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BASIC & CLINICAL PHARMACOLOGY

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LANGE®

SCHEDULE OF CONTROLLED DRUGS[1]

SCHEDULE I

(All nonresearch use illegal under federal law.)

Flunitrazepam (Rohypnol)

Narcotics:

Heroin and many nonmarketed synthetic narcotics

Hallucinogens:

LSD

MDA, STP, DMT, DET, mescaline, peyote, bufotenine, ibogaine, psilocybin, phencyclidine (PCP; veterinary drug only)

Marijuana

Methaqualone

SCHEDULE II

(No telephone prescriptions, no refills.)[2]

Opioids:

Opium

Opium alkaloids and derived phenanthrene alkaloids: codeine, morphine (Avinza, Kadian, MSContin, Roxanol), hydrocodone and hydrocodone combinations (Zohydro ER, Hycodan, Vicodin, Lortab), hydromorphone (Dilaudid), oxymorphone (Exalgo), oxycodone (dihydroxycodeinone, a component of Oxycontin, Percodan, Percocet, Roxicodone, Tylox)

Designated synthetic drugs: meperidine (Demerol), methadone, levorphanol (Levo-Dromoran), fentanyl (Duragesic, Actiq, Fentora), alfentanil (Alfenta), sufentanil (Sufenta), remifentanil (Ultiva), tapentadol (Nycynta)

Stimulants:

Coca leaves and cocaine

Amphetamines: Amphetamine complex (Biphetamine), Amphetamine salts (Adderall), Dextroamphetamine (Dexedrine, Procentra), Lisdexamfetamine (Vyvanse), Methamphetamine (Desoxyn), Methylphenidate (Ritalin, Concerta, Methylin, Daytrana, Medadate), Above in mixtures with other controlled or uncontrolled drugs

Cannabinoids:

Nabilone (Cesamet)

Depressants:

Amobarbital (Amytal)

Pentobarbital (Nembutal)

Secobarbital (Seconal)

SCHEDULE III

(Prescription must be rewritten after 6 months or five refills.)

Opioids:

Buprenorphine (Buprenex, Subutex)

Mixture of above Buprenorphine and Naloxone (Suboxone)

The following opioids in combination with one or more active non-opioid ingredients, provided the amount does not exceed that shown:

Codeine and dihydrocodeine: not to exceed 1800 mg/dL or 90 mg/tablet or other dosage unit

Opium: 500 mg/dL or 25 mg/5 mL or other dosage unit (paregoric)

Stimulants:

Benzphetamine (Didrex)

Phendimetrazine (Bontril)

Depressants:

Schedule II barbiturates in mixtures with noncontrolled drugs or in suppository dosage form

Barbiturates (butabarbital [Butisol], butalbital [Fiorinal])

Ketamine (Ketalar)

Cannabinoids:

Dronabinol (Marinol)

Anabolic Steroids: Fluoxymesterone (Androxy), Methyltestosterone (Android, Testred, Methitest), Nandrolone decanoate (Deca-Durabolin) Non US, Nandrolone phenpropionate (Durabolin) Non US, Oxandrolone (Oxandrin), Oxymetholone (Androl-50), Stanozolol (Winstrol), Testolactone (Teslac), Testosterone and its esters

SCHEDULE IV

(Prescription must be rewritten after 6 months or five refills; differs from Schedule III in penalties for illegal possession.)

Opioids:

Butorphanol (Stadol)

Difenoxin 1 mg + atropine 25 mcg (Motofen)

Pentazocine (Talwin)

Stimulants:

Armodafinil (Nuvigil)

Diethylpropion (Tenuate) not in US

Modafinil (Provigil)

Phentermine (Ionamin, Adipex-P)

Depressants:

Benzodiazepines: Alprazolam (Xanax), Chlordiazepoxide (Librium), Clonazepam (Klonopin), Clorazepate (Tranxene), Diazepam (Valium), Estazolam (ProSom), Flurazepam (Dalmane), Halazepam (Paxipam), Lorazepam (Ativan), Midazolam (Versed), Oxazepam (Serax), Prazepam (Centrax), Quazepam (Doral), Temazepam (Restoril) Triazolam (Halcion)

Chloral hydrate (Somnote)

Eszopiclone (Lunesta)

Lacosamide (Vimpat)

Meprobamate (Equanil, Miltown, etc)

Methobarbital (Mebaral)

Methohexital (Brevital)

Paraldehyde

Phenobarbital

Zaleplon (Sonata)

Zolpidem (Ambien)

SCHEDULE V

(As any other nonopioid prescription drug)

Codeine: 200 mg/100 mL

Difenoxin preparations: 0.5 mg

Dihydrocodeine preparations

Diphenoxylate (not more tha

atropine per dosage unit, as

Ethylmorphine preparations: 1

Opium preparations: 100 mg/100

Pregabalin (Lyrica)

Pyrovalerone (Centroton, Thymergix)

[1]See http://*www.usdoj.gov/dea/pubs/scheduling.html* for additional details.

[2]Emergency prescriptions may be telephoned if followed within 7 days by a valid written prescription annotated to indicate that it was previously placed by telephone.

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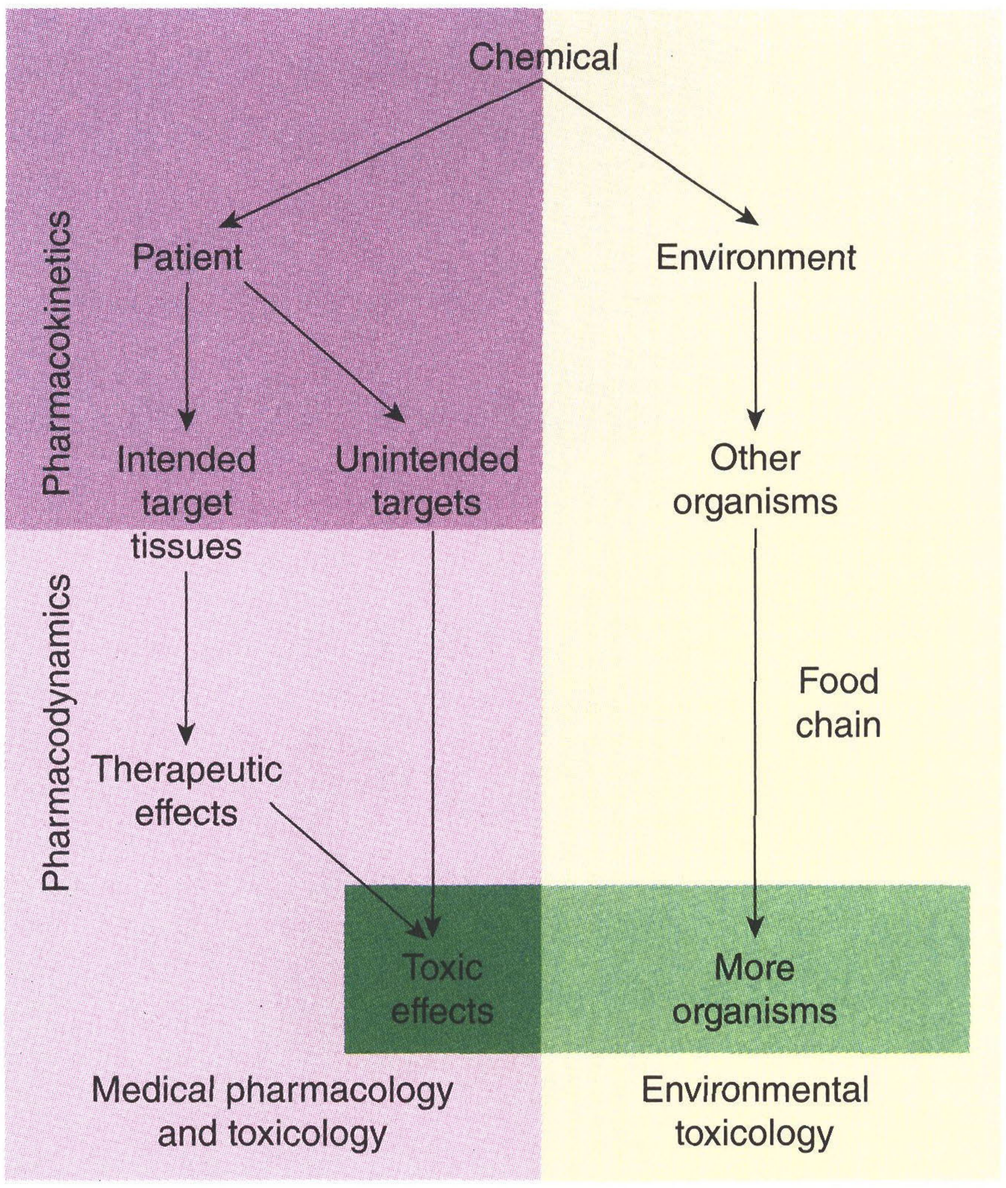

FIGURE 1–1 Major areas of study in pharmacology. The actions of chemicals can be divided into two large domains. The first (*left side*) is that of medical pharmacology and toxicology, which is aimed at understanding the actions of drugs as chemicals on individual organisms, especially humans and domestic animals. Both beneficial and toxic effects are included. Pharmacokinetics deals with the absorption, distribution, and elimination of drugs. Pharmacodynamics concerns the actions of the chemical on the organism. The second domain (*right side*) is that of environmental toxicology, which is concerned with the effects of chemicals on all organisms and their survival in groups and as species.

effects of chemicals on living systems, from individual cells to humans to complex ecosystems (Figure 1–1). The nature of drugs—their physical properties and their interactions with biological systems—is discussed in part I of this chapter. The development of new drugs and their regulation by government agencies are discussed in part II.

THE HISTORY OF PHARMACOLOGY

Prehistoric people undoubtedly recognized the beneficial or toxic effects of many plant and animal materials. Early written records list remedies of many types, including a few that are still recognized as useful drugs today. Most, however, were worthless or actually harmful. In the last 1500 years, sporadic attempts were made to introduce rational methods into medicine, but none was successful owing to the dominance of systems of thought that purported to explain all of biology and disease without the need for experimentation and observation. These schools promulgated bizarre notions such as the idea that disease was caused by excesses of bile or blood in the body, that wounds could be healed by applying a salve to the weapon that caused the wound, and so on.

Around the end of the 17th century, and following the example of the physical sciences, reliance on observation and experimentation began to replace theorizing in medicine. As the value of these methods in the study of disease became clear, physicians in Great Britain and on the Continent began to apply them to the effects of traditional drugs used in their own practices. Thus, **materia medica**—the science of drug preparation and the medical uses of drugs—began to develop as the precursor to pharmacology. However, any real understanding of the mechanisms of action of drugs was prevented by the absence of methods for purifying active agents from the crude materials that were available and—even more—by the lack of methods for testing hypotheses about the nature of drug actions.

In the late 18th and early 19th centuries, François Magendie, and his student Claude Bernard, began to develop the methods of **experimental physiology** and **pharmacology.** Advances in chemistry and the further development of physiology in the 18th, 19th, and early 20th centuries laid the foundation needed for understanding how drugs work at the organ and tissue levels. Paradoxically, real advances in basic pharmacology during this time were accompanied by an outburst of unscientific claims by manufacturers and marketers of worthless "patent medicines." Not until the concepts of rational therapeutics, especially that of the **controlled clinical trial,** were reintroduced into medicine—only about 60 years ago—did it become possible to accurately evaluate therapeutic claims.

Around the same time, a major expansion of research efforts in all areas of biology began. As new concepts and new techniques were introduced, information accumulated about drug action and the biologic substrate of that action, the **drug receptor.** During the last half-century, many fundamentally new drug groups and new members of old groups were introduced. The last three decades have seen an even more rapid growth of information and understanding of the molecular basis for drug action. The molecular mechanisms of action of many drugs have now been identified, and numerous receptors have been isolated, structurally characterized, and cloned. In fact, the use of receptor identification methods (described in Chapter 2) has led to the discovery of many orphan receptors—receptors for which no ligand has been discovered and whose function can only be surmised. Studies of the local molecular environment of receptors have shown that receptors and effectors do not function in isolation; they are strongly influenced by other receptors and by companion regulatory proteins.

Pharmacogenomics—the relation of the individual's genetic makeup to his or her response to specific drugs—is close to becoming an important part of therapeutics (see Chapter 5). Decoding of the genomes of many species—from bacteria to humans—has led to the recog ected relationships between receptor familie eptor proteins have evolved. Discover A can interfere with protein synt has led to investigation of **small** and **micro-RNAs (miRNAs)** as the hort nucleotide chains called **anti tides (ANOs),** synthesized to be complementary to natural RNA or DNA, can interfere with the readout of genes and the transcription of RNA. These intracellular targets may provide the next major wave of advances in therapeutics.

The extension of scientific principles into everyday therapeutics is still going on, although the medication-consuming public is still exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of chemicals. This has resulted in the irrational use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative health care" industry. Unfortunately, manipulation of the legislative process in the United States has allowed many substances promoted for health—but not promoted specifically as "drugs"—to avoid meeting the Food and Drug Administration (FDA) standards described in the second part of this chapter. Conversely, lack of understanding of basic scientific principles in biology and statistics and the absence of critical thinking about public health issues have led to rejection of medical science by a segment of the public and to a common tendency to assume that all adverse drug effects are the result of malpractice.

Two general principles that the student should remember are (1) that *all* substances can under certain circumstances be toxic, and the chemicals in botanicals (herbs and plant extracts, "nutraceuticals") are no different from chemicals in manufactured drugs except for the much greater proportion of impurities in botanicals; and (2) that all dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety as conventional drugs and medical therapies. That is, there should be no artificial separation between scientific medicine and "alternative" or "complementary" medicine. Ideally, all nutritional and botanical substances should be tested by the same randomized controlled trials (RCTs) as synthetic compounds.

I GENERAL PRINCIPLES OF PHARMACOLOGY

THE NATURE OF DRUGS

In the most general sense, a drug may be defined as any substance that brings about a change in biologic function through its chemical actions. In most cases, the drug molecule interacts as an **agonist** (activator) or **antagonist** (inhibitor) with a specific molecule in the biologic system that plays a regulatory role. This target molecule is called a **receptor**. The nature of receptors is discussed more fully in Chapter 2. In a very small number of cases, drugs known as **chemical antagonists** may interact directly with other drugs, whereas a few drugs (osmotic agents) interact almost exclusively with water molecules. Drugs may be synthesized within the body (eg, **hormones**) or may be chemicals *not* synthesized in the body (ie, **xenobiotics,** from the Greek *xenos*, meaning "stranger"). **Poisons** are drugs that have almost exclusively harmful effects. However, Paracelsus (1493–1541) famously stated that "the dose makes the poison," meaning that any substance can be harmful if taken in the wrong dosage. **Toxins** are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.

To interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition. Furthermore, a drug is often administered at a location distant from its intended site of action, eg, a pill given orally to relieve a headache. Therefore, a useful drug must have the necessary properties to be transported from its site of administration to its site of action. Finally, a practical drug should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration.

The Physical Nature of Drugs

Drugs may be solid at room temperature (eg, aspirin, atropine), liquid (eg, nicotine, ethanol), or gaseous (eg, nitrous oxide). These factors often determine the best route of administration. The most common routes of administration are described in Table 3–3. The various classes of organic compounds—carbohydrates, proteins, lipids, and their constituents—are all represented in pharmacology. As noted above, oligonucleotides, in the form of small segments of RNA, have entered clinical trials and are on the threshold of introduction into therapeutics.

A number of useful or dangerous drugs are inorganic elements, eg, lithium, iron, and heavy metals. Many organic drugs are weak acids or bases. This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of such drugs (see text that follows).

Drug Size

The molecular size of drugs varies from very small (lithium ion, MW 7) to very large (eg, alteplase [t-PA], a protein of MW 59,050). However, most drugs have molecular weights between 100 and 1000. The lower limit of this narrow range is probably set by the requirements for specificity of action. To have a good "fit" to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, and other properties, to prevent its binding to other receptors. To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size. The upper limit in molecular weight is determined primarily by the requirement that drugs must be able to move within the body (eg, from the site of administration to the site of action). Drugs much larger than MW 1000 do not diffuse readily between compartments of the body (see Permeation, in following text). Therefore, very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect. In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular compartment by intravenous or intra-arterial infusion.

Drug Reactivity & nds

Drugs interact with rec forces or bonds. These are of three **tatic,** and **hydrophobic.** Covalent bo many cases not reversible under biologic co covalent bond formed between the acetyl group of acetylsalicylic acid (aspirin) and cyclooxygenase, its enzyme target in platelets, is not readily broken. The platelet aggregation–blocking effect of aspirin lasts