baby's bloodstream. A medicine's effect on the unborn baby depends on the medication and the trimester in which the medicine is taken. Drugs that cross the placenta may have a direct toxic effect or a teratogenic effect. The food and drug administration (FDA) classifies drugs into 5 categories (A, B, C, D and X, Table 1) based on the potential for producing birth defects or safety for use during pregnancy. Drugs that fall into either class A or B are considered safe and are routinely used [18-19].

Category A: these drugs have been tested and found to be safe during pregnancy. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote. Category A includes drugs such as folic acid, vitamin B6, and some thyroid medicines in prescribed doses.

Category B: these drugs are frequently used during pregnancy and do not appear to cause major birth defects or other problems. Animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, and animal-reproduction studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters). Category B includes some antibiotics, acetaminophen, aspartame, famotidine, prednisone, insulin, and ibuprofen. Pregnant women should not take ibuprofen during the last three months of pregnancy.

Category C: no studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. It is wise to avoid taking the medications during pregnancy. Drugs should be given only if the potential benefit justifies the potential risk to the fetus. Always the pregnant woman should consult the doctor about taking any medications, whether prescription or over-the-counter.

Category D: there is a positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-