CHAPTER 91

Enzymes

Michael R Franklin, PhD

The functions of all living organisms depend on chemical reactions. For example, conversion of sugar to carbon dioxide and water with the release of energy proceeds through a series of chemical reactions, each of which requires a biological catalyst for the reaction to occur. Enzymes are proteins that serve as biological catalysts. Without these enzymes conditions for reaction would be required that would be incompatible with the life of the cell. Thus, enzymes play a vital role in the function of the normal cell.

The importance of enzymes in normal body function is illustrated dramatically in conditions when an enzyme is nonfunctional as a result of a disease state or a congenital abnormality. Patients with these *inborn errors of metabolism* are strikingly abnormal. Phenylketonuric infants who are born without the enzyme phenylalanine hydroxylase (which is responsible for the conversion of phenylalanine to tyrosine) develop motor disturbances; light coloration of the skin, hair, and eyes; and in early childhood (if not in infancy), remain mentally retarded.

Since most chemical reactions in the body require the action of an enzyme, these biological catalysts often serve as the focal point for the regulation of body function. Increased enzyme activity accelerates the formation of a given product that may be essential for a particular function. The synthesis of norepinephrine illustrates this principle well. Heart rate will increase when norepinephrine is released from the sympathetic nerves. Norepinephrine is synthesized through a series of enzymatic reactions of which the rate-limiting, and therefore the most important, regulating enzyme is tyrosine hydroxylase. Increased tyrosine hydroxylase activity brings about conversion of more tyrosine to dihydroxyphenylalanine (DOPA), which is converted by dopa decarboxylase to dopamine. Dopamine is converted to norepinephrine by the enzymatic activity of dopamine-β-hydroxylase. The formation of norepinephrine can be regulated by a number of factors, including a feedback mechanism. Increased levels of norepinephrine inhibit the enzyme tyrosine hydroxylase so that less norepinephrine is synthesized. Thus, levels of norepinephrine can control the amount of norepinephrine synthesized.

The actions of a considerable number of drugs representing a wide variety of pharmacological agents depend on an enzyme-drug interaction. Notable examples demonstrating this diversity include the following:

The hydrolysis of acetylcholine by cholinesterase is blocked in a competitive manner by physostigmine and in a noncompetitive manner by diisopropyl fluorophosphate, organophosphate insecticides, and several chemical warfare agents.

The oxidation of norepinephrine and serotonin by monoamine oxidase (MAO) is inhibited by the antidepressant phenelzine.

The oxidation of acetaldehyde to acetate by aldehyde dehydrogenase is inhibited by disulfiram.

The oxidation of arachidonic acid to prostaglandins by cyclooxygenase is inhibited by, and is the common mode of action of, nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin.

The hydrolysis of one of the cellular mediators of hormonal action, cyclic 3′,5′-adenosine monophosphate, by phosphodiesterase is inhibited by methylated xanthines, such as caffeine and theophylline.

The 11β-hydroxylation reaction in the synthesis of cortisol, corticosterone and aldosterone is inhibited by metyrapone.

The thyroid peroxidase responsible for the synthesis of thyroxine is inhibited by propylthiouracil and methimazole.

The conversion of xanthine to uric acid by xanthine oxidase is inhibited by allopurinol, which is used therefore in the treatment of gout.

The bacterial synthesis of the essential vitamin folic acid is competitively inhibited by the sulfonamide antibiotics.

The cancer chemotherapeutic agent fluorouracil is converted to a compound that inhibits the enzyme thymidylate synthetase, which is needed for DNA synthesis.

These examples illustrate the importance of drug-enzyme interactions in the pharmacological actions of therapeutic agents. The actions of drugs of the future also undoubtedly will depend on drug-enzyme interaction. Indeed, the pharmacological action of many drugs currently being prescribed by the physician probably will be found to involve such interplay. Since enzymes are involved so intricately in regulation of function, it is only logical to suppose that drugs may increase or decrease function by stimulating or depressing enzyme activity, respectively. A knowledge of enzymes and their properties, therefore, becomes increasingly important to the pharmacist, to understand the action of drugs.

In addition to the action, the pharmacokinetics, drug interactions, and toxicities of many drugs depend on enzyme activity. The enzymes responsible for these phenomena are those generally termed drug-metabolizing enzymes and are located predominately in the liver. Contrary to most others, these enzymes typified by cytochrome P-450 and UDP-glucuronosyl transferase exhibit broad substrate specificity. The ability to metabolize a wide variety of drugs to more-readily excretable products carries with it the potential for mutual competition when several drugs are administered simultaneously, thus altering the pharmacokinetics from that seen if a single drug is given. Toxicities arise from the two-phase nature of drug metabolism, the introduction of a reactive site suitable for conjugation and masking of that site with an endogenous polar molecule to form an excretable water-soluble conjugate. Failure to mask a reactive site allows it to interact with cell macromolecules (proteins, DNA, membranes) to produce cell damage, carcinogenesis, or cell death.

PROPERTIES—Four properties of enzymes make them specialized catalysts.

1. Most enzymes will catalyze only a specific range of reactions, and in many cases only one reaction will be catalyzed by a given enzyme. Some enzymes have a low degree of specificity; eg, pepsin hydrolyzes almost all soluble native proteins, but the hydrolysis is limited to certain very specific peptide linkages. On the other hand, urease is a highly specific enzyme; its only known substrate is urea. Almost all enzymes show a high degree of spatial speci-

ficity. Arginase acts only on L-arginine; it does not attack D-arginine. The specificity of enzymes is one of their most fundamental and important properties.
2. Enzymes are exceedingly efficient. Most enzymatic reactions, under optimal conditions, proceed 10^8 to 10^{11} times more rapidly than the corresponding nonenzymatic reactions.
3. Enzymes as a group are exceptionally versatile catalysts. For example, they effectively catalyze hydrolytic reactions, dehydrations, acyl transfer reactions, oxidation-reduction reactions, polymerizations, aldol condensations, and free-radical reactions.
4. Enzymes are subject to a variety of cellular controls. Their final concentration and rate of synthesis are under genetic control. In addition, enzymes can be present in the cell in both inactive and active forms. The rate of conversion from inactive to active form is influenced by environmental changes; eg, phosphorylase *b* is converted to phosphorylase *a* very rapidly through a series of reactions that are triggered by the release of catecholamines.

NOMENCLATURE—Enzymes usually are named in terms of the reactions that are catalyzed. Usually, the suffix *-ase* is added to the name of the substrate upon which the enzyme acts, ie, the enzyme that attacks urea is urease, and arginine is acted upon by arginase. Enzymes also are classified according to the reaction they catalyze, eg, reductases and dehydrogenases. Some older names that are unrelated to the function of the enzyme remain in usage, eg, renin, trypsin, and pepsin.

The Commission on Enzymes of the International Union of Biochemistry has established a complete but rather complex system of classification and nomenclature. According to this classification enzymes are divided into six general groups:

1. *Oxidoreductases*—catalyzing oxidation-reduction reactions.
2. *Transferases*—catalyzing transfer of a chemical group from one molecule to another.
3. *Hydrolases*—catalyzing hydrolytic reactions.
4. *Lyases*—catalyzing the addition of groups to double bonds or *vice versa*.
5. *Isomerases*—catalyzing intramolecular rearrangements.
6. *Ligases* (also known as synthetases)—catalyzing the condensation of two molecules, coupled with the cleavage of a pyrophosphate bond of ATP or similar triphosphate.

In this system every enzyme is coded in a four-number system according to the type of reaction catalyzed, type of isomerization, type of bond hydrolyzed, etc.

Many enzymes possess nonprotein chemical groups. Thus, an enzyme often can be dissociated into a protein component, an *apoenzyme,* and a nonprotein component, a *prosthetic group*. Prosthetic groups also are referred to as coenzymes or cofactors. Vitamins and certain metals are examples of these prosthetic groups.

Despite the ubiquity of enzymes in normal physiology and as the basis of many drug effects and drug interactions, the use of enzymes as drugs is extremely limited. Being proteinaceous, they can be inactivated by conditions and enzymes present in the gastrointestinal (GI) lumen if given orally and, if given parenterally, can elicit immune responses. Most of the enzymes currently available on the market are hydrolases (Group 3 above). These enzyme preparations are of limited use in (1) debridement, ie, as aids in resolving and removing blood clots or fibrinous or purulent accumulations and (2) replacement therapy to correct certain GI deficiencies (Table 91-1).

ALTEPLASE—page 1332.
ASPARAGINASE—page 1562.

COLLAGENASE

Santyl

A product of *Clostridium histolyticum,* which breaks down native and denatured collagen in necrotic (not in healthy) tissue at physiological pH and temperature. It is a fermentation-produced enzyme complex.

Description—Fine, brown, amorphous powder; heat-labile.

Solubility—Soluble in water or alcohol.

Comments—Collagen constitutes about 75% of the dry weight of the skin and is the main constituent of necrotic debris and of the eschar that covers the surface of an ulcer; hence, collagenase is indicated for debridement of severely burned areas and dermal ulcers. Its effectiveness in the treatment of other necrotic skin lesions requires further investigation. The enzyme is compatible with antibiotics such as polymyxin B sulfate, neomycin, or bacitracin. It is adversely affected by heavy metal antiseptics, detergents, and hexachlorophene, so that these agents must be removed before using the enzyme.

DEOXYRIBONUCLEASE RECOMBINANT

Pulmozyme

Dornase alpha is a purified solution of recombinant human deoxyribonuclease I produced in genetically engineered Chinese hamster ovary cells. It is sensitive to light and heat.

Table 91-1. Pancreatic Enzymes: Dose and Dosage Forms

TRADE NAME	LIPASE[a]	PROTEASE[a]	AMYLASE[a]	DOSE
Pancrease-MT Capsules				In units of lipase activity: *children, 6 mo to 1 yr,* 2000 Units/meal; *1 to 6 yr,* 4000 to 8000 Units/meal; *7 to 12 yr,* 4000 to 12,000 Units/meal; *adults,* 4000 to 16,000 Units/meal
MT4	4	12	12	
Pancrease	5	25	20	
MT10	10	30	30	
MT16	16	48	48	
MT20	20	44	56	
Ultrase MT Capsules				
MT12	12	39	39	
MT20	20	65	65	
MT24	24	78	78	
Ilozyme	11	30	30	
Cotazyme	5	20	20	
Cotazyme-S	8	30	30	1 to 3 capsules prior to each meal or snack
8X Pancreatin Tablets	22.5	180	180	1 or 2 tablets with each meal; 1 tablet with a snack
Creon Capsules	8	13	30	Same as above
Creon 10	10	38	33	1 to 3 capsules with each meal
Creon 20	20	75	66	
Ku-Zyme-HP Capsules	8	30	30	
VioKase				
Tablets	8	30	30	Same as above
Powder	16.8	70	70	For *cystic fibrosis,* 1/4 tsp (0.7 g) with meals
Zymase Capsules	12	24	24	1 or 2 capsules with each meal

[a] In thousands of USP Units/dosage unit.

Comments—Deoxyribonuclease selectively cleaves DNA, which is present at high concentrations in the secretions of cystic fibrosis patients following release from leukocytes that accumulate in response to infection. Its action reduces the viscoelasticity of the secretion.

HYALURONIDASE FOR INJECTION

Wydase

A sterile, dry, soluble, enzyme product prepared from mammalian (bovine) testes and capable of hydrolyzing mucopolysaccharides of the hyaluronic acid type; its potency is not less than the labeled potency in Hyaluronidase Units and it contains not more than 0.25 μg of tyrosine for each Hyaluronidase Unit. It may contain a suitable stabilizer.

Description—White, odorless, amorphous solid or a nearly colorless glass-like solid; it is destroyed by heat; its solutions are colorless.

Comments—Intercellular cement, which binds together the parenchymal cells of organs; appears to be a gel of highly polymerized polysaccharide, hyaluronic acid. The latter is present in all organs but is most abundant in tissues of mesenchymal origin (eg, connective tissue and blood vessels); the testis is the richest source of hyaluronidase in mammals. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond between carbon-1 of the glucosamine moiety and carbon-4 of glucuronic acid. Hyaluronidase accelerates the subcutaneous spread of both particulate matter and solutions by depolymerizing the hyaluronic acid. This results in a larger area of distribution of drugs in the tissue spaces and facilitates their absorption.

The chief clinical use of hyaluronidase is to facilitate administration of fluids by hypodermoclysis. It has been used as an adjunct in subcutaneous urography to improve resorption of radiopaque agents and to enhance absorption of drugs in tissue spaces, transudates, and various edemas. Its use with local anesthetics is not recommended. Hyaluronidase should not be used in infected areas because of the danger of spreading the infection.

LACTASE

Lactaid

A β-D-galactosidase derived from *Kluyveromyces lactis* yeast.

Comments—Added to, or ingested with, milk to convert the disaccharide lactose into glucose and galactose for patients suffering from lactase insufficiency (lactose intolerance).

MALT EXTRACT—page 1076.

PANCREATIC ENZYMES

A substance containing enzymes, principally amylase, protease, and lipase, obtained from the pancreas of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam *Suidae*) or of the ox, *Bos taurus* Linné (Fam *Bovidae*).

Pancreatin contains, in each milligram, not less than 2 Units of lipase activity, not less than 25 Units of amylase activity and not less than 25 Units of protease activity. Pancreatin of a higher digestive power may be labeled with a whole-number multiple of the three minimum activities or may be diluted by admixture with lactose or with sucrose containing not more than 3.25% of starch or with pancreatin of lower digestive power.

Pancrelipase contains, in each milligram, not less than 24 Units of lipase activity, not less than 100 Units of amylase activity, and not less than 100 Units of protease activity.

Description—Cream-colored, amorphous powders, with a faint, characteristic, but not offensive, odor. They hydrolyze fats to glycerol and fatty acids, change protein into proteoses and derived substances, and convert starch into dextrins and sugars. Their greatest activities are in neutral or slightly alkaline media; more than traces of mineral acids or large amounts of alkali hydroxides render them inert. An excess of alkali carbonate also inhibits their action.

Solubility—Slowly and incompletely soluble in water; insoluble in alcohol.

Incompatibilities—*Mineral acids* or excess *alkali hydroxides* or carbonates render it inert. They are precipitated by *strong alcoholic solutions* and by many *metallic salts.*

Comments—In the treatment of patients with cystic fibrosis (mucoviscidosis), chronic pancreatitis, partial or complete surgical pancreatectomy, and other conditions associated with exocrine pancreatic insufficiency. The administration of pancreatin decreases the nitrogen and fat content of the stool. The use of pancreatin except in pancreatic insufficiency is of no known value. The efficacy of pancreatin in the treatment of gaseous distention has not been demonstrated. When treating pancreatic insufficiency, a high-caloric diet that is high in protein and low in fat is recommended. A significant amount of the enzyme activity can be lost by peptic digestion during passage through the stomach. The efficacy of pancreatin is enhanced by simultaneous administration of cimetidine, which increases intragastric pH. Dietary and enzyme regimens are best based on repeated clinical evaluation and, in hospitalized patients, periodic measurements of fecal fat and nitrogen loss. Since the underlying pancreatic deficiency is unchanged, replacement pancreatin therapy is permanent. At high doses, pancreatin can cause nausea, abdominal cramps, and diarrhea. The enzyme dust is irritating to the nasal membrane, so inhalation should be avoided.

PAPAIN

Panafil

A proteolytic enzyme from the fruit of the tropical melon tree, *Carica papaya*. It exhibits broad-spectrum specificity over a wide pH range, including peptides, amides, esters, and thioesters, all being susceptible to papain-catalyzed hydrolysis. Nonviable protein is susceptible, but it is harmless to viable tissue.

Comments—In the debridement of necrotic tissue.

SUTILAINS

Travase

A substance, containing proteolytic enzymes, derived from the bacterium *Bacillus subtilis*. Elaborated by fermentation with *B subtilis* and purified by filtration, salt and solvent precipitation, and lyophilization. Potency not less than 2,500,000 Casein Units of proteolytic activity/g.

Description—Cream-colored odorless powder; *do not taste* (irritating to oral membranes); stable in light, hygroscopic, and decomposes in solvents.

Solubility—1 g in 100 mL of water; insoluble in alcohol or other organic solvents.

Comments—An adjunct to established methods of wound care for biochemical debridement of the following lesions: 2nd- and 3rd-degree burns; decubitus ulcers; incisional, traumatic, and pyrogenic wounds; and ulcers secondary to peripheral vascular disease. The enzyme digests denatured proteins found in necrotic tissues, and a moist environment is essential to optimal enzyme activity. Detergents and antiseptics may render the substrate refractory, and heavy-metal antibacterials may denature the enzyme. It is contraindicated for wounds communicating with body cavities or those containing exposed nerves or nervous tissue, for fungating neoplastic ulcers, and in wounds in women of childbearing potential. It should not be allowed to come in contact with the eyes. If this should occur inadvertently, the eyes should be rinsed immediately with copious amounts of water (preferably sterile water).

CRYSTALLIZED TRYPSIN

Granulex

A proteolytic enzyme crystallized from an extract of the pancreas of the ox, *Bos taurus* Linné (Fam *Bovidae*); its potency is not less than 25,000 Trypsin Units/mg.

Description—White to yellowish white, odorless or amorphous powder.

Solubility—An amount equivalent to 500,000 Units is soluble in 10 mL water or saline TS; pH (1% soln) 3 to 5.5; max activity at pH 8.

Comments—Promotes proteolysis of a variety of protein substrates, including clotted blood, purulent exudates (pus), and necrotic tissue, but not living tissue. Especially in the presence of blood its duration of action is limited because of the presence of inhibiting substrates. Solutions also have been inhaled to liquefy viscous sputum.

OTHER ENZYMES

Fibrinolysin and Deoxyribonuclease [Elase]—A mixture of fibrinolysin of bovine plasma and deoxyribonuclease obtained from bovine pancreas. These two enzymes function together when used topically to lyse fibrin and liquefy pus, thus aiding in the removal of necrotic material from both the skin and certain body cavities. It is used as a debriding agent in surgical wounds, ulcerative lesions, and 2nd and 3rd degree burns and is used intravaginally in severe cervicitis and vaginitis. It is not suitable for parenteral use and is not to be used in thromboembolic diseases. The commercial product named above is supplied as a lyophilized powder (25 units of fibrinolysin and 15,000 units of deoxyribonuclease), from which a solution for topical use may be prepared, and in ointment form (30 units of fibrinolysin and 20,000 units of deoxyribonuclease). It also is available combined with 1% chloramphenicol, but systemic toxicities with the antibiotic have been reported.

DIGESTIVE AIDS

Numerous preparations, both prescription and OTC, are available as aids for digestion, particularly for conditions in which deficiencies of natural digestive enzymes exist. They contain some or all of the following categories of enzymes: amylolytic, proteolytic, cellulytic, and lipolytic. In addition, the preparations often include bile salts or bile extracts. α-D-Galactosidase is used to reduce gassiness or bloating following ingestion of grains, cereals, nuts, seeds, or vegetables containing raffinose, verbascose, and stachyose.

CHAPTER 92

Nutrients and Associated Substances

Joseph I Boullata, PharmD

Food, containing nutrients and associated substances, has been at the forefront of the preventive aspects of healthcare for over a century. In recent years more attention has been given to the specific aspects of the diet that not only prevent deficiencies but also can be used to prevent chronic disease, augment growth and development, and possibly treat select disorders of health.

From a pharmaceutical point of view nutrients and the associated substances typically found in the healthy diet may be consumed through a number of dosage delivery systems. This begins with conventional foods, fresh and processed. Besides providing traditional nutrients, some foods may contain other active ingredients (naturally or through manipulation) that may enhance health (ie, "pharmafoods," "functional foods," or "designer foods"). Nutrients may also be administered as dietary supplements. These products may contain nutrients or associated substances as the sole ingredient, but more often are included in multi-ingredient products. The latter sometimes combine nutrients with botanical and other non-nutrient ingredients in a dietary supplement product. Meal replacement formulas and medical foods intended for patients unable to consume adequate nourishment orally are additional delivery vehicles for nutrients. Some nutrients are found as drug products—in oral and parenteral dosage forms. These nutrient-containing products are often intended for specific disorders. Parenteral nutrients can be combined to form a parenteral nutrient admixture used to support patients unable to otherwise take or assimilate nutrients through the gastrointestinal tract. The analogy to medicines does not end with delivery systems.

Nutrients and associated substances found in foods are physiologically active substances. The chemical structure and structure-activity relationships of individual nutrients are no different than any other natural or synthetic drug. In fact the kinetic behavior of some nutrients is more complex than that of many drugs. Nutrient bioavailability can vary greatly with the delivery vehicle and dosage form. Additionally nutrient absorption, distribution, and elimination will vary with an individual's nutritional status. Pharmacists can be involved to varying degrees in helping consumers and patients alike with preventive strategies as well as therapies involving nutrients.

There exists a nutrition continuum from health to disease, across the life cycle, in which pharmacists have become involved based on their knowledge set and clinical opportunity. Together, as found in foods, nutrients and associated substances are critical to growth and development, as well as health maintenance. Issues relating to nutrients or to an individual's nutritional status is prominent in the management of many diseases, both acute and chronic. In the absence of the anatomic or physiologic ability to consume food products, some patients require enteral or parenteral nutrient formulations to therapeutically maintain or improve their metabolic status lasting from several days to the remainder of their lives. A vast amount of confusion and nonscientific information surrounds the relationship of foods, as specially formulated food products, to health and prevention or cure of various disease conditions. However, food behaviors of increasing numbers of people are influenced by misrepresentations and false claims made for *health* foods, fad diets, and miracle cures by individuals and groups who profit from sale of such foods or ideas. Particularly in the field of nutrition, where misinformation may endanger the health of individuals, consumers must be provided opportunity to learn to make sound decisions regarding their health and nutritional status. Pharmacists can be involved in educating patients on various aspects of nutrition, screening patients for poor nutritional status, suggesting referral for more specific needs, and managing therapeutic regimens in patients requiring dietary supplementation or nutrition support. Furthermore, depending on the setting, pharmacists may be involved in clinical or basic research that involves nutrients. They may also be involved with local or national organizations whether nonprofit or corporate. Pharmacy has a vital role to play directly when it comes to nutrition in support of patient care.

NUTRIENTS

Many materials involved in human metabolism either cannot be synthesized by the body or in quantities insufficient to meet needs. These essential substrates, nutrients, need to be delivered exogenously—ideally through a healthy diet. Nutritional status is considered optimal when nutrient requirements are balanced by nutrient intake, while body composition and function is maintained. The nutrients have been reasonably well classified as either macronutrients or micronutrients. While macronutrients are required in gram quantities daily, the micronutrients are generally required in milligram quantities or less daily. Macronutrients include protein, carbohydrate, lipid, and water. The three carbon-based nutrients flow through common routes of intermediary metabolism and contribute to the energy needs of the body, with most reactions occurring in an environment containing water. Indeed, more than 50% of body weight is made up of water. When completely metabolized, protein, carbohydrate, and fat yield 4, 4, and 9 kcal of energy per gram of nutrient, respectively. Besides roles in energy metabolism, macronutrients provide structural and transport roles within the body, and individual amino acids and fatty acids have specific physiologic roles. Evidence is also growing that the amount and form of carbohydrate and fat have profound effects on development of degenerative diseases.

Although micronutrients provide no calories toward energy needs, this group of nutrients, which includes vitamins and minerals, are physiologically important in regulating metabolism

through roles as co-enzymes and co-factors, free radical scavenging, intracellular signaling, and gene expression. Other components of food are rapidly being recognized for their importance to health, although not currently classified as nutrients. These other compounds found in food include substances such as carotenoids, flavonoids, and other phenolic derivatives. Most of these substances are found in foods of plant origin and are secondary metabolites of plant physiology intended to protect plants from their environments. Some of these substances may have roles in human health. Nutrients and associated substances are included for their roles in health, essentially no different than any other substance adopted into clinical practice that is covered in this section of the book. The current emphasis in practice should be on the overall health effects of food consumption, rather than solely on individual nutrients or associated substances. This does however require knowledge of the individual substances.

Dietary Guidelines and Nutrient Standards

The specifics of a number of nutrients and associated substances, including those found as pharmaceutical preparations, will be discussed in sections below. An appreciation for dosing strategies will be needed. The optimum human diet should meet all nutrient needs through the consumption of a wide variety of food. It should also help maintain appropriate body mass, or growth and development in children and pregnant women. The optimum diet should also prevent illness caused by deficiency or excess nutrient intake. Healthy eating patterns are those that follow the principles of adequacy, balance, and moderation by using all available guidelines related to achieving the optimum diet. Most people do not follow healthy eating patterns. It is not necessary to follow strict meal plans on a daily basis or fad diets that cannot be adhered to long-term to achieve a healthy eating pattern, but merely follow or work toward the general guidelines available.

Guidelines for nutrient intake are based on a number of science-based as well as public policy-driven initiatives. In the US this includes several qualitative and quantitative guidelines. The Healthy People 2010 is a governmental report comprising close to 500 national objectives organized into 28 focus areas, for improving health. Included in the report are about 40 objectives relating to nutrition, with one focus area dedicated to nutrition. It provides outcome targets for the year 2010 for each objective (eg, 75% of people should meet calcium requirements, currently less than 50% do). The government also provides a set of 10 general dietary guidelines for Americans as well as specific guidelines on apportioning calorie, cholesterol, and sodium intake. These guidelines on the percent of calories to be derived from various macronutrients and cholesterol and sodium intake have become similar to nutrition guidelines prepared by various non-governmental organizations (eg, American Heart Association, American Diabetic Association, American Cancer Society) to prevent or manage chronic disease. Beyond the guidelines exist some specific food guides (eg, food guide pyramid) to more easily help consumers in food selection for maintaining health.

All of the aforementioned guidelines, while updated regularly and helpful to the public in terms of making food choices consistent with a healthy eating pattern, are qualitative when it comes to intake of specific nutrients. Nutrient-specific standards are also available. The Dietary Reference Intakes (DRIs) are prepared by expert panels through the Institute of Medicine's Food and Nutrition Board to provide nutrient dosing standards based on the available evidence. These serve as the benchmark for nutritional adequacy in the US and Canada—with similar provisions in many other countries–and are a more complete set of standards that replace the periodic revision of the recommended dietary allowances that began in the 1940s. The dosing levels provided in the DRI reports are intended for healthy persons as part of the normal diet to reduce the risk of chronic disease and developmental disorders, as well as to prevent nutrient deficiencies. The DRIs encompass four types of reference values and 12 life-stage groups as data permits. The reference values include the recommended dietary allowances (RDAs) for each nutrient with adequate supporting data, or the adequate intake (AI) levels in the absence of sufficient data.

In contrast to these nutrient dosing standards, the Food and Drug Administration (FDA) sets nutrient labeling standards for foods to help consumers see how a food fits into an overall healthy eating plan. This includes use of a Daily Value (DV) for a number of nutrients, a term that encompasses two types of reference values–the Daily Reference Values (DRV) for macronutrients, cholesterol, sodium, and potassium, and the Reference Daily Intake (RDI) levels for other micronutrients. In many, but not all cases, the DV levels are the same as the highest RDA or AI level. The DV replaced the term US Recommended Daily Allowance (US RDA) in use since 1974, which itself replaced the Minimum Daily Requirements established by the FDA in 1940. Besides the labeling standards for food, health claims for food products are also under the purview of the FDA. Regarding dietary supplement products, although standards for labeling and claims exist, no review of safety, efficacy, or product quality is currently required as it is for medications. Products are labeled with *Nutrition Facts* if they are regulated as food but with *Supplement Facts* if they are regulated less closely as dietary supplements.

Nutrient Therapy

Poor nutritional status (ie, malnutrition) refers to nutrient intake not in balance with nutrient requirements. It is more common than appreciated, often present alongside a variety of clinical disorders. It can refer to undernutrition, obesity, specific nutrient imbalances, and altered states of metabolism. Poor nutritional status contributes to poor patient outcome and should therefore be regularly evaluated by health care providers. The plan to manage malnourished patients and those at risk for malnutrition will differ based on the patient and the setting. Patient-related factors that can affect nutrient needs include the following:

- Interference with food consumption (eg, impaired appetite, gastrointestinal (GI) disease, traumatic neurological disorders interfering with self-feeding, neuropsychiatric disorders, disease of soft or hard oral tissue, alcoholism, pregnancy anorexia and vomiting, food allergy, adverse drug effects, and disease requiring a restricted diet).
- Interference with absorption (eg, absence of normal digestive secretions, intestinal hypermotility, reduction of effective absorbing surface, impairment of intrinsic mechanism of absorption, and drugs preventing absorption.)
- Interference with utilization or storage (eg, impaired liver function, hypothyroidism, neoplasm of GI tract, and drug therapy or radiation).
- Increased destruction of tissues and/or function (eg, severe trauma, achlorhydria in the GI tract, heavy metals, and other metabolic antagonists).
- Increased excretion or loss of nutrients (eg, lactation, burns, glycosuria and albuminuria, acute chronic blood loss, and drug-induced).
- Increased nutrient requirements (eg, increased physical activity, periods of rapid growth, pregnancy and lactation, fever, hyperthyroidism, and drug therapy).

The approach to the patient requiring nutritional intervention may include education, referral to a dietitian or other health care provider, or a therapeutic regimen. Regimens can include diet therapy under the care of a dietitian, as well as nutrient therapy as dietary supplements, medical foods, drugs, or specialized nutrition support.

Nutrition Support

For patients who are otherwise unable to maintain or improve their nutritional status through an oral diet, specialized nutrition support regimens may be required. The route of adminis-

tration will depend in large part on the status of the GI tract. Enteral nutrition (ie, tube feeding) is used if the GI tract is functional and safe access exists. When enteral feeding is impractical or contraindicated, the alternative is intravenous feeding known as *parenteral nutrition (PN),* sometimes referred to as *total parenteral nutrition*, and previously referred to as *intravenous* or *parenteral hyperalimentation*. Such feeding provides essential macronutrients and micronutrients in a sufficiently concentrated form that does not exceed normal daily fluid requirements. These necessarily hypertonic admixtures are infused at a constant rate throughout the entire day into a large-diameter *central* vein where rapid dilution by high blood-flow minimizes vascular damage and the risk of phlebitis or thrombosis that is likely to occur on injection into a peripheral vein. Ambulatory patients may receive the infusion for only part of the day. The infusion is generally through a catheter whose distal end is in the superior vena cava.

A critical component in PN is a nitrogen source available for repletion and/or maintenance of lean body mass and proteins essential for wound healing, tissue repair, and growth. Solutions of mixed crystalline L-amino acids serve as the nitrogen source. Crystalline L-amino acids appear to be more efficiently metabolized and better tolerated in the body than were the peptides of protein hydrolysates used years ago. Also, individual amino acids may be readily and reproducibly formulated to meet specific requirements of patients (eg, premature infants). So that amino acids may be used for protein synthesis and to achieve positive nitrogen balance and weight gain in debilitated patients it is necessary to provide a nonprotein calorie source. Both concentrated dextrose solutions (50%, 70%) and intravenous lipid emulsions (10%, 20%, 30%) are available as caloric sources. The hydrated dextrose product provides 3.4 kcal/g, while the lipid emulsions provide 9 kcal/g plus the additional calories from the glycerol used to make the product isotonic. The lipid emulsion is also a source of essential fatty acids. Occassionally, based on PN stability or clinical circumstances, the lipid emulsion is not included in the admixture. If administered separately the 10% and 20% emulsion products may be administered through central or peripheral veins. If an intravenous emulsion is not used at all, large amounts of dextrose are required to achieve caloric balance and this may increase the risk of adverse effects from the dextrose.

In addition to amino acids, dextrose, and lipids, PN admixtures will contain vitamins, minerals, and electrolytes (often added to meet individual patient requirements). The final, patient-specific admixture is compounded using aseptic technique, under laminar airflow conditions and usually dispensed in an appropriate single, daily container. The preparation of the admixture is expected to follow accepted guidelines and standards of practice for dosing, labeling, and compounding with particular attention to stability and compatibility.

PROTEINS AND AMINO ACIDS

Proteins serve a structural role in all cells of the body and function as enzymes, hormones, and membrane transporters. The fundamental units of any protein are the amino acids. Protein and amino acids are consumed in the human diet. Some amino acids are considered indispensable (essential) in that they cannot be synthesized endogenously, and therefore are required in the diet (Table 92-1). The remaining amino acids are dispensable (non-essential) although many of them become indispensable under certain physiologic or pathologic conditions and are referred to as conditionally indispensable (conditionally essential) amino acids (see Table 92-1). The recommended protein requirement for healthy individuals across the life stages is provided in Table 92-2. Specific dosing requirements for individual amino acids are being generated as well. In recent years certain free amino acids have been prescribed for a variety of medical conditions for which neither drug nor food approval have been obtained. Regulations on the food-additive use are limited to providing protein requirements. Therefore, these uses of single amino acids are without approved status. Consumption of high levels of single amino acids has been associated with severe metabolic and medical consequences. For patients unable to consume food orally, a source of amino acids can be provided enterally or parenterally.

Commercially available amino acid injections used in preparing PN vary in the amount of protein (3.5–15 g/100 mL), nitrogen (0.55–2.37 g/100 mL), indispensable and dispensable amino acids, pH (4.5–7), osmolarity (357–1388 mOsm/L), and electrolyte content. These synthetic, crystalline L-amino acids replaced use of protein hydrolysates. A number of amino acids are either too poorly soluble and/or unstable to be included in amino acid products (eg, cysteine, glutamine).

CHEMISTRY—The USP has provided monographs of standards and tests for each of the crystalline amino acids used in amino acid dosage forms. For comparative purposes the formulas and chemical names of the L-amino acids are given in Chapter 26 and other chemical data are provided in Table 92-3.

Each of the amino acids is synthesized readily, by a variety of methods, but always as a DL-mixture. Resolution to obtain the L-form in most cases is conveniently accomplished.

The articles that follow describe a few amino acids that are used for certain nonnutritional purposes as well as components of nutritional formulations.

ARGININE HYDROCHLORIDE

R-Gene 10

L-Arginine monohydrochloride [1119-34-2] $C_6H_{14}N_4O_2$.HCl (210.66). For the structural formula of arginine, see Chapter 26.

Preparation—Arginine is present in the hydrolysis products of many proteins; for a method of separating it from gelatin hydrolysate. See *J Biol Chem* 1940; 132: 325. It is converted to the hydrochloride by reaction with HCl.

Description—White crystals or crystalline powder; practically odorless.

Solubility—Soluble in water; slightly soluble in hot alcohol.

Comments—Arginine has been variously used in clinical practice. Intravenous administration in the symptomatic management of severe encephalopathies associated with ammoniacal azotemia, on the theory that arginine combines with ammonia to form asparagine, has not been of value in significantly reducing blood ammonia levels or in improving the clinical status of patients, and use of the amino acid for this purpose is no longer approved by the FDA. Oral administration to patients with cystic fibrosis to correct malabsorption and steatorrhea and by inhalation as a mucolytic have not been effective. It is used as a nutritional supplement in conditions in which its dibasic amino character or possible blood ammonia–reducing power is useful. As a precursor of nitric oxide, its clinical use should be approached with caution.

Table 92-1. Amino Acids

INDISPENSABLE	CONDITIONALLLY INDISPENSIBLE	DISPENSABLE
Histidine	Arginine	Alanine
Isoleucine	Cysteine	Aspartate
Leucine	Glutamine	Asparagine
Lysine	Glycine	Glutamate
Methionine	Proline	Serine
Phenylalanine	Tyrosine	
Threonine		
Tryptophan		
Valine		

Table 92-2. Dietary Reference Intakes—Macronutrients

LIFE STAGE GROUP	Protein (g/kg/d)	Carbohydrate (g/d)	Fat (g/d)	Energy (kcal/d)	Fiber (g/d)
Infants					
0–6 months	1.52*	60*	31*	520-570	ND[1]
7–12 months	1.5	95*	30*	676-743	ND
Children					
1–3 years	1.1	130	ND[1]	992-1046	19*
4–8 years	0.95	130	ND	1642-1742	25*
Males					
9–13 years	0.95	130	ND	2279	31*
14–18 years	0.85	130	ND	3152	38*
19–30 years	0.8	130	ND	3067 – x [2]	38*
31–50 years	0.8	130	ND	3067 – x	38*
51–70 years	0.8	130	ND	3067 – x	30*
>70 years	0.8	130	ND	3067 – x	30*
Females	0.95	130	ND	2071	26*
9–13 years	0.85	130	ND	2368	36*
14–18 years	0.8	130	ND	2403 – y [3]	25*
19–30 years	0.8	130	ND	2403 – y	25*
31–50 years	0.8	130	ND	2403 – y	21*
51–70 years	0.8	130	ND	2403 – y	21*
>70 years					
Pregnancy					
≤18 years		175	ND	2368-2820	28*
19–30 years		175	ND	2403-2855	28*
31–50 years		175	ND	2403-2855	28*
Lactation					
≤18 years		210	ND	2698-2768	29*
19–30 years		210	ND	2733-2803	29*
31–50 years		210	ND	2733-2803	29*

* Adequate Intake Level, otherwise values represent Recommended Dietary Allowances:
[1] Not determined or not described in the current recommendations.
[2] x = 10 kcal/d for each year above 19 years is subtracted from 3067 kcal/d.
[3] y = 7 kcal/d for each year above 19 years is subtracted from 2403 kcal/d.

Table 92-3. L-Amino Acids

AMINO ACID[a]	MOLECULAR FORMULA	MOLECULAR WEIGHT	SOLUBILITY IN WATER	pK VALUES
L-Alanine 56-41-7	$C_3H_7NO_2$	89.09	1 g in 6 mL	pK_1 3.34 pK_2 8.17
L-Arginine 74-79-3	$C_6H_{14}N_4O_2$	174.20	1 g in 5 mL	pK_1 2.18 pK_2 9.09 pK_3 13.2
L-Aspartic acid 56-84-8	$C_4H_7NO_4$	133.10	1 g in 200 mL	pK_1 1.88 pK_2 3.65 pK_3 9.60
L-Cysteine 52-90-4	$C_3H_7NO_2S$	121.16	Freely soluble	pK_1 1.71 pK_2 8.33 pK_3 10.78
L-Cystine 56-89-3	$C_6H_{12}N_2O_4S_2$	240.30	1 g in 9 L	pK_1 1 pK_2 2.1 pK_3 8.02 pK_4 8.71
L-Glutamic acid 56-86-0	$C_5H_9NO_4$	147.13	1 g in 115 mL	pK_1 2.19 pK_2 4.25 pK_3 9.67
L-Glutamine 56-85-9	$C_5H_{10}N_2O_3$	146.15	1 g in 31 mL	pK_1 2.17 pK_2 9.13
L-Glycine	$C_2H_5NO_2$	75.07	1 g in 4 mL	pK_1 2.34 pK_2 9.6
L-Histidine 71-00-1	$C_6H_9N_3O_2$	155.16	1 g in 24 mL	pK_1 1.78 pK_2 5.97 pK_3 8.97
L-Hydroxyproline	$C_5H_9NO_3$	131.13	1 g in 3 mL (α-form)	pK_1 1.82 pK_2 9.65
L-Isoleucine[b] 73-32-5	$C_6H_{13}NO_2$	131.17	1 g in 25 mL	pK_1 2.36 pK_2 9.68
L-Leucine[b] 61-90-5	$C_6H_{13}NO_2$	131.17	1 g in 42 mL	K_a 2.5 × 10^{-10} K_b 2.3 × 10^{-2}
L-Lysine[b] 56-87-1	$C_6H_{14}N_2O_2$	146.19	Freely soluble	pK_1 2.20 pK_2 8.90 pK_3 10.28

(continues)

Table 92-3. *(continued)*

AMINO ACID[a]	MOLECULAR FORMULA	MOLECULAR WEIGHT	SOLUBILITY IN WATER	PK VALUES
L-Methionine[b] 63-68-3	$C_5H_{11}NO_2S$	149.21	Soluble	pK_1 2.12 pK_2 9.28
L-Phenylalanine[b] 63-91-2	$C_9H_{11}NO_2$	165.19	1 g in 34 mL	pK_1 2.16 pK_2 9.18
L-Proline 147-85-3	$C_5H_9NO_2$	115.13	1 g in 0.7 mL	pK_1 1.99 pK_2 10.60
L-Serine 56-45-1	$C_3H_7NO_3$	105.09	1 g in 20 mL	pK_1 2.19 pK_2 9.21
L-Taurine 107-35-7	$C_2H_7NO_3S$	125.14	1 g in 16 mL	pK_1 1.50 pK_2 8.74
L-Threonine[b] 72-19-5	$C_4H_9NO_3$	119.12	Freely soluble	pK_1 2.15 pK_2 9.12
L-Tryptophan[b] 73-22-3	$C_{11}H_{12}N_2O_2$	204.22	1 g in 88 mL	pK_1 2.38 pK_2 9.39
L-Tyrosine 60-18-4	$C_9H_{11}NO_3$	181.19	1 g in 2.2 L	pK_1 2.20 pK_1 9.11 pK_2 10.07
L-Valine[b] 72-18-4	$C_5H_{11}NO_2$	117.15	1 g in 12 mL	pK_1 2.32 pK_2 9.62

[a] The number below the name of each amino acid is its *Chemical Abstracts Service* (CAS) Registry Number. For structures and nomenclature see Chapter 26.
[b] Indispensable amino acids.

It stimulates pituitary release of growth hormone and prolactin and pancreatic release of glucagon and insulin, and arginine hydrochloride is used diagnostically to evaluate pituitary growth hormone reserve and detect deficiency of the hormone in various conditions. It is administered by intravenous infusion, and blood samples are taken at 30-min intervals after beginning infusion, for 2.5 hr; the plasma growth hormone levels in these samples and in others taken 30 min before and at the start of infusion are determined and diagnostically evaluated.

GLYCINE

Aminoacetic Acid; Glycocoll

NH_2CH_2COOH [56-40-6] $C_2H_5NO_2$ (75.07).

Preparation—Aminoacetic acid is a constituent of many proteins. It may be synthesized by many processes; industrially it is prepared by interaction of ammonia with chloroacetic acid.

Description—White, odorless, crystalline powder, with a sweetish taste; solution is acid to litmus; pK_a 9.78.

Solubility—1 g in 4 mL water or 1254 mL alcohol; very slightly soluble in ether.

Comments—As an irrigating fluid in transurethral resection of the prostate. The acid also is used in an antacid preparation, as a complex salt. However, its limited buffering capacity does not warrant the expense of such a preparation. It is used primarily in admixture with other amino acids in PN formulations.

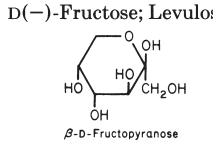
CARBOHYDRATES

Carbohydrates include simple pentoses and hexoses, as well as disaccharides and polymers of the simpler molecules. In the form of D-glucose (dextrose) carbohydrates provide cellular energy. Specific carbohydrates have alternative physiologic roles beyond energy (eg, ribose in nucleic acids). The chemistry of the sugars is discussed in Chapter 26. As part of a healthy eating pattern carbohydrates should make up about 45% to 65% of energy intake. The recommended dietary intake is provide in Table 92-2. For patients unable to consume food orally, a source of carbohydrate can be provided enterally or parenterally. In the section below are listed only those sugars that are used in medicine as aliments. Some of the carbohydrates also have important uses as pharmaceutical necessities, in parenteral fluids, as diuretics, as osmotic filler for injection of other drugs, etc; consequently, the monographs of certain nutrient carbohydrates may be found elsewhere in this volume.

DEXTROSE—page 1085.
DEXTROSE INJECTION—page 1323.
DEXTROSE AND SODIUM CHLORIDE INJECTION—page 1324.

FRUCTOSE

D(−)-Fructose; Levulose



D-Fructose [57-48-7] $C_6H_{12}O_6$ (180.16); a sugar usually obtained by the inversion of aqueous solutions of sucrose and subsequent separation of fructose from glucose.

Preparation—Sucrose is inverted by treatment with dilute acid at moderate temperature, and the fructose is separated by precipitation of the lime-fructose complex. Fructose is released from the complex with carbon dioxide, which precipitates the calcium as carbonate. After filtering, the fructose solution is purified with activated carbon and ion-exchange resins and evaporated to dryness.

Description—Colorless crystals or a white, crystalline or granular powder, which is odorless and has a sweet taste; specific rotation, −89 to −91°.

Solubility—1 g in about 15 mL alcohol or about 14 mL methanol; freely soluble in water.

Comments—A ketohexose used parenterally as a carbohydrate nutrient. It is converted to liver glycogen and metabolized more rapidly than dextrose, without requiring insulin, and thus may be used in diabetic patients. It is indicated in patients requiring fluid replacement and caloric feeding but contraindicated in hypoglycemia, for which dextrose should be used. It also is contraindicated in patients with hereditary fructose intolerance.

LACTOSE—page 1087.
LIQUID GLUCOSE—page 1086.
SUCROSE—page 1067.
SYRUP—page 1071.

OTHER SUGARS

Invert Sugar

[8013-17-0]—An equimolar mixture of glucose and fructose, produced by hydrolysis of sucrose. Forms clear, colorless solutions with a pH of 3.5 to 6. *Comments:* Instead of dextrose, for parenteral administration of carbohydrate. While it has the same caloric value as dextrose (4 kcal/g), invert sugar is utilized more rapidly and may be administered intravenously twice as fast as dextrose.

LIPIDS AND FATTY ACIDS

Dietary fat provides much of the energy required and is more calorically dense than carbohydrate. Dietary lipids contain predominantly triglycerides, which are made up of 3 fatty acids on a glycerol backbone. There are about 3 dozen fatty acids found in nature that vary in terms of carbon chain length and in degree of saturation. Some fatty acids contribute to increasing chronic disease risk while others may reduce it. Only two fatty acids are considered to be essential—linoleic acid, and α-linolenic acid. As part of a healthy eating pattern, lipids should make up about 20% to 35% of energy intake. The amounts of saturated and trans fatty acids should be limited in preference for unsaturated fatty acids. The ideal amount of monounsaturated, ω-6 or ω-3 polyunsaturated fatty acids required for health continue to be investigated. Besides energy provision, fatty acids play a role in transport, membrane structure and integrity, serving as eicosanoid precursors and in intracellular signaling and gene expression.

In recent years, it has been shown that the digestion and absorption of short- and medium-chain triglycerides (MCTs) are different from those of the long-chain triglycerides that are characteristic of most food fat. The hydrolysis and absorption of MCTs are faster than those of long-chain triglycerides, and it is possible for MCTs to be absorbed directly into the intestinal mucosa without first being hydrolyzed, making it possible to absorb MCTs in the absence of pancreatic juice and bile. MCTs only yield about 7 kcal/g. Coconut oil contains more medium-chain fatty acids than other fats and oils and is used as a source for fractionation and preparation of MCTs. MCTs are commercially available as relatively pure 8-carbon or 10-carbon triglycerides and as a 4:1 mixture. MCTs have been found to be useful in conjunction with the usual therapy in the treatment of diseases such as pancreatic insufficiency, cancer of the pancreas, cystic fibrosis of the pancreas, obstruction of the bile duct, certain abnormalities in the lymphatic system, regional enteritis, and postoperative cases involving the removal of much of the stomach or small intestine. The most consistent beneficial effects reported from the use of MCTs are a decrease in the fecal loss of fat and less diarrhea. There is commercial interest in continuing to develop triglycerides that contain mixtures of long-chain, medium-chain, and even short-chain fatty acids on the same glycerol backbone (ie, structured triglycerides).

For patients unable to consume food orally, a source of fatty acids can be provided enterally or parenterally.

Intravenous fat emulsions typically contain safflower and/or soybean oil, egg yolk phospholipids, glycerin, and water for injection. The fat particles containing long-chain triglycerides are less than 0.5 μm in diameter, similar in size to naturally occurring chylomicrons. These emulsions are available in 10%, 20%, and 30% products and provide the essential fatty acids. Dosing does not usually exceed 1 g/kg daily. Although not yet available on the US market, intravenous lipid emulsions containing physical mixtures of long-chain and medium-chain triglycerides are available elsewhere. Additionally, use of structured triglycerides for intravenous use continues to be investigated.

Intravenous Fat Emulsion [Liposyn; Intralipid]—*Description:* Water emulsions of 10%, 20%, and 30% using safflower and/or soybean oil; osmolarity of 258–310 mOsm/L; pH 6–9; particle size less than 0.5 μm in diameter. *Comments:* As source of calories and essential fatty acids, usually for patients requiring parenteral nutrition for more than 5 days. The predominant fatty acids in these products are linoleic acid (50–66%) and oleic acid (18–26%), with lesser quantities of several other fatty acids including linolenic acid (4–11%).

CORN OIL—page 1071.
OLIVE OIL—see RPS-19, page 1400.
PEANUT OIL—page 1072.

WATER

Human water requirements are individualized to maintain fluid balance and daily solute load. For the average adult consuming a typical diet and maintaining a moderate activity level a daily dose of 30–40 mL/kg is considered adequate. Recently published DRIs for water and the electrolytes suggest adult AI levels for water of 2.7 L (women) and 3.7 L (men) from foods as well as beverages. While water is most appropriately administered orally with a diet, or through an enteral access device along with an enteral nutrient formulation, some patients require intravenous administration. Options to deliver water intravenously must necessarily take into consideration physiologic issues. Administration of hypotonic fluid into the vascular space will decrease serum osmolality leading to lysis of cells if severe. For this reason sterile water for injection can only be administered as part of an admixture with an estimated osmolarity closer to the physiologic range. Very specific clinical exceptions exist for the use of hypertonic admixtures. Dextrose-containing intravenous fluid may be used to deliver water (ie, electrolyte-free water).

WATER FOR INJECTION—pages 809 and 1070.
DEXTROSE IN WATER INJECTION—page 1323.

VITAMINS

Vitamins are organic compounds required for normal human growth, development, and maintenance that are unable to be synthesized by anabolic processes. Those with adequate data supporting dietary recommendations are listed in Table 92-4 (fat-soluble) and Table 92-5 (water-soluble). These compounds are effective in small amounts, do not furnish energy, and are not used as building units for the structure of the organism, but are essential for transformation of energy and for regulation of the metabolism of structural units. In addition to protein, carbohydrates, fats, mineral salts, and water, it is essential that the food contain small amounts of these organic substances. If any one of these compounds is lacking in the diet, biochemical alterations result in changes in tissue/organ structure/function that subsequently results in clinical manifestations known as deficiency diseases.

Table 92-4. Dietary Reference Intakes — Fat-Soluble Vitamins

LIFE STAGE GROUP	Vitamin A (μg/d)[1]	Vitamin D (μg/d)[2]	Vitamin E (mg/d)[3]	Vitamin K (μg/d)
Infants				
0-6 months	400*	5*	4*	2*
7-12 months	500*	5*	6*	2.5*
Children				
1-3 years	300	5*	6	30*
4-8 years	400	5*	7	55*
Males				
9-13 years	600	5*	11	60*
14-18 years	900	5*	15	75*
19-30 years	900	5*	15	90*
31-50 years	900	5*	15	90*
51-70 years	900	10*	15	90*
>70 years	900	15*	15	90*
Females				
9-13 years	600	5*	11	60*
14-18 years	700	5*	15	75*
19-30 years	700	5*	15	90*
31-50 years	700	5*	15	90*
51-70 years	700	10*	15	90*
>70 years	700	15*	15	90*
Pregnancy				
≤18 years	750	5*	15	75*
19-30 years	770	5*	15	90*
1531-50 years	770	5*	15	90*
Lactation				
≤18 years	1200	5*	19	75*
19-30 years	1300	5*	19	90*
31-50 years	1300	5*	19	90*

* Adequate Intake Level, otherwise values represent Recommended Dietary Allowances:
[1] As retinol activity equivalents (RAE), 1 μg RAE = 1 μg all-trans retinol or 12 μg β-carotene or 24 μg α-carotene or β-cryptoxanthin
[2] As cholecalciferol, 1 μg = 40 IU vitamin D
[3] As α-tocopherol, including RRR-α-tocopherol and the 2R-stereoisomeric forms, but not the 2S-stereoisomeric forms of α-tocopherol

Table 92-5. Dietary Reference Intakes—Water-Soluble Vitamins

LIFE STAGE GROUP	Thiamine (mg/d)	Riboflavin (mg/d)	Niacin (mg /d)1	Vitamin B6 (mg/d)	Folate (μg/d)2	Vitamin B12 (μg/d)	Pantothenic Acid (mg/d)	Biotin (μg/d)	Choline (mg/d)	Vitamin C (mg/d)
Infants										
0-6 months	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*	40*
7-12 months	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*	50*
Children										
1-3 years	0.5	0.5	6	0.5	150	0.9	2*	8*	200*	15
4-8 years	0.6	0.6	8	0.6	200	1.2	3	12	250*	25
Males										
9-13 years	0.9	0.9	12	1	300	1.8	4*	20*	375*	45
14-18 years	1.2	1.3	16	1.3	400	2.4	5*	25*	550*	75
19-30 years	1.2	1.3	16	1.3	400	2.4	5*	30*	550*	90
31-50 years	1.2	1.3	16	1.3	400	2.4	5*	30*	550*	90
51-70 years	1.2	1.3	16	1.3	400	2.4	5*	30*	550*	90
>70 years	1.2	1.3	16	1.3	400	2.4	5*	30*	550*	90
Females										
9-13 years	0.9	0.9	12	1	300	1.8	4*	20*	375*	45
14-18 years	1	1	14	1.2	400	2.4	5*	25*	400*	65
19-30 years	1.1	1.1	14	1.3	400	2.4	5*	30*	425*	75
31-50 years	1.1	1.1	14	1.3	400	2.4	5*	30*	425*	75
51-70 years	1.1	1.1	14	1.5	400	2.4	5*	30*	425*	75
>70 years	1.1	1.1	14	1.5	400	2.4	5*	30*	425*	75
Pregnancy										
≤18 years	1.4	1.4	18	1.9	600	2.6	6*	30*	450*	80
19-30 years	1.4	1.4	18	1.9	600	2.6	6*	30*	450*	85
31-50 years	1.4	1.4	18	1.9	600	2.6	6*	30*	450*	85
Lactation										
18 years	1.4	1.6	17	2	500	2.8	7*	35*	550*	115
19-30 years	1.4	1.6	17	2	500	2.8	7*	35*	550*	120
31-50 years	1.4	1.6	17	2	500	2.8	7*	35*	550*	120

* Adequate Intake Level, otherwise values represent Recommended Dietary Allowances
[1] As niacin equivalents, 1 mg niacin = 60 mg tryptophan
[2] As dietary folate equivalents (DFE), 1 μg DFE = 1 μg food folate = 0.6 μg folic acid consumed with food = 0.5 μg folic acid supplement taken on an empty stomach

Vitamins are unlike each other in chemical composition and function. They are alike only in that they cannot be synthesized at all or at least not at an adequate rate in human tissues. The functions they serve fall into two categories, the maintenance of normal structure and of normal metabolic functions.

It is convenient in a discussion of this subject to divide these nutritional substances into two groups, the *fat-soluble* and the *water-soluble factors*, although a more clinical distinction is needed (eg, therapeutic index). Vitamins A, D, E, and K fall into the fat-soluble group, since they can be extracted with fat solvents and are found in the fat fractions of tissues. The water-soluble vitamins include ascorbic acid and the B group of vitamins, which consists of some 10 or more well-defined compounds. The characterization of vitamins as essential metabolic factors with discrete chemical structures required their isolation in pure form from natural sources and subsequent laboratory synthesis. Commercial chemical or microbiological syntheses, some from relatively simple compounds, are the source of most of the vitamins now used in pharmaceutical preparations, dietary supplements, and fortified foods.

Vitamin activity or potency has been measured by three principal types of methods: biological, microbiological, and chemical assays.

The status of vitamin methods of assay is now such that manufacturers of vitamin preparations find it possible to state with precision the potency of their products, and tables of vitamin content of foods are, for most vitamins, quite complete. Methods of assay are described briefly in the individual vitamin sections.

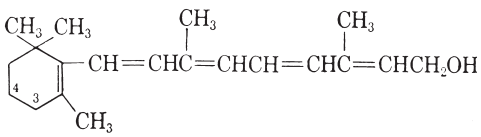
In the interest of improvement and uniformity of expressing the results of such assays, the World Health Organization (WHO) of the United Nations has sponsored the preparation and distribution of Standards. The USP provides such reference standards for the US. As a rule, an International Standard is no longer provided once the substance responsible for its characteristic activity has been isolated, identified, and made readily available. Availability of the vitamins in pure form encouraged transition from the use of International Units to the use of weight in expressing amounts present in vitamin products, although the FDA has yet to implement this for labeling provisions.

The Fat-Soluble Vitamins

VITAMIN A

Vitamin A was the first fat-soluble vitamin discovered. Animal nutritionists observed growth failures in calves born of cows maintained on wheat or oats alone, whereas whole corn plants supported growth and development of the animals. The vitamin was found to be related to chlorophyll and carotenoid-containing plants. Later study revealed that the vitamin is essential for the maintenance of normal tissue structure and for other important physiological functions such as vision and reproduction.

Chemistry and Assay—Vitamin A is represented primarily by the cyclic polyene alcohol vitamin A_1 (retinol) with an empirical formula of $C_{20}H_{30}O$ and whose four conjugated double bonds in the side chain are in the *trans* arrangement.

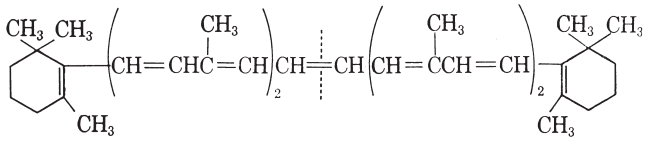


Vitamin A (Retinol) (Vitamin A_1)

Other naturally occurring forms have low biological activity and no commercial significance.

Vitamin A_1 is a pale yellow crystalline compound, is soluble in lipid solvents, and has a UV absorption maximum at 328 nm. The vitamin is not readily destroyed by heat but is oxidized easily and is less stable in acid than in alkaline solution. The esters of vitamin A_1 with the fatty acids acetic and palmitic are commercially important, since they are considerably more stable than the alcohol.

An additional source of vitamin A is the carotenoid pigments, the yellow-colored compounds in all chlorophyll-containing plants. At least 10 different carotenoids exhibit provitamin A activity, but only α- and β-carotene and cryptoxanthin are important in animal nutrition, β-carotene being the most important.



β-Carotene

Theoretically one molecule of β-carotene should yield two molecules of vitamin A_1; however, the availability of carotene in foods as sources of vitamin A for humans is low and extremely variable. This utilization efficiency of carotene is generally considered to be 1/12 for humans; that is, 1 μg of β-carotene would have the same biological activity as 0.083 μg of retinol. This conservatively takes into account the decremental effects on carotene utilization of absorption, transport, and tissue conversion to the active vitamin. The conversion of the provitamin to vitamin A occurs primarily in the walls of the small intestine and perhaps to a lesser degree in the liver; conversion is linked to body stores of vitamin A. Like vitamin A_1, the carotenes are soluble in fat solvents, in crystalline form appear deep orange or copper-colored, and have characteristic absorption spectra.

Total synthesis of vitamin A_1 and β-carotene is achieved commercially, vitamin A usually being prepared as the acetate. Concentration of vitamin A from animal fats and fish liver oil is still important. The principal steps in the process are molecular distillation, saponification and crystallization of the distillate, and acylation to the desired ester.

The USP Unit for vitamin A is identical to the International Unit and equals the biological activity of 0.3 μg of the all-trans isomer of retinol. The USP Reference Standard for vitamin A is a 3.7% solution of crystalline vitamin A acetate in cottonseed oil and peanut oil.

Vitamin A can be assayed by direct measurement of its ultraviolet absorption by photometric evaluation of the color reaction with antimony trichloride in chloroform (the Carr-Price reaction), by high-pressure liquid chromatographic separation and ultraviolet and visible spectrometry, or by a biological method based on the resumption of growth of rats when the vitamin activity is added to a vitamin A–deficient diet.

Metabolic Functions—Vitamin A and its metabolites can serve as ligands for several binding proteins and receptors important for transport and effect. Of the known functions of vitamin A in the body, its role in the visual process is established best. The retina of man contains two distinct photoreceptor systems. The rods, which are the structural components of one system, are especially sensitive to light of low intensity. A specific vitamin A aldehyde is essential for the formation of rhodopsin (the high-molecular-weight glycoprotein part of the visual pigment within the rods) and the normal functioning of the retina. By virtue of this relation to the visual process, vitamin A alcohol has been named retinol, and the aldehyde form named retinal. A vitamin A–deficient person has impaired dark adaptation *(night-blindness)*.

Vitamin A also participates in the maintenance of the integrity of the epithelial membranes such that normal structures may be substituted by stratified keratinizing epithelium in the eyes, paraocular glands, and respiratory, alimentary, and genitourinary tracts under the stresses of a deficiency. The basal cells do not lose their function under such conditions, however, and are able to be restored to normal when sufficient vitamin A is absorbed. Abnormalities of nerve and connective tissue and of bones are further consequences of a dietary deficiency of the vitamin. In severe deficiency the affected epithelial and connective tissue may become the site of infections because of the cells' reduced resistance to bacterial invasion. This gave rise to the notion that administration of vitamin A was useful in the treatment of skin infections. Both topical and oral vitamin A, and especially vitamin A acid (*trans*-retinoic acid, tretinoin), are prescribed by some physicians to treat acne vulgaris; however, *trans*-retinoic acid has been shown to be equally effective, with less harmful side effects than oral isotretinoin (*cis*-retinoic acid).

There is a growing body of epidemiological data that suggest that foods that are a good source of vitamin A and carotenoids are protective against a variety of epithelial cancers. This association simply may be a result of a chronic vitamin A deficiency, since vitamin A is required for normal cell differentiation of stem cells in epithelial tissue. Also, there is the possibility that the observed protective effect could have been due to other undetected carotenoids, other vitamins, or compounds present in these foods. Some, but not all, animal studies show a positive effect for vitamin A and synthetic retinoids against epithelial cancers of the skin, lung, bladder, and breast.

The common severe deficiency symptoms are increased susceptibility to microbial infections, xerophthalmia and other eye disorders, loss of appetite and weight, and sterility, conditions that require a long time for their development. Although the recommended dietary allowance is no more than 900 μg/day, in a deficiency much greater amounts are indicated. For example, a therapeutic single oral dose range is from 7.5–30 mg for older children and non-pregnant adults.

If large doses of vitamin A are ingested for long periods of time, manifestations of toxicity develop. In the absence of a deficiency, chronic administration of 7.5–15 mg of vitamin A daily induces pathological changes in bone and periosteal tissues, skin and mucous membranes, and liver and changes in behavior. Doses as low as 5.5 mg of a water-dispersed vitamin A preparation daily for 1 to 3 months are reported to be toxic for infants 3 to 6 months of age. Vitamin A toxicity has occurred in infants who were given liver daily for a period of 3 months. Animal studies show that levels as low as four times the requirements increase the incidence of birth defects. Epidemiological studies in humans have indicated that levels as low as 4.5 mg during the first trimester of pregnancy may increase the risk of birth defects.

Dietary Requirement and Food Sources—The current dietary intake requirements for vitamin A for all life-stages can be found in Table 92-4.

About 1/2 of the vitamin A activity in the average American diet comes from β-carotene and related compounds. The other 1/2 is provided by the vitamin itself present in foods of animal origin. Not all of the carotene present in the food eaten is converted into vitamin A. Some passes through the digestive tract and is excreted as such. Of that absorbed, only the amounts necessary to meet requirements are converted to vitamin A. The rest is stored in the body or excreted. Intake of large amounts of carotene frequently causes a yellow-orange color to the skin, which is considered to be harmless. The richest sources of carotene are yellow and green (leafy) vegetables and yellow fruits. Preformed vitamin A_1 is supplied primarily from the fat of dairy products and egg yolk, but other important sources in some diets are liver, kidney, and fish. Federal regulations provide for the optional addition of 4.5 mg of vitamin A per pound of margarine. Almost all margarine is so fortified. There are also provisions for marketing vitamins A- and D–fortified nonfat dry milk containing 150 μg vitamin A and 2.5 μg vitamin D/8 fl oz reconstituted.

VITAMIN A PREPARATIONS

Contains a suitable form of retinol ($C_{20}H_{30}O$; vitamin A alcohol). It may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. It may be diluted with edible oils, or it may be incorporated in solid, edible carriers or excipients, and it may contain suitable antimicrobial agents, dispersants, and antioxidants.

Note—In stating the potency and dosage of vitamin A dosage forms μg of retinol is preferred. It was customary to use either the International Unit (IU) or the equivalent USP Unit, where one USP Unit (or International Unit) of vitamin A is defined as the specific biological activity of 0.3 μg of the all-*trans* isomer of retinol.

Description—Yellow to red, oily liquid that may solidify upon refrigeration; in solid form, it has the appearance of any diluent that has been added; may be nearly odorless or may have a fish odor but has no rancid odor or taste; unstable to air and light.

Solubility—In liquid form, insoluble in water or glycerin; soluble in absolute alcohol or vegetable oils; very soluble in ether or chloroform. In solid form, may be dispersible in water.

Comments—The only valid therapeutic uses are in the treatment of vitamin A *deficiency* or in the *prophylaxis* of deficiency in persons with a known dietary deficiency, a high requirement, or an absorption defect. Large doses produce toxicity (see the general statement), symptoms of which may not be evident for 6 months or longer. Daily doses larger than 7500 μg should not be prescribed unless severe deficiency exists.

Vitamin A Acetate [Retinol Acetate; $C_{22}H_{32}O_2$]—Light-yellow to red oil with a slight fishy odor; light and oxygen cause deterioration; tasteless. Soluble in lipid solvents; insoluble in water. *Comments:* A form of vitamin A; 0.344 μg is equivalent to 1 USP Unit or to 0.6 μg of β-carotene.

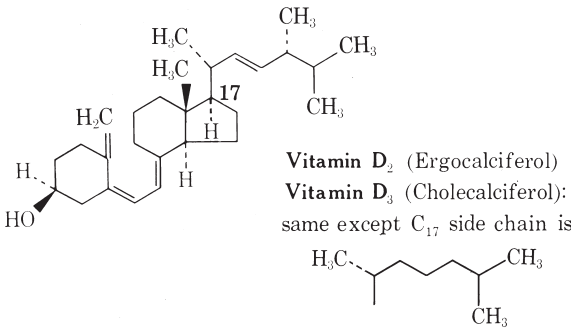
Vitamin A Palmitate [Retinol Palmitate; $C_{36}H_{60}O_2$]—Light-yellow to red oil; odorless in the pure state but otherwise has a slight fishy odor; unstable in light and air. Soluble in oils and lipid solvents; insoluble in water. *Comments:* A form of vitamin A.

TRETINOIN—pages 1288 and 1585.

VITAMIN D

Vitamin D is the antirachitic vitamin effective in promoting calcification of the bony structures of man. It sometimes is known popularly as the *sunshine* vitamin because it is formed by the action of the sun's ultraviolet rays on precursor sterols in the skin. Exposure to sunlight, therefore, has a powerful antirachitic effect. The term *rachitic* denotes the condition of a person affected with the deficiency disease rickets, in which bone is poorly mineralized and unable to support the weight of the body.

Chemistry and Assay—The two immediate biological precursors (provitamins) of the vitamins D are the steroid alcohols ergosterol (ergosta-5,7,22*E*-trien-3β-ol) and 7-dehydrocholesterol (cholesta-5,7-dien-3β-ol). Under the influence of UV light, each undergoes scission of the 9(10) bond of the steroid nucleus with the simultaneous creation of a 10(19) double bond yielding, respectively, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol).



Pure vitamins D_2 and D_3 are white, odorless crystals that are soluble in fat solvents such as ether, alcohol, or chloroform but insoluble in water. The compounds have characteristic absorption spectra, useful in their identification. Both forms of the vitamin are stable to oxidation by air and to moderate heat in neutral and alkaline solutions. Upon alkaline saponification of fats, the vitamin appears in the nonsaponifiable fraction. It withstands autoclaving temperatures of 120° in the absence of air but at this temperature is subject to oxidation, and it is destroyed completely by heating at 170°. Vitamin D is stable over long periods of storage in oil solution but is quite unstable in the presence of mineral salts, such as tricalcium phosphate, when compounded in tablet form. It may be stabilized by dispersion in gelatin or a similar protective coating.

The international standard for vitamin D is a crystalline preparation of pure vitamin D_3 assigned a potency of 40 million units/g or 40 units/μg. The USP adopted an equivalent standard of vitamin D_3 with the same assigned potency. The USP unit for vitamin D, therefore, is equivalent to the IU, and USP reference standards exist for both cholecalciferol and ergocalciferol.

The provitamins D are found in both plant and animal tissue; 7-dehydrocholesterol is found principally in animal skin and ergosterol in relatively large amounts in yeasts, although it was first isolated from ergot. The vitamin D that is absorbed through the intestinal wall from dietary sources or that is formed in the skin from 7-dehydrocholesterol enters the circulatory system and excesses are stored. Vitamin D is stored predominantly in the adipose tissue and muscle of man. The liver oils, particularly of fish, are the most potent natural sources of the vitamin. The vitamin D of commerce now is synthesized principally from readily available, structurally related compounds, such as cholesterol, which often are obtained as packing house by-products.

There are three methods for quantitative physicochemical assay of vitamin D. For years, the biological assay based on the curative effects of the vitamin on experimental rickets in young rats has been used to measure the total biological activity of the vitamin in complex materials of low potency. Minimal amounts of the vitamin are needed by the rat; therefore, the rachitic condition is produced by using an extremely low-calcium, low-phosphorus diet. Now the preferred method for minimal amounts is high-pressure liquid chromatography for separation and UV spectrometry. For relatively concentrated solutions of vitamin D in alcohol (but not in oil), UV spectrometric determination is made at the wavelength of maximum absorption. Antimony trichloride reacts with various vitamins D in a Carr-Price reaction to yield a yellow color whose intensity is proportional to the vitamin D present. The reaction is satisfactory only for concentrated preparations; cholesterol and vitamin A interfere only when present in amounts in excess of certain limits.

Metabolic Functions—Both vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are biologically inactive molecules. After absorption, they are converted, primarily in the liver, to 25-hydroxy(OH) D_2 and D_3 (25-OH D_3), respectively, and are the most predominant forms found in the blood. Both of these compounds appear to facilitate phosphate resorption in the renal tubule; however, their most important function is as a precursor of 1,25-$(OH)_2$ calciferol, which is formed

in the kidney. This compound is a true hormone, referred to as calcitriol, and is excreted in response to specific stimuli from an organ distal to its target organ. Calcitriol is transported in the blood bound to a protein. There is a rapid turnover of 1,25-$(OH)_2$ calciferol, which depends on vitamin D status (greater turnover if body stores and plasma levels are low). Normal plasma values range from 18 to 60 pg/mL in children and 15 to 45 pg/mL in adults. It is likely that some forms of vitamin D–resistant rickets can be explained by possible genetic inability of the body to produce adequate amounts of either 25-OH calciferol or 1,25—$(OH)_2$ calciferol. Conversely, some children may have an enhanced capacity to convert vitamin D to the more active metabolites and, thereby, manifest a hyperreactivity to amounts of the ingested vitamin very slightly in excess of recommended dietary allowances.

Vitamin D, through the action of these active metabolites on molecular targets via vitamin D receptors, aids in the absorption of calcium from the intestinal tract and the resorption of phosphate in the renal tubule. Vitamin D is necessary for normal growth in children, probably having a direct effect on the osteoblast cells that influence calcification of cartilage in the growing areas of bone. 1,25—$(OH)_2$ calciferol also plays an essential management role in the regulation of various genes important to cell proliferation and lymphokine expression in systems not involved in mineral homeostasis.

A deficiency of vitamin D leads to inadequate absorption of calcium and phosphorus from the intestinal tract and retention of these minerals in the kidney and thence to faulty mineralization of bone structures. The inability of the soft bones to withstand the stress of weight results in skeletal malformations. Early rickets is difficult to diagnose, but fully developed cases in infants and children present characteristic signs. These include delayed closure of the fontanelles and softening of the skull; soft fragile bones with bowing of the legs and spinal curvature; enlargement of wrist, knee, and ankle joints; poorly developed muscles; and restlessness and nervous irritability. A form of *adult rickets* called osteomalacia similarly may occur. It, too, represents a failure of the process of calcification caused by simple vitamin D lack and calcium or phosphorus inadequacy.

With adequate calcium-phosphorus intake, adult osteomalacia and uncomplicated rickets can be cured by the ordinary daily intake of 10 μg of vitamin D. Larger doses (about 40 μg or more daily) are more rapidly effective, the first evidence of improvement—a rise in serum phosphorus—occurring in about 10 days.

Vitamin D has a serious toxic potential. There is a wide range of susceptibility to the toxic effects of vitamin D. Most adults will require more than 1250 μg of vitamin D/day to produce intoxication. However, levels as low as 375 μg/kg for 2 weeks have produced acute toxicity in adults. Long-term consumption of as little as 25 μg/kg may lead to hypercalcemia and attendant complications, such as metastatic calcification and renal calculi in adults, provided there are high levels of calcium in the diet. As little as 50 μg can inhibit linear growth of normal children. In advanced stages, demineralization of bones occurs, and multiple fractures may result from very slight trauma. Chronic excessive intake will result in liver accumulation, and detoxification will take many months. Classic features of vitamin D intoxication are hypercalcaemia, hyperphosphatemia, and impaired renal function. Painful joints and muscle weakness also may occur, which impair mobility.

Dietary Requirement and Food Sources—Requirements for vitamin D vary with the amount of exposure to UV light. Some individuals can obtain their entire requirements by skin irradiation, but age, skin pigment, and other conditions can effect the need for dietary supplies. Current recommendations are included in Table 92-4 and assume limited sun exposure.

Vitamin D is not found naturally in many food sources. Egg yolks, which are the best food source, vary in content from winter to summer depending most upon the content of the vitamin in the hen's diet. Unfortified dairy products contain some vitamin D, but again the potency varies with the season. Varieties of fish, whose muscle tissues contain substantial quantities of oil and fat, may supply an appreciable part of the dietary requirement. The livers of a number of fish, or the oils extracted from the livers, are extremely rich in vitamin D. Addition of vitamin D to appropriate foods has been an important factor in the prevention of any significant incidence of rickets in this country, although deficits of this vitamin do continue to be reported.

The major sources of vitamin D in the diets of most Americans are those foods that have been fortified. Vitamin D–fortified whole milk, nonfat dry milk, and evaporated milk containing 400 IU/qt (or reconstituted quart in the case of nonfat dry milk and evaporated milk) are particularly effective because of their use in infant feeding during the stage of growth most susceptible to rachitic changes. Fortification is accomplished by addition of vitamin D concentrates, mainly in the form of vitamin D_3. Fortification of other foods, such as processed cereals and margarine, is practiced to a limited degree.

VITAMIN D PREPARATIONS

CHOLECALCIFEROL

(3β)-9,10-Secocholesta-5,7,10(19)-trien-3-ol, Vitamin D_3; Activated 7-Dehydrocholesterol

9,10-Secocholesta-5,7,10(19)-trien-3β-ol [67-97-0] $C_{27}H_{44}O$ (384.64); an antirachitic vitamin obtained from natural sources or prepared synthetically.

Description—White, odorless crystals; affected by air and light; melts between 84 and 88°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, or fatty oils.

Comments—The only valid therapeutic (as opposed to dietary) uses are in the *treatment* of vitamin D *deficiency* or in the *prophylaxis* of deficiency in persons with a known deficiency, a high requirement or an absorption defect. However, the substance may be employed to treat *hypocalcemic tetany* and *hypoparathyroidism*. Also, there is a growing medical opinion that it facilitates the prophylaxis of osteoporosis by calcium in postmenopausal women. It should not be employed in the presence of renal insufficiency or hyperphosphatemia.

COD LIVER OIL

Oleum Morrhuae; Oleum Jecoris Aselli; Oleum Gadi

The partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of the Family *Gadidae;* contains in each gram not less than 255 μg (850 USP Units) of vitamin A and not less than 2.125 μg (85 USP Units) of vitamin D.

It may be flavored by the addition of not more than 1% of a suitable flavoring substance or a mixture of such substances.

Preparation—The highest grade of this medicinal oil is manufactured from fresh cod livers from healthy fish, removed from the fish within a few hours after they are caught. The oil is separated from the livers by heating with low-pressure steam. When livers of high quality are used and the manufacturing procedure is carried out under carefully controlled sanitary conditions the resulting crude oil is a light yellow color and has good flavor and odor. Such an oil requires no purification or chemical refining.

Due, however, to long-established trade demands, it is necessary to remove the cod liver stearin so that the oil will remain clear at temperatures above freezing. To accomplish this, the oil is chilled to precipitate the stearin, which is removed by pressure filtration. To preserve the natural vitamin content of the oil it should be stored out of contact with air and light, preferably in a cold place.

Constituents—Consists chiefly of unsaturated glycerides but contains *palmitin* and *stearin,* as well as traces of *chlorine, bromine, phosphorus,* and *sulfur*. American cod liver oils may contain as much as 3 ppm of arsenic, but there is little evidence as to how completely it may be assimilated. American cod liver oils are rich in *iodine*—one sample was found to contain nearly 15,000 parts of iodine/billion parts of oil.

The vitamins of this oil occur in the unsaponifiable fraction. Since some persons object to taking oils, tablets and capsules containing the unsaponifiable fraction of the oil are manufactured. In general the procedure consists of saponifying the oil, separating the unsaponifiable portion, and extracting it with suitable solvents. The extract is diluted with corn oil and filled with capsules or mixed with solid materials and manufactured into tablets. The vitamin potency of these preparations can be adjusted to the patient's requirements, but obviously they do not supply the constituents present in the saponifiable portion of the oil from which they were prepared.

Description—Thin, oily liquid, with a characteristic, slightly fishy, but not rancid, odor and a fishy taste; specific gravity, 0.918 to 0.927.

Solubility—Slightly soluble in alcohol; freely soluble in ether, chloroform, carbon disulfide, or ethyl acetate.

Comments—A source of vitamins A and D. The vitamins are present in such proportion that an oral dose of 5 mL can provide a significant portion of the daily requirements for children or adults of both of these dietary essentials. It has been employed in the prophylaxis of rickets in infants.

DIHYDROTACHYSTEROL—page 1458.

ERGOCALCIFEROL

(3β,5*Z*,7*E*,22*E*)-9,10-Secoergosta-5,7,10(19),22-tetraen-3-ol, Calciferol; Vitamin D_2

[50-14-6] $C_{28}H_{44}O$ (396.65). It is obtained by exposing ergosterol to UV light for the proper length of time. Insufficient irradiation results in the production of products with little or no antirachitic activity, and prolonged exposure causes the production of toxic products.

Note—In stating the potency and dosage of vitamin D (cholecalciferol, ergocalciferol) dosage forms μg of calciferol is preferred. It was customary to use either the International Unit (IU) or the equivalent USP Unit. One USP Unit (or International Unit) of vitamin D (cholecalciferol or ergocalciferol) is defined as the specific biological activity of 0.025 μg of the crystalline international standard or pure vitamin D_3.

Description—White, odorless crystals; affected by light and air; melting range, 115° to 118°.

Solubility—Insoluble in water; soluble in alcohol, chloroform, ether, or fatty oils.

Comments—Like other forms of vitamin D, it exhibits both antirachitic and calcemic effects. It has a relatively high potency and is thus especially useful for the treatment of severe or refractory *rickets*. It also may be used in the management of *hypocalcemia* and *hypoparathyroidism*. The IM dosage form is no longer available.

Care must be exercised to prevent overdosage. It should not be employed when renal insufficiency or hyperphosphatemia prevails. The serious toxic effects that may be caused by vitamin D are summarized in the general statement on *Vitamin D* under *Metabolic Functions*.

Calcifediol (3β,5*Z*,7*Z*)-9,10-Secocholesta-5,7,10(19)-triene-3,25-diol monohydrate $C_{27}H_{44}O_2.H_2O$ (418.66) Calderol—The form of vitamin D_3 found in the circulation; differs from calcitriol (below) in that hydroxylation in the liver occurs only at C-25. Produced synthetically. A white powder practically insoluble in water. *Comments:* In the treatment and management of metabolic bone disease or hypocalcemia associated with chronic renal failure. It should not be given to patients with hypercalcemia or evidencing toxicity to vitamin D.

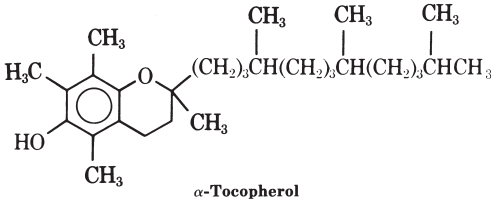
Calcitriol—The form of vitamin D_3 that stimulates intestinal calcium transport. Based on the observation that in acutely uremic rats it stimulates intestinal calcium absorption, it has been suggested that a vitamin D–resistant state exists in uremic patients because of failure of the kidney to convert precursors to calcitriol; hence the indication for use of the latter compound in the management of hypocalciuria in patients undergoing chronic renal dialysis. Its efficacy in not only reversing the calcium metabolic disorder but also reducing elevated parathyroid hormone levels in some patients has been demonstrated.

Other vitamin D analogs include dihydrotachysterol and ergocalciferol for hypocalcemia, and doxercalciferol and paricalcitol for hyperparathyroidism.

VITAMIN E

Vitamin E designates the group of compounds (tocol and tocotrienol derivatives) that exhibit qualitatively the biological activity of α-tocopherol. Studies that led to its discovery as an essential factor in animal metabolism showed that it was, among other things, necessary for reproduction in rats. It often was referred to as the antisterility vitamin, an inappropriate term, since it is not known to specifically function in this capacity in humans.

Chemistry and Assay—As with several of the other vitamins, there are a series of closely related compounds, tocopherols, known to occur in nature. Biological activity associated with the vitamin nature of the group is exhibited by several major compounds: α-, β-, γ-, and δ-tocopherol, each of which can exist in various stereoisomeric forms as well as the tocotrienols. These are all methyl-substituted tocols or tocotrienols; α-tocopherol, the most important member of the series because of its activity and occurrence, is 5,7,8-trimethyltocol, ie, 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol. Tocotrienols differ by possessing an unsaturated phytyl tail. The term vitamin E refers to tocopherols with the biologic activity of α-tocopherol.



α-Tocopherol

The tocopherols are oily liquids at room temperature. High temperatures and acids do not affect the stability of vitamin E, but oxidation does take place readily in the presence of iron salts or in rancid fats. The tocopherols themselves act as antioxidants, γ-tocopherol having the greatest antioxidant power in vitro. Decomposition also occurs in UV light. Tocopherols are isolated on a commercial scale from vegetable oils, usually by molecular distillation, extraction with organic solvents or by absorption chromatography, α-tocopherol is usually the most important homolog isolated from these sources; it also can be prepared synthetically and made available as the acetate and acid succinate esters.

The international standard for vitamin E used as a reference in all assays for this vitamin is a 250 mg quantity of α-tocopherol, α-tocopheryl acetate, or α-tocopheryl succinate. Results of an assay are expressed in terms of milligrams of the vitamin. The following relationship has existed between the former USP Vitamin E Units (equal to the former International Units) and the respective weights of the common forms: 1 USP (or IU) = 1 mg *dl*-α-tocopheryl acetate = 1.12 mg *dl*-α-tocopheryl succinate = 0.91 mg *dl*-α-tocopherol = 0.735 mg *d*-α-tocopheryl acetate (the ester of the natural form) = 0.827 mg *d*-α-tocopheryl succinate = 0.671 mg *d*-α-tocopherol (the natural form). It is currently more accurate to refer to *dl*-α-tocopherol as all-racemic-α-tocopherol, and to refer to *d*-α-tocopherol as *RRR*-α-tocopherol. The IU represented biological activity as determined by the rat antisterility test. Given the limited relevance of this test to humans, and the fact that only the 2*R*-stereoisomers are now used to establish vitamin E intake, current recommendations support using 0.45 mg for each USP Vitamin E Unit of all rac-α-tocopherol and its esters, and 0.67 mg for each USP Vitamin E Unit of *RRR*-α-tocopherol and its esters.

The usual methods for quantitative assay of vitamin E depend either directly or indirectly upon the ease with which free α-tocopherol is oxidized. The esters, which are almost exclusively used in pharmaceuticals, must first be hydrolyzed. The free alcohol, then, because of its instability, must be handled with care in all other analytical operations. The physicochemical methods generally applied employ either of two oxidation-reduction reactions: (1) the formation of a red orthoquinone by treatment of the tocopherol with concentrated nitric acid or (2) the reduction of ferric chloride in the presence of α,α′-dipyridyl, which forms a red-colored complex with ferrous ions. Both methods are relatively nonspecific and are suitable only when combined with adequate separation procedures. A gas-liquid chromatographic procedure coupled with a visible-light detector and a high-pressure liquid chromatographic procedure using a UV detector provides highly specific determinations.

The classic biological method is the rat assay in which female rats are depleted of vitamin E and mated with normal males. The dose of the material to be tested and of the standard is administered over a period of several days after conception. On the 20th day of pregnancy the female rats are killed, and the numbers of living and dead fetuses and resorption sites are recorded. Another, simpler bioassay is based on the dialuric acid hemolysis test in which the red-blood-cell fragility is measured as a criterion of vitamin E status in the rat.

Metabolic Functions, Dietary Requirement, and Food Sources—The exact biochemical mechanisms whereby vitamin E functions in the body continue to be investigated; however, its most critical function occurs in the membranous parts of cells and intracellularly. At the cell membrane, it interdigitates with phospholipids, cholesterol, and triglycerides, the three main structural elements of membranes. Since vitamin E is an antioxidant, a favored reaction at this site is with very reactive and usually destructive compounds called free radicals. These are products of oxidative deterioration of such substances as polyunsaturated fat. Vitamin E converts the free radical into a less reactive, nonharmful form. In its role as a protector against oxidation, vitamin E shows nutritional interactions with a wide variety of nutrients: vitamin A, the trace element selenium, the sulfur amino acids methionine and cysteine/cystine, polyunsaturated fatty acids, and, to a lesser extent, vitamin C. Interestingly enough, the order of antioxidant power among the tocopherols, as measured by their effect on the rate of peroxide formation in fats, is the reverse of the order of biological potencies. Other physiological functions probably include participation in nucleic acid metabolism, and it appears also that the tocopherols may be a component of the cytochrome reductase segment of the terminal respiratory chain in intermediary metabolism. In general, it appears that vitamin E plays an important role in ensuring the stability and integrity of cellular membranes; thus far in man, the only such demonstrated effect is on the red blood cell. The effect also is modified by the level of polyunsaturated fatty acids in the diet.

The therapeutic effectiveness of vitamin E in the prevention of abortion, in certain menstrual disorders, in the improvement of lactation, in muscular dystrophy, or in cardiovascular diseases has not been substantiated fully. One use that is established and sound is in hemolytic anemia in premature infants. Vitamin E also generally is considered to provide protection against pulmonary oxygen poisoning. Essentially all other examples of clinical indications of need for vitamin E at nutritional levels are related to malnourishment or malabsorption problems. The latter are found in humans with cystic fibrosis, liver cirrhosis, postgastrectomy, obstructive jaundice, pancreatic insufficiency, and sprue.

There are some data that suggest that vitamin E may be useful in protecting the epithelial tissue of the lungs from free radical damage associated with air pollution, but more research is needed to achieve a consensus of medical opinion. Similarly, more data are required to substantiate claims that vitamin E promotes rapid healing of tissue damaged by severe burns or other skin injuries. Studies that suggest

that vitamin E is useful for preventing some forms of cancer and preventing and treating coronary heart disease have been supported by epidemiological data, but replication of the finding is still needed using human subjects in prospective clinical trials.

A clearly defined uncomplicated vitamin E–deficiency disease has not been recognized as a public health problem. A deficiency state with respect to vitamin E has been demonstrated in human subjects, especially in premature and newborn infants and in infants with steatorrhea. The evidence rests mainly on determination of *in vitro* hemolysis and blood tocopherol level. However, peripheral neuropathy and vitamin E–deficient nerves in deficient patients have been reported. Requirements for vitamin E are known to increase with high intakes of polyunsaturated fatty acids and in selenium deficiency, and are correlated with metabolically active weight. Dietary dosing recommendations can be found in Table 92-4.

Vitamin E is ubiquitous in its distribution and is found particularly in vegetable fats and oils, dairy products and meat, eggs, cereals, nuts, and leafy green and yellow vegetables. Vitamin E is distributed so widely in nature that it is difficult to prepare a diet that does not meet RDAs for all life stage groups. However, attainment of levels expected to be needed for lowering the risk of cancer and heart disease likely will require supplementation. In direct contrast to the more rapid turnover of some of the water-soluble vitamins, vitamin E is stored in fatty tissue and is removed from it only when the fat is mobilized. This means that many months of deprivation would have to pass to deplete the body stores.

VITAMIN E PREPARATIONS

Preparation—A form of alpha-tocopherol [$C_{29}H_{50}O_2$ (430.71)]. It includes the following: *RRR-* or *all-racemic*-alpha-tocopherol ($C_{29}H_{50}O_2$); *RRR-* or *all-racemic*-alpha-tocopheryl acetate [$C_{31}H_{52}O_3$ (472.75)]; *RRR-* or *all-racemic*-alpha-tocopheryl acid succinate [$C_{33}H_{54}O_5$ = 530.79].

The generic title *Vitamin E Preparation* is officially recognized for any single form of the vitamin with one or more inert substances. The product may be in liquid or solid form, and it must contain not less than 95.0% and not more than 120.0% of the labeled amount of the vitamin. For a preparation labeled to contain a *dl*-form of the vitamin allowance is made for it to contain a small amount of a *d*-form occurring as a minor constituent of an added substance.

Alpha-tocopherol (also written α-tocopherol) is a trivial generic name that embraces all stereoisomeric forms of 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol. The term *d*-alpha-tocopherol (*RRR*-α-tocopherol) is employed in the pharmaceutical field to designate that form of the compound that (1) occurs naturally and (2) is dextrorotatory. The term *dl*-alpha-tocopherol (all-racemic-α-tocopherol) designates the mixture of stereoisomers prepared synthetically, commonly from racemic isophytol.

The phenolic hydroxyl is readily susceptible to acylation, and the resulting esters, eg, the acetate and acid succinate, are much more resistant to oxidation and discoloration on exposure to air and light than the phenolic form.

Description—Little or no odor or taste. *The alpha-tocopherols and alpha-tocopheryl acetates:* clear, yellow, viscous oils. *d-Alpha-tocopheryl acetate:* may solidify in the cold. *Alpha-tocopheryl acid succinate:* white powder; the *d*-isomer melts at about 75°, and the *dl*-form melts at about 70°. *The esters:* stable to air and to light but unstable to alkali; *the acid succinate:* also unstable when held molten.

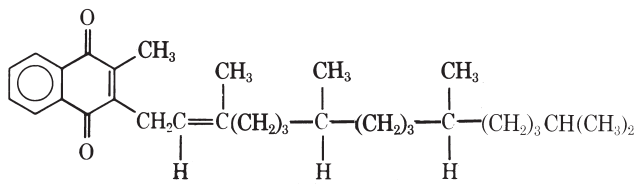
Solubility—*Alpha-tocopheryl acid succinate:* insoluble in water; slightly soluble in alkaline solutions; soluble in alcohol, ether, acetone, or vegetable oils; very soluble in chloroform. *Other forms of vitamin E:* insoluble in water; soluble in alcohol; miscible with ether, acetone, vegetable oils, or chloroform.

Comments—The only valid therapeutic use is as a supplement to the diet of the newborn infant, especially if premature, or in the treatment of the infant with steatorrhea, in which the GI absorption of it is impaired. No need for administration to children or adults has been demonstrated. For additional information see the general statement.

Vitamin K

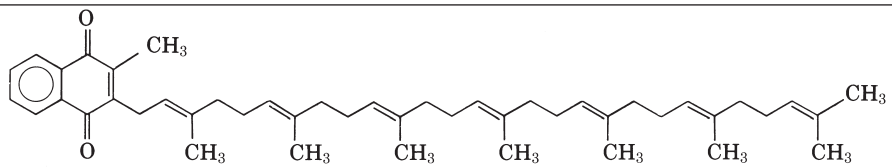
Vitamin K refers to a group of substances, widespread in nature, with similar biological activity; one form was isolated first from alfalfa and the other from putrefied fish meal. The primary activity that makes the vitamin essential in humans is its function in posttranslational modification (γ-carboxylation) of glutamic acid residues on specific proteins. This is important to proteins involved in coagulation and bone metabolism.

Chemistry and Assay—The parent structure of the K family of vitamins is 2-methyl-1,4-naphthoquinone, also designated as menadione. The various forms of vitamin K differ in the hydrophobic substituent at the 3-position. This fat-soluble compound and several water-soluble derivatives such as the sodium bisulfite and diphosphoric acid ester are the common commercial forms used in medical practice. Vitamin K_1 (isolated from plants) is 2-methyl-3-phytyl-1,4-naphthoquinone and preferably referred to as phylloquinone.



Vitamin K_1—phylloquinone; phytonadione

Vitamin K_2 exists as a chemical series that, instead of the phytyl side chain in the 3-position, has side chains of varying numbers of unhydrogenated isoprene units, depending on the bacterial source. This group of compounds is now referred to as the menaquinones. The compound initially called vitamin K_2 with a 35-carbon side-chain (7 isoprenoid units) and originally isolated from the putrefied fish meal is 2-methyl-3-all-*trans*-farnesylgeranylgeranyl-1,4-naphthoquinone, now referred to as menaquinone-7 (MK-7). The synthetic compound, menadione, lacks a hydrophobic group at position 3 but can be alkylated in mammalian liver. The synthetic form is used as a source of vitamin K in most commercial animal feeds.



Vitamin $K_{2(35)}$

The naturally occurring substances in pure form are light-yellow solids or oils, insoluble in water but soluble in fat solvents. Transparent colloidal solutions of vitamin K_1 can be prepared by means of nonionic surfactants. Although menadione, too, is fat-soluble, it is easily soluble in boiling water, and it is also slightly volatile at room temperature. Vitamins K_1 and K_2 as well as menadione are redox substances stable in the quinone form. In this respect there is a structural analogy between the vitamins K and E and a series of naturally occurring quinones called *ubiquinones*. The latter do not possess any demonstrable vitamin activity. Vitamins K have characteristic absorption spectra in the UV range and are sensitive to alkali, light, and ionizing radiation.

There is neither an international nor a USP standard (or Unit) for vitamin K. There is, however, a USP Reference Standard of menadione. The activity of test materials is generally measured in terms of biological equivalency to milligrams or micrograms of menadione in a chick-feeding test.

After extraction and separation from interfering substances, the vitamins K can be determined by their UV spectra or by color reactions. They react with sodium ethylate to give a blue color, which changes to brown. A more sensitive reaction occurs with sodium diethyldithiocarbamate to give a transient blue color. A method for assay of menadione in injections is the photometric assay of Menotti, in which 2,4- dinitrophenylhydrazine in ethanol is heated with menadione in the presence of HCl. The vitamin thus is converted to the hydrazone, which when treated with ammonia yields a blue-green color. Vitamin K also can be assayed by the use of high-performance liquid chromatography (HPLC) coupled with UV detection. Vitamin K_1 content of food homogenates and plasma is analyzed using reverse-phase HPLC with postcolumn solid-phase reduction of vitamin K_1 to its hydroquinone form, followed by fluorometric detection.

The chick is suited particularly for the biological assay of vitamin K because of the ease in producing a dietary vitamin deficiency and the

high requirement, and the criterion of activity (blood *prothrombin time*) is readily measurable, but species differences in biological activity are known to occur.

Metabolic Functions, Dietary Requirement, and Food Sources—Vitamin K is necessary for the formation of prothrombinogen and other blood-clotting factors in the liver. During clotting, circulating prothrombin is required for the production of thrombin; in turn, the thrombin converts fibrinogen to fibrin, the network of which constitutes the clot. It is obvious from this description that interference with formation of prothrombin will reduce the clotting tendency of the blood. In a severe deficiency of the vitamin, a condition of hypoprothrombinemia occurs, and blood-clotting time may be prolonged greatly or even indefinitely. Internal or external hemorrhages may ensue, either spontaneously or following injury or surgery. Other vitamin K-dependent proteins, including osteocalcin and matrix gla protein, have been identified in bone.

A group of substances termed vitamin K antagonists are characterized by their property to decrease plasma prothrombin levels and their usefulness in medicine as anticoagulants. Representative of this group is dicumarol, originally isolated from spoiled sweet clover hay, in which it is formed by bacterial action on coumarin. An important use of vitamin K is in the treatment of hypoprothrombinemia consequent to prothrombopenic anticoagulant therapy. Vitamin K_1 is the preferred form. Large doses of salicylates also antagonize vitamin K.

Optimal absorption of vitamins K requires the presence of bile or bile salts in the intestine. Menadione, the synthetic water-soluble analog, is absorbed easily in the absence of bile. The average diet apparently contains adequate amounts of vitamin K_1, since few if any malnourished humans have presented findings of dietary lack of vitamin K uncomplicated by intestinal disease, which prevents absorption. Current dietary recommendations are listed in Table 92-4.

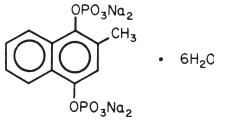
The premature infant appears to be particularly sensitive to a lack of the vitamin and to an excess in the case of menadione. Because of this potential toxicity, the inclusion of menadione in OTC dietary supplements for the pregnant women is prohibited. Vitamin K_1 does not exhibit this toxicity and is the preferred form. For newborn infants and especially those born prematurely (and anoxic), a single dose of 1 mg of vitamin K_1, immediately after birth, is often a routine measure to prevent hemorrhagic disease. Vitamin K_1 may be administered to the mother 12 to 24 hr prior to the expected delivery or at the first sign of labor, especially if the mother has been receiving prothrombopenic anticoagulants. Requirements normally decrease after the neonatal period; however, it is important to ensure that adequate amounts of vitamin K_1 are present in infant formulas, since these are likely to be the sole nutriment during this period. Milk-substitute formulas containing less than 4 μg/100 kcal are required to have vitamin K_1 added to attain the level of 4 μg/100 kcal required by infant formula regulations.

Although extensive measurements of dietary intakes and food content of vitamin K_1 have not been made, primarily because suitable analytical methods have not been developed, most diets contain sufficient amounts as evident by adequate body stores for a very high proportion of the population. The green, leafy vegetables, tomatoes, cauliflower, egg yolk, soybean oil, and liver of all kinds are good sources. Since it is insoluble in water, there is no loss in ordinary cooking. The human may use to a limited extent vitamin K synthesized by certain enteric bacteria.

VITAMIN K PREPARATIONS

MENADIOL SODIUM DIPHOSPHATE

1,4-Naphthalenediol, 2-methyl-, bis(dihydrogen phosphate), tetrasodium salt, hexahydrate; Kappadione; Synkavite



2-Methyl-1,4-naphthalenediol bis(dihydrogen phosphate) tetrasodium salt, hexahydrate [6700-42-1] $C_{11}H_8Na_4O_8P_2.6H_2O$ (530.18); *anhydrous* [131-13-5] (422.09).

Preparation—Reduction of menadione to the diol compound by treatment with zinc in the presence of acid, followed by double esterification with HI, metathesis of the resulting 1,4-diiodo compound with AgH_2PO_4, and neutralization of the bis(dihydrogen phosphate) ester thus formed with NaOH.

Description—White to pink powder, with a characteristic odor; hygroscopic; solutions are neutral or slightly alkaline to litmus, pH about 8.

Solubility—Very soluble in water; insoluble in alcohol.

Comments—See *Phytonadione*. In the body it is converted to menadione, and consequently, it has the same uses and limitations, except that it is water-soluble and does not require the presence of bile salts for its absorption; therefore, it is especially useful in the presence of biliary obstruction.

PHYTONADIONE

***R*-[*R**,*R**(*E*)]]-1,4-Naphthalenedione, 2-methyl-3-(3,7,11,15-tetramethyl-2-hexadecenyl)-, 2-Methyl-3-phytyl-1,4-naphthoquinone; Vitamin K_1; Mephyton**

Phylloquinone [84-80-0] $C_{31}H_{46}O_2$ (450.70). It is a mixture of *cis*- and *trans*-isomers; it contains not more than 20.0% of the *cis*-isomer.

Description—Clear, yellow to amber, very viscous, odorless or nearly odorless liquid; specific gravity about 0.967; stable in air but decomposes on exposure to sunlight; solution (1 in 20) in alcohol is neutral to litmus; refractive index, 1.523 to 1.526 at 25°.

Solubility—Insoluble in water; soluble in dehydrated alcohol, benzene, chloroform, ether, or vegetable oils.

Comments—The natural product, vitamin K_1. For the metabolic functions of vitamin K, see the general statement.

It has a more prompt and prolonged action than menadiol and other synthetic analogs of vitamin K, and it is more reliable in restoring prothrombin to the blood in conditions of *hypoprothrombinemia*. *Hypoprothrombinemia in the newborn* may be prevented or treated by the administration of phytonadione to the mother shortly before parturition or by giving the infant a single dose shortly after birth. In *hypoprothrombinemia consequent to prothrombopenic anticoagulant therapy,* an adequate intravenous injection usually will stop hemorrhage within 3 to 4 hr and restore the plasma prothrombin level to normal in 12 to 24 hr. In hypoprothrombinemia resulting from liver disease it may have limited value, especially if the disease is hepatocellular; in *biliary obstruction or fistula,* in which only the absorption of vitamin K is impaired, hypoprothrombinemia responds promptly to parenteral phytonadione. In other enteric diseases in which absorption is defective—as in *sprue, regional enteritis, enterocolitis, ulcerative colitis, dysentery, extensive bowel resection, and other causes of intestinal failure*—it will correct hypoprothrombinemia if given parenterally.

It must be emphasized that it cannot be used to check bleeding irrespective of its origin. It is of no benefit in diseases of the blood-forming organs, thrombocytopenic purpura, hemophilia, etc.

The Water-Soluble Vitamins

Except for ascorbic acid, all the vitamins in this category belong to the B-group of vitamins. Some still retain their original individual designations, such as B_6, and B_{12}, whereas comparable names for other vitamins have become obsolete.

In 1930, when it was clear that vitamin B was of multiple nature, the term vitamin B complex was coined to refer to the group of water-soluble animal growth factors found in relatively high concentrations in such products as liver, yeast, and rice bran. This was a convenient term to use in the early scientific literature, but it was not intended to be a specific name for pharmaceutical preparations that contain varying proportions of the B vitamins. The term was intended to apply to a group of vitamins whose identity was still being sought, rather than to a group of compounds whose identity had been established. Since the nature of the *complex* has been characterized, the term vitamin B complex is no longer appropriate.

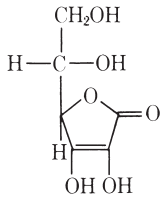
Ascorbic Acid (Vitamin C)

Vitamin C, or ascorbic acid (antiscorbutic vitamin), is necessary for the prevention and cure of the deficiency disease scurvy.

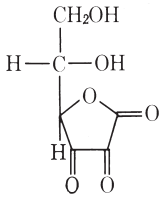
Scurvy has been recognized since the Middle Ages and was found widespread in northern Europe and among the crews of sailing ships. During the 18th century it was learned that when fresh fruit was made available aboard sailing vessels, scurvy was avoided. In 1907 Holst and Frolich observed a scurvy-like syndrome in guinea pigs that was similar to human scurvy and cured it by feeding citrus juices. This gave an experimental means for the rapid development of our knowledge of vitamin C, to which many workers have contributed.

Chemistry and Assay—Ascorbic acid is a white, crystalline compound structurally related to the monosaccharides. It exists in nature in both a reduced and the oxidized form, dehydroascorbic acid. These sub-

stances are in a state of reversible equilibrium in biological systems, and both have the same biological activity.



L-Ascorbic Acid



Dehydroascorbic Acid

Ascorbic acid is stable in the dry state but is easily oxidized in aqueous solution in the presence of air. Oxidation is accelerated by heat, light, alkalies, oxidative enzymes, and traces of copper and iron. Because of its relative instability, ascorbic acid is readily lost during cooking if simple precautions to avoid aeration are not taken. Also, because of its high aqueous solubility, the vitamin is lost to a considerable extent when large amounts of cooking water are discarded. Progressive loss of vitamin C in fresh fruits and vegetables occurs during storage.

Solutions of ascorbic acid are strongly reducing, and the vitamin is oxidized easily. In animal tissues the greater part of the vitamin is in the reduced form, but as scurvy develops, the ratio of oxidized to reduced form rises. This property of reversible oxidation-reduction is the most likely basis for the role of the vitamin in biochemical reactions.

The article of commerce is produced exclusively by synthesis. Sorbitol, a hexose occurring in several fruits but commercially obtained by hydrogenating dextrose, is the raw material for production of ascorbic acid. Amounts of ascorbic acid are expressed in terms of weight, as milligrams. The USP provides a Reference Standard of L-ascorbic acid for assay purposes. The practical methods of ascorbic acid assay are based on its powerful reducing properties, which enable determination by oxidimetric titration. The three most-used reagents for this titration are chloramine-T, 2,6-dichlorophenolindophenol, and iodine. Another practical assay is based on the conversion of ascorbic acid to oxalic acid 2-nitrophenylhydrazide by treatment with diazotized 2-nitroaniline. This yields a colored compound that is measured photometrically. Still another is the photometric assay of total ascorbic acid (ascorbic acid plus dehydroascorbic acid) by conversion of the vitamin to its 2,4-dinitrophenylhydrazone.

Metabolic Function, Dietary Requirement, and Food Sources—Vitamin C is known to be essential for the formation of intercellular collagen. In scorbutic tissues the amorphous ground substance and the fibroblasts in the area between the cells appear normal but without the matrix of collagen fibers. These bundles of collagenous material appear within a few hours after the administration of ascorbic acid. This points to the relationship of the vitamin in maintenance of tooth structures, matrix of bone, and the walls of capillaries. In scurvy, these are the tissues found to be faulty.

The picture of clinical scurvy in humans is one that can be related to the general breakdown of intercellular collagen substance. Bleeding is common, particularly at sites of pressure. The occurrence of petechiae, pinpoint hemorrhages that occur in the skin under reduced pressure, has been used as a diagnosis of scurvy. This is an indication of weakness or fragility of the walls of capillaries. Bones become brittle and cease to grow, and normal structures are replaced by connective tissue that contains calcified cartilage. Anemia is a common occurrence in scurvy, caused by an impairment of hematopoiesis. Also, vitamin C has been shown to change iron absorption. Tooth enamel, cementum, and particularly dentin change in structure, and the gums about the teeth become spongy and bleed easily. Keratoconjunctivitis sicca, xerostomia, salivary gland enlargement, xerosis, hyperpigmentation, ichthyosis, neuropathies, and mental depression may occur, even when the full-blown picture of scurvy is absent.

Vitamin C is essential for the healing of bone fractures. Such fractures heal slowly in a patient deficient in vitamin C. Wound-healing also is impaired.

There is evidence to indicate that the vitamin functions in the metabolism of tyrosine. There is an abnormal excretion of homogentisic, *p*-hydroxyphenylpyruvic, and *p*-hydroxyphenyllactic acids in scorbutic guinea pigs following administration of tyrosine, which, of course, is corrected with ascorbic acid. The excretion of *tyrosyl* derivatives in humans on a low–vitamin C diet given 20 g of tyrosine daily also is affected by ascorbic acid administration. In some newborns, the occurrence of tyrosinemia possibly accruing to high protein intakes suggests that this relationship be taken into consideration in evaluating the ascorbic acid requirement for the infant.

An intake of 10 to 20 mg a day of ascorbic acid is sufficient to protect an adult from classical scurvy, and 45 mg a day will maintain an adequate body pool of 1500 mg. The current dietary recommendations are provided in Table 92-5. Smokers likely require an additional 35 mg daily. The vitamin C requirements are increased following trauma, during infections, and during periods of vigorous physical activity; in such circumstances the requirement may be 100 to 200 mg a day.

The regular ingestion of 1 g or more of ascorbic acid a day has been suggested as a means of shortening the illness period and alleviating the symptoms of the *common cold* and other disorders but is not fully supported by the evidence.

A number of epidemiological studies show a protective association between the consumption of foods that contain vitamin C and cancers of the esophagus, stomach, and cervix. Animal studies testing precursors of known carcinogens showed a reduced number of tumors when the animals were given vitamin C. Biochemical studies suggest that vitamin C blocks the formation of active carcinogens from precursors. There is also the hypothesis that vitamin C has an effect as a free radial scavenger. Although vitamin C in large amounts may have some pharmacological effects, these are not related to the normal functioning of the vitamin at nutritional levels. There is no evidence that levels exceeding the recommended amount have any additional benefit, and contrary to those who advocate the use of megadose quantities (gram quantities), such practices can be harmful to some individuals.

The prolonged ingestion of supplements of ascorbic acid in excess of about 2 g a day (the upper tolerable intake level) is not without potential danger. GI disturbances (nausea followed by diarrhea), kidney or bladder stone formation (resulting from an increased excretion of oxalate, urate, and calcium), prenatal conditioning of the fetus to deficiency symptoms, interference with simple tests for glycosuria, and interference with the anticoagulant effect of heparin are clinical problems that may occur.

For therapeutic purposes in treatment of adult scurvy, 1000 mg of ascorbic acid a day, in divided doses, for 1 week is recommended, then 500 mg until all signs disappear. It also is used in the treatment of idiopathic methemoglobinemia to reduce the ferric iron in heme to the ferrous state.

Ascorbic acid facilitates the absorption of dietary iron by keeping the iron in the reduced form. A few microcytic anemias respond to ascorbic acid treatment, which may be in part due to improved absorption of iron.

Vitamin C is found in all living plant cells, is synthesized during the germination of seeds, and is concentrated relatively in the rapidly growing parts of the plant. It is present in all animal tissues as well, but only guinea pigs, primates, a few exotic animal species and humans are unable to meet body needs by synthesis and must rely upon a dietary source.

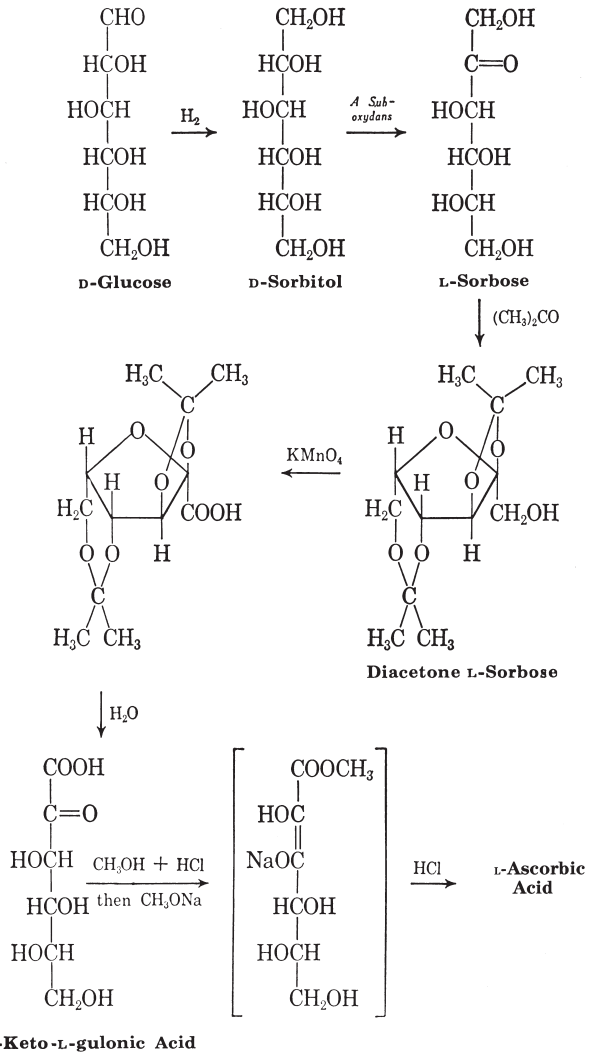
Although vitamin C appears to be present in all living tissues, our best sources of supply are fresh fruits such as citrus fruits, strawberries, and melons and green vegetables such as lettuce and cabbage. An average serving of potatoes contains enough vitamin C when first harvested to meet the adult RDA, but contains only half that amount by the following spring. It is a common practice, and a sound one, to rely to a large extent on citrus fruits and juices as important vitamin C carriers, particularly in infant feeding. An ounce of orange or lemon juice a day is sufficient to prevent scurvy in humans on an otherwise low–vitamin C diet.

It is fairly common practice to add ascorbic acid to foods for technical purposes; eg, as an antioxidant to protect natural flavors and colors.

VITAMIN C PREPARATIONS

L-Ascorbic acid [50-81-7] $C_6H_8O_6$ (176.13).

Preparation—The article in commerce is produced exclusively by synthesis. Sorbitol, a hexose sugar, occurring in several fruits but commercially obtained by hydrogenating dextrose in the presence of a Cu-Cr catalyst, is the raw material for the production of ascorbic acid. The D-sorbitol in aqueous solution is converted by the action of the organism *Acetobacter suboxydans* to L-sorbose, which is a ketose. The L-sorbose then is condensed with acetone by means of sulfuric acid to form diacetone sorbose. The object of the acetonation is to protect the hydroxyl group from oxidation in the subsequent steps. The diacetone sorbose, after suitable purification, is oxidized by potassium permanganate and then hydrolyzed, forming 2 keto-L-gulonic acid. This acid is esterified with methanol, and an intermediate sodio compound is formed with sodium methoxide. Hydrolysis with aqueous HCl removes the methyl group and sodium and lactonizes it to form ascorbic acid. The process is illustrated as follows.



Description—White or slightly yellow crystals or powder; odorless and on exposure to light gradually darkens; in the dry state, reasonably stable in air, but in solution rapidly deteriorates in the presence of air; melts at about 190°; specific rotation (1 in 10 aqueous solution) between +20.5 and +21.5°; aqueous solution has the acidic properties of a monobasic acid, and it forms salts with metallic ions. pK_a 4.2 and 11.6.

Solubility—1 g in about 3 mL water or 40 mL alcohol; insoluble in chloroform, ether, or benzene.

Incompatibilities—Stable in the dry state but in solution oxidizes rapidly in the presence of air. The reaction is accelerated by *alkalies and certain metals,* especially *copper;* it is retarded by acids. Aqueous solutions are strongly acidic, with a pH of 2 to 3.

Comments—It is sometimes given orally with iron salts in the treatment of iron-deficiency anemia; it functions to keep the iron in the ferrous state and hence to improve absorption. Apart from coadministration of vitamin C and iron preparations, a few cases of hypochromic anemia improve upon increasing the intake of vitamin. For additional information, see the general statement on *Ascorbic Acid*.

It also is used as a urinary-acidifier to enhance the effectiveness of methenamide by lowering the pH of the urine and thus aiding in the formation of formaldehyde.

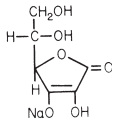
The effect of megadoses (10 or more times the RDA) has not been proved, and large overdoses should be discouraged.

Numerous, unapproved uses for ascorbic acid have been claimed, such as in the prevention and treatment of cancer, for infections of the gingiva, hemorrhagic states, mental depression, dental caries, acne, collagen disorders, ulcers of the skin, hay fever, and the common cold.

No more than the RDA should be given to the pregnant woman; the metabolism of the fetus adapts to high levels of the vitamin, and scurvy may develop after birth when the intake drops to normal levels.

SODIUM ASCORBATE

L-Ascorbic acid, monosodium salt; Cevalin



Monosodium L-ascorbate [134-03-2] $C_6H_7NaO_6$ (198.11).

Description—White or very faintly yellow crystals, or crystalline powder; odorless or practically odorless; relatively stable in air; on exposure to light it gradually darkens; pH (1 in 10 solution) between 7.5 and 8.

Solubility—1 g in 1.3 mL of water; very slightly soluble in alcohol; insoluble in chloroform or ether.

Comments—A pharmaceutical necessity for *Decavitamin Capsules* and *Decavitamin Tablets*. It also is used as an antioxidant in fruit and vegetable canning and in the processing of meat.

THE B VITAMINS

The *water-soluble B* of McCollum, or the *antiberiberi vitamine* of Funk, has now been differentiated into at least 11 separate and distinct chemical entities. It has been established that 8 of these are required in human nutrition. They are thiamine, riboflavin, niacin, folic acid, pyridoxine, vitamin B_{12}, biotin, pantothenic acid, and choline. When the dietary intake of methionine is adequate, choline can be synthesized endogenously; therefore, the human requirement is relative to the methionine intake, similar to the relationship between niacin and tryptophan. *p*-Aminobenzoic acid, and inositol have an essential part in cellular metabolism in plants and animals, but this alone does not constitute presumptive evidence of their importance in human nutrition. It can be stated categorically that the human does not require either an exogenous or endogenous source of *p*-aminobenzoic acid. Although inositol deficiency has not been demonstrated in humans, it may be an important nutrient in infant nutrition. Mammalian milk contains inositol, and since milk is the sole item of the diet of infants during this critical growth period, it is appropriate to include it in non-milk-based formulas, a practice that has existed since the early 1960s.

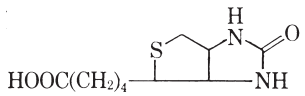
There is no one natural source of the B vitamins as a group that is necessarily superior to another source. No natural source contains all the water-soluble factors in the proportions that are needed in human nutrition, and the therapeutic value of any vitamin-containing material depends on the needs of the individual to whom it is being administered. Nevertheless, multiple deficiencies of B vitamins often coexist. Furthermore, the repair of one B-vitamin deficiency may increase the need for another; thus, the administration of thiamine in clinical or subclinical beriberi increases the need for riboflavin. Consequently, there is some justification for multivitamin therapy with those five B vitamins for which clinical deficiencies occur (thiamine, niacin, riboflavin, folic acid, and vitamin B_{12}). Human deficiencies in biotin and pantothenic acid have only been produced experimentally, and pyridoxine deficiency has occurred in infants fed an unfortified formula.

Biotin

***cis*-Hexahydro-2-oxothieno[3,4-*d*]imidazole-4-valeric acid**

Before this nutritional factor was identified as a discrete chemical substance, it variously was called vitamin H, anti-egg-white injury factor, coenzyme R, Bios II, and others. Its discovery was an outgrowth of studies on the *toxicity* of large amounts of unheated egg white as the sole source of protein for rats.

Chemistry and Assay—Biotin is a colorless, crystalline, monocarboxylic acid, only slightly soluble in water or alcohol (its salts are quite soluble). Water solutions are stable at 100°, and the dry substance is both thermostable and photostable. Biotin is unstable, however, in strong acids and alkaline solutions and in oxidizing agents. The vitamin is optically active, and the natural isomer, which alone possesses biological activity, is the D-form (rings are *cis*-fused and the isomer is designated (+)-biotin).



Biotin

Although biotin with the above structure is the compound present in food sources, the sulfur atom can be replaced with an oxygen atom without reduction in its metabolic activity. Biotin occurs in animal and plant

tissues primarily in combined forms that are liberated by enzymatic hydrolysis during digestion. One of the simplest such complexes is biocytin, ε-*N*-biotinyl-L-lysine. The amount of the vitamin in a product is expressed solely in terms of the weight of the chemically pure substance, the free monocarboxylic acid.

Only microbiological methods are feasible for the quantitative assay of biotin because of their sensitivity to the low concentrations usually encountered. After simple aqueous or acid extraction combined with heating, a microbiological assay using growth of the test organisms *Allescheria boydii* or *Lactobacillus arabinosus* as the criterion is carried out.

Metabolic Functions, Dietary Requirement, and Food Sources—Attempts to induce deficiency in man by inclusion of large amounts (200 g) of dried unheated egg white for several days in the diet have resulted in the appearance of vague symptoms such as change in skin color and dermatoses, slight change in lingual papillae of the tongue, muscle pains, loss of appetite, sleeplessness, and extreme lassitude. Raw egg white contains a protein, avidin, which combines with biotin and prevents absorption of the vitamin from the intestine. Rapid relief from such symptoms was observed with administration of biotin. This condition is difficult to produce in human subjects, and since a frank and specific deficiency disease is not discernible, there is uncertainty as to the exact nature of the deficiency syndrome as well as the need for a dietary source of biotin in human nutrition. Intestinal synthesis is undoubtedly an important factor in the supply of biotin to the body.

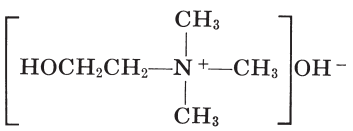
Biotin functions in carbon dioxide fixation reactions in intermediary metabolism, transferring the carboxyl group to acceptor molecules. It similarly acts also in decarboxylation reactions. For its part in these vital enzymatic steps, in catalyzing deamination of amino acids and in oleic acid synthesis, biotin is essential in human metabolism and presumed to be a dietary essential in the absence of adequate microbial synthesis in the intestine.

Diets providing a daily intake of 150 to 300 μg of biotin are considered adequate. The current dietary requirements are found in Table 92-5. These amounts are readily met and exceeded when milk, meat, and eggs are frequent items of the diet.

Choline

Although it is synthesized in the human body, choline plays an important role both as a structural component of tissues and in biological methylation reactions. Dietary deficiency of it leads to gross pathology in several species of animals.

Chemistry—Choline is (β-hydroxyethyl)trimethylammonium hydroxide. Since it is completely dissociated, it is comparable to alkali hydroxides as a base. Consequently, it does not exist as a base at body pH but rather as a salt; the anion is that present in its immediate biological environment. The β-(hydroxyethyl)trimethylammonium cation is the biologically important moiety. The cation is incorporated into phospholipids, such as lecithin and sphingomyelin, and acetylcholine, a substance released at cholinergic nerve junctions during transmission of nerve impulses. Acid hydrolysis of phospholipids yields the free choline salt, which is very soluble in water and to a lesser extent in ethanol. Assay for choline is accomplished with a microbiological method using a mutant strain of *Neurospora*.



Choline

Metabolic Functions, Dietary Requirement, and Food Sources—Besides its vital function as a precursor of acetylcholine, which is important in the sequence of nerve-muscle stimulations, choline is an important contributor of methyl groups needed for the *in vivo* synthesis of metabolites and perhaps some hormones. The biogenesis of choline appears to be universal in nature and is the result of the three-step transfer of methyl groups to an acceptor, which may be either free aminoethanol or phosphatidyl aminoethanol. Such transfers require methionine as a methyl donor (actually, *S*-adenosylmethionine). Choline is indirectly a source of methyl groups; it is first oxidized to betaine, which then may transfer a methyl group to homocysteine to form methionine. By thus regenerating methionine lost in transmethylation reactions, exogenous choline can spare the amino acid for use in protein synthesis. Methionine is an essential amino acid.

Choline has the property of preventing the deposition of excess fat or of causing the removal of excess fat from the liver of experimental animals fed high-fat diets and, because of this, it is often classified as a *lipotropic agent.* The lipotropic action probably relates to the incorporation of choline into phosphatidylcholine (lecithin), which, in turn, is incorporated into phospholipids and lipoproteins. The lipotropic action is independent of the function of choline as a reservoir of methyl groups.

There is presumptive evidence from nutritional and metabolic studies and teleological considerations that choline is important, if not essential, for the infant. It is appropriate to ensure, therefore, that choline is present in infant formulas at least to the level found in human milk. This is about 90 mg/L. Most infant formulas contain about 1 1/2 times this amount. It is equally appropriate to include choline in chemically defined diets to be used as the sole source of nutrients for critically ill patients.

An average mixed diet consumed by man in the US has been estimated to contain 500 to 900 mg of choline a day, an amount known to be adequate when compared with animal requirements. Current requirements for choline are listed in Table 92-5. Foods that supply large amounts of choline are liver, kidney, brain, muscle meats, fish, nuts, beans, peas, and eggs. Moderate amounts exist in cereals, milk, and a number of vegetables.

CHOLINE PREPARATIONS

Choline Bitartrate [(2-Hydroxyethyl)trimethylammonium Bitartrate; [87-67-2] $C_9H_{19}NO_7$ (253.25)]—*Preparation:* See *Choline Chloride,* below. *Description and Solubility:* A white, hygroscopic, crystalline powder with an acidic taste; odorless or may have a faint trimethylamine-like odor. Freely soluble in water, slightly soluble in alcohol, and insoluble in benzene, chloroform, or ether. *Comments:* As a nutrient or dietary supplement.

Choline Chloride [(2-Hydroxyethyl)trimethylammonium chloride; [67-48-1] $C_5H_{14}ClNO$ (139.62)]—*Preparation:* For the preparation of choline, see *Choline Dihydrogen Citrate. Description and Solubility:* White, deliquescent crystals; a 10% aqueous solution has a pH of about 4.7. Very soluble in water or alcohol. *Comments:* The salt is used to reduce fatty infiltration of the liver and thus supposedly to prevent degeneration and cirrhosis. Such infiltration may occur after exposure to certain chemical intoxicants, such as carbon tetrachloride, chloroform, and various other halogenated hydrocarbons (including several general anesthetics), divinyl ether, etc. Moderate-to-severe ethanol intoxication and habitual ingestion of ethanol also predispose to fatty infiltration of the liver. Patients who are acutely ill and cannot eat or persons on a high-fat diet frequently develop fatty livers, for which this vitamin may be given. In none of these conditions has there been clearly demonstrable efficacy. Furthermore, a high-protein diet, especially one that includes eggs, meat, liver, and milk, not only provides some of this vitamin but also methionine, which promotes the endogenous synthesis of *Choline*. Once cirrhosis occurs, it is probably too late for any possible benefits. There is no evidence that it is helpful in infectious hepatitis. For the above reasons, there is no longer any official preparation of it. Since the anion is irrelevant to the metabolic effects, the chloride is neither superior nor inferior to other salts. Its value in patients requiring long-term parenteral nutrition is being evaluated.

Choline Dihydrogen Citrate [(2-Hydroxyethyl)trimethylammonium Dihydrogen Citrate; [77-91-8] $C_{11}H_{21}NO_8$ (295.29)]—*Preparation:* By treating aqueous trimethylamine with ethylene oxide. Conversion to the dihydrogen citrate is conveniently effected by dissolving the base in a suitable solvent such as ethanol and treating with an equimolar portion of citric acid. *Description and Solubility:* Colorless, translucent crystals, or a white, granular to fine, crystalline powder; odorless or may have a faint trimethylamine odor and has an acidic taste; hygroscopic when exposed to air; melts between 103 and 107.5°; 1 g dissolves in 1 mL water or 42 mL alcohol; very slightly soluble in ether, chloroform, or benzene. *Comments:* See *Choline Chloride,* above.

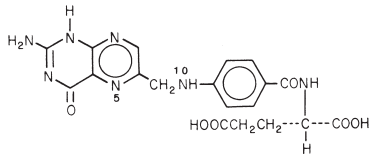
Folic Acid

The vitamin derives its name from the Latin word *folium,* leaf. It was first isolated from spinach leaves where it is now known to occur in relatively minute amounts compared with other food sources. Several apparently unrelated factors had been isolated in various laboratories before realization that they had in common the same parent compound, pteroyl-L-glutamic acid: Factor U (a chick growth factor), vitamin M (a factor for monkeys), vitamin B_c (a chick antianemia factor), liver and yeast *L casei* factors (bacterial growth factors), and others., Folates found in nature may contain numerous glutamate residues and may exist in a number of reduced forms, but folic acid refers specifically to pteroyl-mono-glutamate. The term folate is used to describe all the aforementioned compounds. However, the USP continues to call pteroylglutamic acid by the descriptor folic acid, and medical and biochemical practice usually does the same.

Chemistry and Assay—Pteroylglutamic acid crystallizes from cold water, in which it is only slightly soluble, as yellow spear-shaped platelets. It is readily destroyed by boiling in acid solution, and its solu-

tions will deteriorate in sunlight. It is insoluble in alcohol or the usual organic solvents but readily dissolves in dilute solutions of alkali hydroxides and carbonates. The characteristic UV absorption spectrum of pteroylglutamic acid in dilute NaOH is used to aid in identification and measurement of the compound.

A series of compounds with several molecules of glutamic acid attached to the first glutamic acid radical in peptide linkage have been synthesized. Compounds with one, two, three, and seven glutamic acid groups have been isolated. The latter three are known as conjugates. Some animals and man can utilize them as a source of pteroylglutamic acid, presumably because appropriate digestive enzymes can hydrolyze them. Microorganisms can use them to only a variable and limited extent unless they are first hydrolyzed to the free form with liver, kidney, or pancreatic enzymes, called conjugases.



The functional form of this vitamin group is basically the 5,6,7,8-tetrahydrofolic acid in which a formyl group (-CHO), when present, is attached at either or both the N^5 or N^{10} positions. The hydrogenated N^5-formyl compound, formerly called *folinic acid,* or leucovorin, is available, as is the monosodium salt of folic acid, as a discrete pharmaceutical preparation. It properly is termed 5-formyltetrahydrofolic acid. These compounds similarly serve as standards during assay of the vitamin. A USP Reference Standard Folic Acid is available. Separately, the three moieties that make up the folic acid molecule (pteroic acid, *p*-aminobenzoic acid, and glutamic acid) have no vitamin activity.

The quantitative assay of folate in natural products is mainly by biological or microbiological methods. In the chick assay, the birds are placed on a folic acid–free diet until they became anemic, after which folic acid supplements and the test material are administered. The degree of recovery is related to the quantity of reference folic acid fed. The two organisms most used in the microbiological method are *Lactobacillus casei* and *Streptococcus faecalis*. The method is based on the fact that pteroylglutamic acid is a required growth factor for each; however, the assay is complicated when biological material is analyzed, because naturally occurring folic acid derivatives do not all have the same biological activity for the two organisms.

Folic acid can be determined by either of two physicochemical methods, provided the compound is present in relatively pure form. One method is the spectrophotometric measurement of the extinction maxima of the UV absorption curve; the other is the spectrometric measurement after oxidative fission of folic acid to 4-aminobenzoylglutamic acid followed by diazotization and coupling to give an azo dye. Folic acid also can be determined with high-pressure liquid chromatography.

Metabolic Functions—Folic acid is one of the important hematopoietic agents necessary for proper regeneration of the blood-forming elements and their functioning. Although the mechanism whereby folic acid performs this vital role is not understood, much is known about the involvement of folic acid as a coenzyme in intermediary metabolic reactions in which one-carbon units are transferred. These reactions are important in interconversions of various amino acids and in purine and pyrimidine synthesis. This role is in contrast to that of choline in furnishing and transferring so-called labile methyl groups in transmethylation reactions. The biosynthesis of purines and pyrimidines is linked ultimately with that of nucleotides and ribo- and deoxyribonucleic acids, functional elements of all cells.

The concept of antivitamins or vitamin antagonists is exemplified in a particular aspect of folic acid metabolism. By virtue of its structural similarity, sulfanilamide competes with *p*-aminobenzoic acid in the biological synthesis of folic acid. The organism is thus deprived of needed folic acid. Sulfonamides act, therefore, as growth inhibitors of certain pathogenic organisms, a competitive antagonism that is responsible for the antibacterial action of sulfa drugs. Since mammals use preformed folic acid, sulfonamides do not disrupt the host metabolism.

Numerous analogs of pteroylglutamic acid have been prepared that exhibit potent antifolic acid activity. Several compounds, notably aminopterin (4-aminopteroylglutamic acid) and methotrexate (4-amino-N^{10}-methylpteroylglutamic acid), compete with folic acid in nucleic acid synthesis and have been used in the treatment of various cancers, psoriasis, and certain immune disorders. The antimicrobial drugs trimethoprim and pyrimethamine are also antifolate drugs.

Dietary Requirement and Food Sources—Folic acid deficiency results in megaloblastic anemia, glossitis, diarrhea, and weight loss. A deficiency is best diagnosed by reduced levels of folic acid in the serum or red blood cells. The condition of megaloblastic anemia arising as a result of dietary folate deficiency occurs most frequently after the age of 65, in persons suffering from malabsorption syndromes, in women during the last trimester of pregnancy, and in infants receiving unfortified proprietary formulas or goat's milk. In the treatment of megaloblastic or macrocytic anemia, folic acid should be administered as the sole therapy only when the possibility of pernicious anemia and other primary diseases of the small bowel has been excluded absolutely, a restriction necessitated by the vitamin's ability to mask other diagnostic signs of these conditions.

In recent years folic acid has been linked as a possible agent in lowering the risk of rare but serious defects in fetal development of the brain and spinal cord, including spina bifida and anencephaly. These conditions generally are referred to as neural tube defects (NTDs). In some interventional and observational studies in which women of childbearing age were given folic acid supplements, lower levels of NTDs were observed than with placebo controls. It should be noted that these studies were accomplished in areas where the pretreatment rates of NTDs were near or above 2 per 1000 live births, and supplemental levels of folic acid were between 0.4 and 4 mg/day. Also, data obtained for populations in which folic acid intakes were exceedingly low showed no relationship with the rates of NTDs, and therefore, the condition does not appear to be caused by classic folic acid deficiency. Furthermore, research with animals has not shown any increase in NTDs with folic acid–deficient diets.

No mechanism for the observed relationship of folic acid consumption and NTD rates in humans has been proposed. The US Public Health Service has recommended that all women who are capable of becoming pregnant should consume 0.4 mg of folic acid per day throughout their childbearing years for the purpose of reducing their risk of an NTD pregnancy.

The current dietary recommendations for folate intake levels are provided in Table 92-5. Note that they are described in units of dietary folate equivalents (DFE), where 1 μg DFE = 1 μg food folate = 0.6 μg folic acid consumed with food = 0.5 μg folic acid supplement taken on an empty stomach based on differing bioavailability.

A balanced American diet for adults contains approximately 0.2 to 0.6 mg of total folic acid activity, and the intestinal microflora also provide some absorbable amounts of the vitamin. Since 1998 grain products in the US have been fortified with 140 μg folic acid per 100 g of grain. Other food sources of folic acid are liver, kidney, dry beans, asparagus, mushrooms, broccoli, and collards, as well as spinach, peanuts, lima beans, cabbage, sweet corn, chard, turnip greens, lettuce, and milk.

FOLIC ACID PREPARATIONS

L-Glutamic acid, *N*-[4-[[(2-amino-1,4-dihydro-4-oxo-6-pteridinyl)-methyl]amino]benzoyl]-, PGA; Folacin; Pteroylglutamic Acid; Folvite

N-[*p*-[[(2-Amino-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-L-glutamic acid [59-30-3] $C_{19}H_{19}N_7O_6$ (441.40).

Preparation—Commercial syntheses use different processes. In one of these, 2,3-dibromopropionaldehyde, dissolved in a water-miscible organic solvent (alcohol, dioxane), is added to a solution of equal molecular quantities of 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid, maintaining a pH of about 4 by the controlled action of alkali as the reaction progresses. The scheme of the reaction is analogous to that described for *Methotrexate,* the only difference being the starting pyrimidine compound.

Description—Yellow or yellowish orange, odorless, crystalline powder.

Solubility—Very slightly soluble in water; insoluble in alcohol, chloroform, or ether; readily dissolves in dilute solutions of alkali hydroxides or carbonates and is soluble in hot diluted hydrochloric or sulfuric acid, forming very pale yellow solutions.

Comments—The only valid therapeutic use is in the treatment of a deficiency of the vitamin or prophylactically in instances in which the folate requirement is increased, as in pregnancy. *Megaloblastic anemias* in which folic acid deficiency occurs may result from malabsorption syndromes, such as *sprue, idiopathic steatorrhea, celiac disease, intestinal reticulosis, regional jejunitis, jejunal diverticulosis, blind loop syndrome, and gastroenterostomy* and from antacid use in the elderly. Megaloblastic anemia of infancy is generally the result of generalized malnutrition, as is nutritional megaloblastic anemia. In all of the above-named megaloblastic anemias vitamin B_{12} deficiency often coexists, and folic acid, alone, may be inadequate. Pernicious anemia should be ruled out, lest the vitamin mask the disease (see below). In the megaloblastic anemias of nutrient deficiency, a low serum folic acid level is likely. However, in megaloblastic anemias consequent to treatment with pyrimethamine, phenytoin and related substances, or methotrexate, the serum folic acid levels may be normal; the signs of deficiency result from the antimetabolite effects of the drugs, and they may be overcome com-

petitively by increasing its intake. It is not effective in the treatment of aplastic anemia, leukemia, anemias of infection and nephritis, and general reduction in bone marrow activity of unknown origin.

The vitamin usually is absorbed readily from the GI tract and from parenteral sites of administration. The portion of administered folic acid that is excreted in the urine varies directly with the dose; only a small fraction appears in the urine following the oral ingestion of 0.1 mg, but up to 90% may be excreted by the kidney when a single dose of 15 mg is ingested. The fate of the unrecovered vitamin is unknown. The indications for parenteral use are rare. A solution in water for injection, prepared with the aid of sodium hydroxide or sodium carbonate, is the preferred form for injection.

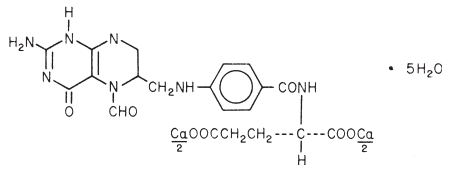
It is capable of bringing about an incomplete and temporary hematopoietic response in pernicious anemia, which may cause the clinician to overlook the basic disorder. But it does not affect the progressive neurological lesions of the disease, which may appear explosively and in an irreversible stage. Doses that will correct a deficiency but do not generally cause a remission in pernicious anemia are on the order of 0.1 to 0.4 mg.

Infants fed on a goat milk formula should have a 50 μg a day supplement of folic acid.

For additional information concerning folic acid see the general statement on *Folic Acid*.

LEUCOVORIN CALCIUM

L-Glutamic acid, *N*-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-, calcium salt (1:1), pentahydrate; Folmic Acid; Citrovorum Factor



Calcium *N*-[*p*-[[(2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino]benzoyl]-L-glutamate (1:1) pentahydrate [6035-45-6] $C_{20}H_{21}CaN_7O_7.5H_2O$ (601.58); *anhydrous* [1492-18-8] (511.51).

Preparation—Folic acid simultaneously is hydrogenated and formylated in 90 to 100% formic acid under the influence of platinum oxide catalyst at low temperature and atmospheric pressure to yield leucovorin. Conversion to the calcium salt may be accomplished by dissolving the leucovorin in NaOH solution, treating with $CaCl_2$, and precipitating with ethanol.

Description—Yellowish white or yellow, odorless powder; pK_a 3.8, 4.8, and 10.4.

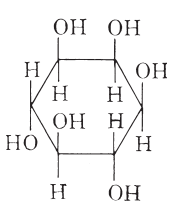
Solubility—Very soluble in water; practically insoluble in alcohol.

Comments—Leucovorin is folinic acid. The calcium salt is a convenient pharmaceutical form that is preferred for intramuscular injection. Consequently, its uses and limitations in the *treatment of the megaloblastic anemias* are the same as those for folic acid. However, it is superior to folic acid in *counteracting the excessive effects of the folic acid antagonists* (*methotrexate*), since the antagonists competitively antagonize the conversion of folic acid to leucovorin and not the leucovorin itself and also since leucovorin is an excellent competitor for the inward transport system.

Sodium Folate [Monosodium Folate [6484-89-5] $C_{19}H_{18}N_7NaO_6$ (463.38); Folvite Sodium]—*Preparation:* Folic Acid is reacted with $NaHCO_3$. *Description and Solubility:* Clear, mobile liquid with a yellow or orange-yellow color; pH between 8.5 and 11. *Comments:* Has the actions of *Folic Acid*; however, the salt is preferred for parenteral use.

INOSITOL

Inositol is hexahydroxycyclohexane (1,2,3,4,5,6-cyclohexanhexol; *i*-inositol; *myo*-inositol; *meso*-inositol). Actually, there are nine stereoisomeric cyclohexanols, all of which now are referred to commonly as inositols. Several occur in nature; the isomer described above is by far the most prevalent and is the only one that is biologically active.



Inositol

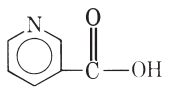
Inositol occurs normally in nearly all plant and animal cells, either free or combined, suggesting that it is an essential cell constituent. In animal tissues it occurs as a constituent of phospholipids. In plants it usually is found as *phytic acid,* the hexaphosphate ester of inositol. There has as yet been no demonstration of need for inositol in human nutrition. In fact, large amounts of phytic acid in the diet interfere with the absorption of minerals, especially calcium, zinc, and iron.

Although inositol possesses weak lipotropic activity, it is not as effective as methionine or choline. There is no known valid therapeutic use of the compound. It may, however, be important to ensure its presence, at levels customarily found in human milk, in foods that are fed to infants and critically ill patients as the sole item of the diet. Inositol is measured by a microbiological assay.

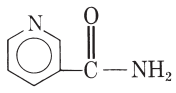
Niacin (Nicotinic Acid or Nicotinamide)

Nicotinic acid (niacin) and nicotinamide (niacinamide) have identical properties as vitamins. Both compounds had been known for approximately 20 years before their biological significance was realized. In 1867 nicotinic acid was synthesized by the oxidation of nicotine with nitric acid. But it was not until 1937 that it was isolated from biological sources and found to be effective in the cure of black tongue in dogs and, later, pellagra in humans. The vitamin has none of the pharmacological properties of nicotine, however. In the 1940s the term *niacin* was adopted as a synonym for food labeling purposes to avoid association with the nicotine of tobacco. The term *niacin* is used generically to include both nicotinic acid and nicotinamide.

Chemistry and Assay—Nicotinic acid is pyridine-3-carboxylic acid. The structures of nicotinic acid and nicotinamide are shown below.



Nicotinic Acid



Nicotinamide

Niacin, the most stable of the vitamins, is not destroyed by heating in acid or alkaline solution. It withstands mild oxidation and retains its biological activity during the processing of food and the preparation and storage of pharmaceuticals. It is readily soluble in water or alcohol but insoluble in ether or chloroform. Niacinamide, on the other hand, may be extracted from water solution with ether. The amide is hydrolyzed readily to the free acid by heating in acid or alkaline solution.

The usual commercial synthesis of nicotinic acid used in foods and drugs is by the oxidation of quinoline with potassium permanganate or manganese dioxide, and monodecarboxylation of the purified quinolinic acid with controlled heating. Nicotinamide usually is prepared by esterifying nicotinic acid with methanol followed by ammonolysis.

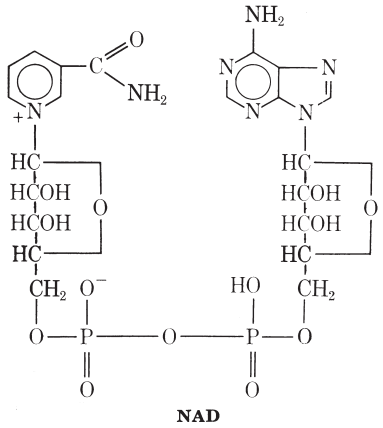
The activity of both forms of the vitamin is expressed in milligrams of the chemically pure substance. Because they have identical biological activity and their molecular weights are nearly identical, they are equivalent on a weight basis. Reference Standard Niacin and also Niacinamide Reference Standard are available from the USP.

Niacin may be determined in food, drugs, and biological materials by microbiological assay or by chemical methods. No animal biological method exists. The chemical determination involves reaction of the pyridine ring with cyanogen bromide and coupling of the fission product with an aromatic amine. The yellow polymethine dye that is formed is measured in a spectrometer at 436 nm. In natural products niacin occurs mainly in combined form as a coenzyme and must be liberated by acid hydrolysis before assay.

The microbiological assays employ *Lactobacillus arabinosus* as the test organism. A quantitative discrimination between nicotinic acid and nicotinamide in a sample is possible by assaying with both this organism, which uses both forms, and *Leuconostoc mesenteroides,* which can use only nicotinic acid.

Metabolic Functions—In the body niacin is converted to nicotinamide, which is an essential constituent of coenzymes I and II that occur in a wide variety of enzyme systems involved in the anaerobic oxidation of carbohydrates. The coenzyme serves as a hydrogen acceptor in the oxidation of the substrate. These enzymes are present in all living cells and take part in many reactions of biological oxidation.

Nicotinamide adenine dinucleotide (NAD) is the inner salt of the 5′-ester of 3-carbamoyl-1-D-ribofuranosylpyridinium hydroxide with adenosine 5′-pyrophosphate and has the structure shown below. Nicotinamide adenine dinucleotide phosphate (NADP) differs only in that the adenosine moiety is esterified at its 2′-position with phosphoric acid.



NAD

These coenzymes are synthesized in the body and take part in the metabolism of all living cells. Since they are of such widespread and vital importance, it is not difficult to see why serious disturbance of metabolic processes occurs when the supply of niacin to the cell is interrupted.

The observations of numerous nutritionists that the daily requirement for niacin is influenced by the amount and kind of dietary protein led to the discovery that the amino acid tryptophan functions as a potential precursor of niacin. The efficiency of the conversion indicates that 60 mg of dietary tryptophan is equivalent to 1 mg of niacin. This relationship has given rise to the use of the term *niacin equivalent,* which is defined for the purpose of estimating the adequacy of diets in this vitamin as 1 mg of niacin or 60 mg of dietary tryptophan.

Niacin is absorbed readily from the intestinal tract, and large doses may be given orally or parenterally, with equal effect. Niacin, as nicotinic acid, is prescribed widely by physicians in gram amounts for the purpose of lowering blood cholesterol levels. The mechanism for this action is not fully understood; however, the effect is known to occur as a result of decreased cholesterol synthesis in the liver. Only the nicotinic acid form of the vitamin provides the effects. The use of such high doses of nicotinic acid can have serious side effects, including impairment of liver function. Nicotinic acid at these levels should be used only in conjunction with appropriate monitoring of normal liver function.

The principal excretory product of niacin in the urine is *N*-methylnicotinamide, a fluorescent compound formed in the liver. On a normal diet approximately one-fourth of the niacinamide ingested is excreted as *N*-methylnicotinamide. With increased levels of niacin intake the percentage of ingested niacin excreted as the fluorescent substance is decreased.

Dietary Requirement and Food Sources—Pellagra, which means rough skin, is the primary deficiency disease due to lack of sufficient niacin in the diet, and it appears only after months of dietary deprivation. The condition involves the GI tract, the skin, and the nervous system. Loss of weight, anorexia, weakness, insomnia, headache, and diarrhea are common and appear without obvious cause. Other early symptoms may include abdominal pain, nervousness, and mental confusion.

Typical manifestations of pellagra in a well-advanced stage are diarrhea, dermatitis, and dementia. GI difficulties vary in severity, and absence of gastric secretion is a common finding. In the more advanced state, diarrhea is severe. Dermatitis has a characteristic appearance and occurs at those sites subject to exposure or irritation. The skin lesions are usually bilaterally symmetrical and appear first as erythematous patches, changing to brown pigmented areas, followed by desquamation and thickening. Glossitis is common; it is characterized by swelling and redness at the margins and tip of the tongue. Because of inflammation and superficial desquamation, the tongue, gums, and lips appear scarlet and smooth. Mental symptoms vary in occurrence and intensity; they include irritability, mental depression, and emotional instability. A confused mental state with hallucinations, mania, and delirium is seen in advanced stages of the disease. Pellagra is a complex deficiency, and symptoms of riboflavin, thiamine, and folate deficiency frequently complicate the clinical picture.

Treatment of the disease requires immediate change to a nutritionally adequate diet and the administration of niacin or niacinamide. When neurological symptoms are present, use of thiamine and riboflavin may be necessary as well. Recovery from the acute condition is dramatic in most instances and occurs within 24 to 48 hr. Small doses given frequently during the day have been found to be more effective than a single large daily dose. Niacinamide is preferable to niacin because it does not produce vasodilation in the skin with sensations of itching, burning, or tingling. With severe nausea and diarrhea, intravenous injection of niacinamide is of additional advantage.

In considering dietary requirement and the foods that contribute to it, one must consider the content of preformed niacin and the niacin available by conversion from tryptophan, an essential amino acid present in all good-quality proteins. The minimum requirement to prevent pellagra is the equivalent of about 4.4 mg of niacin/1000 kcal/day. The recommended dietary allowance is provided in Table 92-5. Most diets consumed in the US supply from 500 to 1000 mg or more of tryptophan a day and 8 to 17 mg of preformed niacin, equivalent to 16 to 33 mg of niacin.

Poultry, meats, and fish constitute the most important single food group source of niacin. Organ meats are somewhat superior to muscle tissue. Potatoes, legumes, and some green leafy vegetables contain moderate amounts of preformed niacin, as do whole grains. An important public-health nutrition practice, begun in the 1940s, is the nutrient enrichment of cereal products: wheat flour, farina, corn products, rice, macaroni and noodle products, and bread. Niacin, thiamine, riboflavin, and iron are mandatory ingredients in products that are labeled *enriched.* The level of enrichment for niacin is such that a significant proportion of the daily requirement is obtainable from a generous serving of these foods.

NIACIN PREPARATIONS

3-Pyridinecarboxylic acid; Nicotinic Acid

Nicotinic acid [59-67-6] $C_6H_5NO_2$ (123.11).

Preparation—Niacin may be variously prepared, as by oxidation of nicotine with nitric acid or potassium permanganate, by oxidation of quinoline, or synthesis from pyridine.

Description—White crystals or crystalline powder; odorless or with a slight odor; melts at about 235°; pK_a 4.85.

Solubility—1 g in about 60 mL water; freely soluble in boiling water, boiling alcohol, or also solutions of alkali hydroxides or carbonates; practically insoluble in ether.

Comments—Chiefly in the treatment of pellagra, a disease common among the poor in subtropical countries because of diet deficiency. It also has been found useful in conjunction with thiamine and riboflavin in the treatment of nutritional deficiency in chronic alcoholism.

In doses of 20 mg or more in humans, niacin elicits a vasodilator effect that occurs a few minutes after oral ingestion or immediately after intravenous injection and lasts for a few minutes to an hour. Symptoms of flushing, itching, burning, or tingling occur, along with an increased skin temperature and increased motility and gastric secretion. Nicotinyl alcohol also shares this vasodilator property, and at one time both nicotinic acid and the alcohol popularly were used in the treatment of peripheral vascular disease and senility (as a cerebral vasodilator). These uses are obsolete and now are but an annoying side effect of large doses. The vasodilator effect of the oral drug is lessened if it is given with a meal.

Larger doses lower blood cholesterol, phospholipids, triglycerides, and free fatty acids, and the drug is used in the treatment of hypercholesterolemia, mostly in combination with cholestyramine, colestipol, or clofibrate. Nicotinamide does not possess the hypolipemic or the vasodilator property.

Large doses, especially those over 3 g a day, cause abnormalities in liver function, including jaundice. The risk may be greater with SR products.

Niacin is absorbed well orally, and the oral and parenteral doses are the same. With large doses, a considerable amount is excreted into the urine, so it is advisable to give several small doses during the day rather than one large one.

For additional information see the general statement on *Niacin*.

NIACINAMIDE

3-Pyridinecarboxamide; Nicotinamide; Nicotinic Acid Amide

Nicotinamide [98-92-0] $C_6H_6N_2O$ (122.13).

Preparation—From niacin by various methods, as by reaction with thionyl chloride followed by treatment with ammonia, or by interaction of ammonia gas with molten niacin.

Description—White, crystalline powder; odorless or nearly so, and with a bitter taste; solutions are neutral to litmus paper; melts between 128 and 131°.

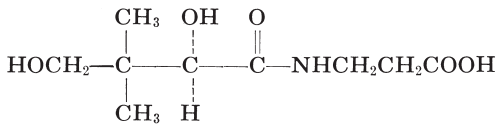
Solubility—1 g in 1.5 mL water, 5.5 mL alcohol, or 10 mL glycerin.

Comments—This drug lacks the vasodilator, GI, hepatic, and hypolipemic actions of niacin. Consequently, it is preferred to niacin in the treatment of deficiency.

Pantothenic Acid

Knowledge of the identity and importance of pantothenic acid grew principally from experimental studies on microorganisms and chicks. Because of its wide distribution in nature it was named *pantothenic* (Greek, *pantothen,* from all sides). The terms vitamin B_3 and chick antidermatitis factor once were applied to variously purified concentrates of the factor, but they are now obsolete. No known therapeutic value exists for pantothenic acid, except perhaps in the treatment of frank or suspected cases of combined nutritional deficiencies.

Chemistry and Assay—Pantothenic acid is optically active (chiral). Maximum vitamin activity resides only in the D-form, and it is readily available as either the sodium or calcium salt, which are crystalline substances. Another commercially available form used in liquid preparations is D-pantothenyl alcohol (panthenol). Chemically, pantothenic acid is a composite structure of β-alanine and 2,4-dihydroxy-3,3-dimethylbutyric acid γ-lactone, connected in peptide linkage.



D-Pantothenic Acid

The free acid is fairly stable in neutral solution but sensitive to acids, bases, and heat. The salts are somewhat more stable, but even these are destroyed by autoclaving.

Pantothenic acid, its salts and alcohol, can be assayed by both chemical and microbiological methods. A chick growth method has been used, but it is time-consuming and has been replaced since suitable methods are available for releasing the bound vitamin (a protein enzyme) from its firm combination in plant and animal tissue. The first step in chemical assay is acid or alkaline hydrolysis. This cleaves the molecule at the peptide linkage into an alanine part and a pantoic acid part. These fission products then can be determined photometrically by suitable color reactions. In addition both gas-liquid chromatography and high-pressure liquid chromatographic methods now exist. *Saccharomyces carlsbergensis* and *Lactobacillus plantarum* are used for the microbiological assay of pantothenic acid and its salts. There is available a USP Reference Standard Calcium Pantothenate.

Metabolic Functions, Dietary Requirement, and Food Sources—Pantothenic acid is of the highest biological importance because of its incorporation into coenzyme A (CoA), which is involved in many vital enzymatic reactions transferring a two-carbon compound (the acetyl group) in intermediary metabolism. It is involved in the release of energy from carbohydrate, in the degradation and metabolism of fatty acids, and in the synthesis of such compounds as sterols and steroid hormones, porphyrins, and acetylcholine. CoA is composed of one mole each of adenine, ribose, and β-mercaptoethylamine and three moles of phosphate for each mole of pantothenate.

Many microorganisms depend on the same metabolic pathways for their growth and reproduction as do animal species and humans and thus also require pantothenic acid. Some have the ability to synthesize pantothenic acid at a life-sustaining rate from proper precursors. Synthesis by the bacterial flora of the intestine in humans appears to be an important source of the vitamin and is the probable explanation, in part, of why pantothenic acid deficiency in humans is seldom encountered. A deficiency syndrome has been experimentally induced in human volunteers by the oral administration of a pantothenic acid antagonist, ω-methylpantothenic acid, imposed on a pantothenic acid–deficient diet. It has been impossible so far to induce an isolated deficiency of the vitamin in less than at least 9 months on anything resembling a natural diet alone, because of the occurrence of significant amounts of pantothenic acid in such a wide variety of foods.

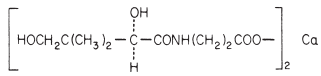
The symptoms that appear to be specific for a lack of available pantothenic acid from the studies using the antivitamin are neuromuscular disorders (paresthesias of the hands and feet and cramping of the legs and impairment of motor coordination), loss of normal eosinopenic response to adrenal corticotrophic hormone (ACTH), heightened sensitivity to a test dose of insulin, and, in concert with pyridoxine, a loss of antibody production. Fatigue, malaise, headache, sleep disturbances, nausea, abdominal cramps, epigastric distress, occasional vomiting, and an increase in flatus were subjective observations of the pantothenic acid–deficient human volunteers.

Usual diets of adult Americans furnish about 10 to 15 mg of pantothenic acid a day, with a probable range of 6 to 20 mg. The recommended daily intake of pantothenic acid is found in Table 92-5. Human milk contains about 2 mg/L; cow's milk, about 3.5 mg/L. Liver and other organ meats and eggs are particularly good sources. Broccoli, cauliflower, white and sweet potatoes, tomatoes, and molasses are quite high in pantothenic acid. Muscle tissue of beef, pork, lamb, and chicken also is a good source.

PANTOTHENIC ACID PREPARATIONS

CALCIUM PANTOTHENATE

β-Alanine, *(R)-N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-, calcium salt (2:1); Dextro Calcium Pantothenate



Calcium D-pantothenate (1:2) [137-08-6] $C_{18}H_{32}CaN_2O_{10}$ (476.54); the calcium salt of the dextrorotatory isomer of pantothenic acid.

Preparation—Several syntheses are available. In one, isobutyraldehyde is converted to the lactone of 2,4-dihydroxy-3,3-dimethylbutyric acid, the D-enantiomer of which, obtained by resolution, is combined with β-alanine to form D-pantothenic acid and then converted to the calcium salt.

Description—Slightly hygroscopic, white powder; odorless, has a bitter taste and is stable in air; unstable to heat both in the dry state and in acid or alkaline solution; most stable at pH 5.5 to 6.5, and its solutions may be autoclaved at this pH for a short time without appreciable loss; solutions are neutral or slightly alkaline to litmus, with a pH of 7 to 9; specific rotation (calculated on the dried basis and in a 5% solution) +25 to +27.5°.

Solubility—1 g in about 3 mL water; soluble in glycerin; practically insoluble in alcohol, chloroform, or ether.

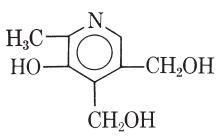
Comments—See the general statement on *Pantothenic Acid*. Since a deficiency of pantothenic acid alone is virtually unknown, the primary indication for use is a general nutritional deficiency. Clinical cases have been too few to supply creditable data on dosage.

Pyridoxine (Vitamin B_6)

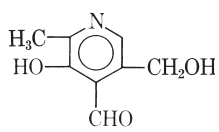
Vitamin B_6 does not denote a single substance but is rather a collective term for a group of naturally occurring pyridines that are metabolically and functionally interrelated; namely, pyridoxine, pyridoxal, and pyridoxamine. They are interconvertible *in vivo* in their phosphorylated form. There is no information on the relative biological activity of the three compounds in humans, and since pyridoxine is the most stable, it probably contributes the most vitamin activity to the diet.

Chemistry and Assay—Pyridoxine as the free base has a bitter taste and is readily soluble in water, alcohol, or acetone. It crystallizes as the hydrochloride and is prepared in this form for commercial use. Pyridoxine is one of the more stable vitamins and in the alcohol form withstands heating in acid or alkaline solution. Pyridoxal and pyridoxamine are less stable, however, and are known to undergo destruction in the more severe heat treatments sometimes used in food processing. Under most conditions of processing and storage of foods and pharmaceutical preparations, the vitamin is retained well.

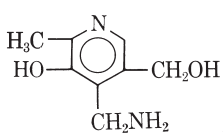
The structures of the three active forms of the vitamin and the phosphorylated form of one of them, pyridoxal phosphate, are shown below.



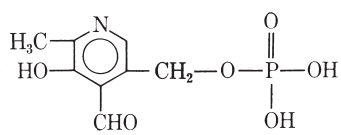
Pyridoxine



Pyridoxal



Pyridoxamine



Pyridoxal Phosphate

The biological activity of the vitamin is expressed in milligrams of the chemically pure substance, usually pyridoxine hydrochloride, for which a USP Reference Standard is available. Chicks and rats have been used for the biological assay of vitamin B_6 by placing the animals on a defi-

cient basal diet that, when supplemented with known amounts of the test vitamin, supports a degree of growth related to the amount present. It is necessary to measure the three forms of vitamin B_6 to determine accurately the total biological activity. This can be accomplished with a high-pressure liquid chromatographic method. Microbiological assays also can discriminate between the individual vitamin B_6 components. A very useful technique employed in this type of assay is the preliminary separation of the different vitamin forms by a column chromatographic procedure using an ion exchanger. The column eluates then are analyzed by procedures suited to the vitamin form present in the eluates. The organisms most commonly used are *Saccharomyces carlsbergensis, Lactobacillus casei,* and *Streptococcus faecalis*.

Metabolic Functions, Dietary Requirement, and Food Source—Vitamin B_6 in the form of pyridoxal phosphate or pyridoxamine phosphate functions in carbohydrate, fat, and protein metabolism; its major functions are most closely related to protein and amino acid metabolism. The vitamin is a part of the molecular configuration of many enzymes (a coenzyme), notably glycogen phosphorylase, various transaminases, decarboxylases, and deaminases. The latter three are essential for the anabolism and catabolism of proteins.

The biological activity of vitamin B_6 seems to be a function of the molecule as a whole, since small changes in structure render it inactive. Deoxypyridoxine, a derivative of the vitamin in which one of the methanol groups is reduced to a methyl group, has potent antivitamin activity, but it is of limited experimental use in man because of its toxicity. The antivitamin isonicotinic acid hydrazide (isoniazid) has been used widely in the treatment of tuberculosis. It is chemically related to pyridoxine and acts also as an antagonist, thus requiring physicians to be alert to the pyridoxine nutriture of patients so treated. A similar antagonism is possible during treatment of hypertension with the drug hydralazine.

No classic syndrome of pyridoxine deficiency exists, probably because it is distributed widely in nature and unique or unusual dietary habits have not so far produced an uncomplicated deficiency. That it is essential for the growth of animals and human infants is well-established. Other manifestations of deficiency in humans are probably an acrodynia-like syndrome characterized by edema and loss of hair, nerve degeneration resulting in behavioral changes, and, in infants, convulsive seizures. The latter symptom was shown to result when infants were fed a proprietary milk-based formula, unsupplemented with pyridoxine, in which the natural vitamin content was destroyed inadvertently during sterilization. In this instance, marked changes in electroencephalogram patterns of the infants were produced, and they returned to normal minutes after pyridoxine administration.

In infants, although daily requirements of the vitamin are met by consumption of adequate quantities of normal breast milk, the protein–vitamin B_6 relationship is critical. General experience with proprietary formulas suggests that metabolic requirements are satisfied if the vitamin is present in amounts of 0.015 mg/g of protein, or 0.04 mg/100 kcal. The recommended dietary allowances are provided in Table 92-5.

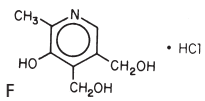
The best food sources of vitamin B_6 are muscle meats, liver, green vegetables, and whole-grain cereals. The bran from the cereal grains has especially large amounts. Nuts, corn, eggs, and milk are also good sources.

If large doses of vitamin B_6 are ingested for long periods of time, peripheral neuropathies develop. In most observations these involve levels in excess of 250 mg a day.

VITAMIN B_6 PREPARATIONS

PYRIDOXINE HYDROCHLORIDE

3,4-Pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride; Vitamin B_6 Hydrochloride



Pyridoxol hydrochloride [58-56-0] $C_8H_{11}NO_3.HCl$ (205.64).

Preparation—Several processes are available. One may be viewed as a cyclizing dehydration of ethyl glycinate (I), ethyl pyruvate (II), and 1,4-diethoxy-2-butanone (III) followed by saponification and decarboxylation at position 2 and cleavage of the three ethoxy groups with HI or another suitable reagent. Reaction of the base with HCl yields the hydrochloride. US Pats 2,904,551, 3,024,244, and 3,024,245.

Description—Colorless or white crystals or a white, crystalline powder; stable in air and slowly affected by sunlight; solutions are acid to litmus, with a pH of about 3; melting range 202 to 206°, with some decomposition.

Solubility—1 g in 5 mL water or 115 mL alcohol; insoluble in chloroform or ether.

Comments—Deficiency in adults is extremely difficult to induce, and the therapeutic need for this vitamin, alone, in the adult is of rare occurrence. However, it is justified to give it along with other B vitamins when there is evidence of a *multiple B-vitamin deficiency*. It may be used prophylactically to prevent, or to treat, peripheral neuritis in *patients treated with isoniazid*. It has been claimed that the vitamin controls the *nausea and vomiting of pregnancy* or of *radiation sickness,* but unequivocal proof has never been presented. In infants with *convulsive seizures due to pyridoxine dependency,* administration of the vitamin promptly corrects the condition (see the general statement on *Pyridoxine*). It has been claimed to be medically effective in treating the carpal-tunnel syndrome; however, more data are required to substantiate this claim. Extremely high doses (600 to 3000 mg per day) have been administered to schizophrenics, autistic children, and children exhibiting hyperkinesis. However, clear evidence of benefit has not been established. Caution needs to be exercised with these levels of administration because of reports of severe sensory-nervous-system dysfunction after daily consumption of 2 to 5 g. It may be effective in correcting hypochromic or megaloblastic anemia in patients with adequate levels of iron who have not responded to other hematopoietic agents. Since it antagonizes levodopa, patients with Parkinson's disease treated with the latter drug should not take multivitamin supplements containing pyridoxine.

Riboflavin

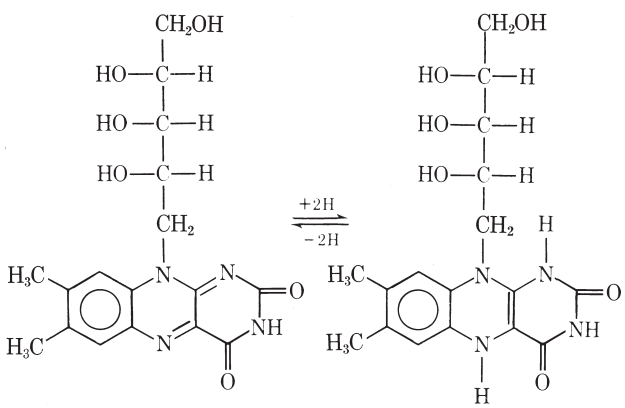
Riboflavin was formerly known as vitamin B_2 or G and lactoflavin. It owes its discovery as one of the components of the B-vitamin group to its characteristic fluorescence and pigmenting quality in such common foods as milk and egg yolk. Isolation and characterization of the yellow protein enzyme originally from yeast led to studies on the essential nature of the flavin pigment part of the enzyme in human metabolism, growth, and health.

Chemistry and Assay—Riboflavin is a yellow to orange-yellow, crystalline powder with a slight odor. When dry, it is not appreciably affected by diffused light.

In alkaline solution it is readily soluble but quite unstable to heat and to light, forming lumiflavin, a fluorescent degradation product that is without biological activity. Riboflavin is more stable to heat in acid solution, particularly from pH 1 to 6.5, but upon irradiation forms lumichrome, also biologically inactive. Photodegradation occurs in the skin, and infants with kernicterus who are treated with UV light may become riboflavin-deficient. Riboflavin is adsorbed readily from acid or neutral solution on such agents as frankonite, fuller's earth, and certain zeolites and eluted with acetone or pyridine solutions. Adsorbates have been used in pharmaceutical preparations, but from some of these the vitamin has been found to be unavailable to the human because of difficulty of elution in the intestinal tract.

Solutions of riboflavin have a characteristic yellow-green fluorescence that has a maximum absorption at 565 nm in the acid pH range. This property is made use of in the chemical determination of riboflavin. It is reduced rapidly by hydrosulfite, or by hydrogen in the presence of zinc in acid solution, to the leuco form, which is colorless and nonfluorescent. The leucoriboflavin is reoxidized easily by shaking in air. This oxidation-reduction property (see below) is the probable basis for the biological importance of riboflavin in the respiratory enzyme systems.

One gram dissolves in 3000 to about 20,000 mL of water, the variations in the solubility being due to differences in the internal crystalline structure of the riboflavin; it is more soluble in isotonic sodium chloride or alkaline solution than in water and less soluble in alcohol. It is insoluble in most lipid solvents. Derivatives such as the phosphate or acetate have been prepared for use in pharmaceutical preparations when higher concentrations are desired.



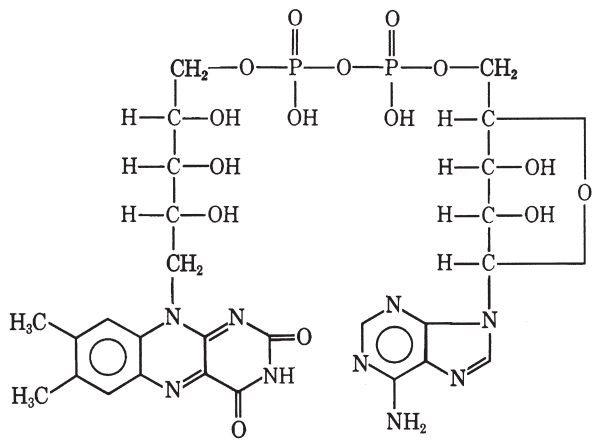
Riboflavin **Leucoriboflavin**

The activity of riboflavin is expressed in milligrams of the chemically pure substance, and a USP Reference Standard Riboflavin is available for assay purposes. In early work, the riboflavin content of substances was measured by a rat growth bioassay method, but this has been replaced by both physicochemical and microbiological methods.

Chemical determinations are based on colorimetric and fluorometric procedures. Straightforward measurement of the intrinsic yellow color of riboflavin is often sufficient for assaying pharmaceutical preparations. The fluorometric method is more sensitive and free of interferences and is therefore more suited to the assay of the vitamin in foods. It depends upon the extraction of the vitamin with dilute acid, filtration, treatment of the filtrate with permanganate and hydrogen peroxide to destroy interfering pigments, and measurement of the fluorescence. Assays also can be accomplished using high-pressure liquid chromatography and a fluorometric detector.

Lactobacillus casei is used as the test organism for microbiological assay of riboflavin. It is determined by measurement of the growth stimulation of the organism or by alkaline titration of the acid produced during incubation.

Metabolic Functions—Riboflavin plays its physiological role as the prosthetic group of a number of enzyme systems that are involved in the oxidation of carbohydrates and amino acids. It functions in combination with a specific protein, either as a mononucleotide containing phosphoric acid (FMN) or as a dinucleotide combined through phosphoric acid with adenine (FAD).



Flavin-adenine dinucleotide (FAD)

The specificity of each of the enzymes is determined by the protein in the complex. By a process of oxidation-reduction, riboflavin in the system either gains or loses hydrogen. The substrate, either carbohydrate or amino acid, may be oxidized by a removal of hydrogen. The first hydrogen acceptor in the chain of events is NAD or NADP, the di- or trinucleotide containing nicotinic acid and adenine. The oxidized riboflavin system then serves as hydrogen acceptor for the coenzyme system and in turn is oxidized by the cytochrome system. The hydrogen finally is passed on to the oxygen to complete the oxidative cycle. A number of flavoprotein enzymes have been identified, each of which is specific for a given substrate.

There is evidence that some of the flavin enzymes contain metallic constituents. These metalloflavoproteins may contain iron, copper, or molybdenum. Succinic dehydrogenase, for example, contains iron, and xanthine oxidase contains molybdenum as well as iron.

After phosphorylation, riboflavin is absorbed from the intestinal tract and excreted in the urine. A human adult on an ordinary diet excretes from 0.5 to 1.5 mg in 24 hr, depending on the content of the diet. Of a 10-mg dose taken by mouth, 50% to 70% is excreted within 24 hr. In riboflavin deficiency there is little or none found in the urine. Measure of excretion has been used as a diagnostic sign of deficiency. Riboflavin, like thiamine, is stored to a limited extent, and constant dietary supply is needed to maintain normal body levels. Liver, kidney, and heart tissues contain relatively large amounts of riboflavin because of their high enzyme content.

Dietary Requirement and Food Sources—Symptoms of human ariboflavinosis include cheilosis (reddening of the lips and the appearance of fissures at the corners of the mouth), characteristic changes in color of the mucous membranes, inflammation of the tongue, and denuding of the lips. Lesions of a seborrheic nature also have been observed as a result of riboflavin deficiency. Ocular manifestations that appear in man are characterized chiefly by corneal vascularization, in which the cornea is extensively invaded by small capillaries. This usually is accompanied by sensations of itching, burning, and roughness of the eyelid and lacrimation, photophobia, and visual fatigue. Some of these conditions may, of course, arise from other causes and do not necessarily indicate riboflavin deficiency.

Riboflavin deficiency in humans has not been found to be widespread in any part of the world, but is undoubtedly a complicating factor in other deficiency diseases such as pellagra. For therapeutic purposes, doses of 1 to 10 mg a day have been given. Rapid disappearance of symptoms of ariboflavinosis occurs with 10-mg doses, and some question the need for administering amounts larger than this.

Studies dealing with the quantitative riboflavin requirement of the human indicate that it is related to body size, metabolic rate, and rate of growth. The parameter used to express these most closely is metabolic body size, represented as kilograms of body weight taken to the 3/4 power. The recommended daily dietary allowance of the Food and Nutrition Board for riboflavin is listed in Table 92-5. In general, the minimum requirement for riboflavin is about 0.3 mg for adults and 0.8 mg for infants on a 1000-kcal-intake basis. From a physiological point of view, an intake of more than 0.5 to 0.6 mg/1000 kcal may be of little extra value in normal adult persons.

Riboflavin is widely distributed in nature, in both plants and animals, as an essential constituent of all living cells, and therefore is found widely distributed in small amounts in foods. It is quite stable during the processing of food, except when there is excessive exposure to light. Because of its water solubility, there is moderate loss of riboflavin in cooking when the cooking water is discarded. This loss, however, is generally smaller than that of thiamine, niacin, or ascorbic acid.

Foods that make important contributions of riboflavin to the diet are liver and other organ tissues, milk, and eggs. Vegetables and fruits furnish a small but constant supply.

Many species of microorganisms are capable of synthesizing riboflavin, and because of the extensive bacterial growth in the human intestinal tract, this may form an important and constant source of supply of riboflavin and may account for the limited occurrence of deficiency in humans, although this has yet to be well studied.

When it was recognized that cereal products would be a good vehicle to use to improve the content of riboflavin in many diets, its mandatory addition as an enriching ingredient was adopted. In concert with thiamine, niacin, and iron, riboflavin is present in nutritionally significant amounts in enriched wheat flour, farina, corn products, bread, macaroni, and noodle products. Because of certain cooking habits and the apparent unacceptability of the unnatural yellow color, the enrichment of rice with riboflavin has been resisted.

RIBOFLAVIN PREPARATIONS

Lactoflavin; Vitamin B_2

Riboflavin [83-88-5] $C_{17}H_{20}N_4O_6$ (376.37).

Preparation—Mostly by synthesis. In one method, 1-(6-amino-3,4-xylidino)-1-deoxy-D-ribitol (I) is condensed with alloxan (II) in acetic acid with boric acid as a catalyst. Among other ways, I may be prepared by condensing D-ribitol with 4,5-dimethylphenylenediamine. US Patent 2,807,611.

Description—Yellow to orange-yellow, crystalline powder with a slight odor; melts at about 280°; saturated solution is neutral to litmus; when dry not appreciably affected by diffused light, but when in solution, light induces quite rapid deterioration, especially in the presence of alkalies.

Solubility—Very slightly soluble in water, alcohol, or isotonic sodium chloride solution; very soluble in dilute solutions of alkalies; insoluble in ether or chloroform.

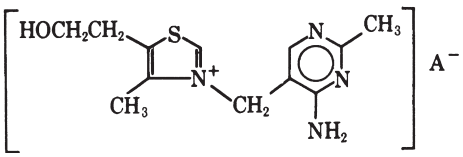
Comments—To treat ariboflavinosis (riboflavin deficiency) and also to supplement other B vitamins in the treatment of pellagra and beriberi (see the general statement on *Riboflavin*).

Thiamine

Concentrates of thiamine, often termed vitamin B_1, were given the latter name by early workers in this country who recognized that at least two accessory dietary factors were needed for normal growth of laboratory rats, one in butter fat and the other in *milk sugar*. The names they suggested for these factors were fat-soluble vitamin A and water-soluble vitamin B. It was shown subsequently by a number of investigators that the latter consisted of a group of substances rather than a single compound, but vitamin B_1 was finally the first pure compound of the group to be laboriously isolated from rice polishings. In the pioneer studies on this substance it was found that a thiamine concentrate prevented polyneuritis in chickens, which later was found to be caused by the ab-

sence of thiamine in their diet. Deriving from this observation, an early name for the factor is aneurin (from antineuritic), which has persisted in some countries.

Chemistry and Assay—Thiamine is a generic term applied to all substances possessing vitamin B_1 activity, regardless of the anion attached to the molecule. The cationic portion of the molecule, which is the part that may properly be called *thiamine,* is made up of a substituted pyrimidine ring connected by a methylene bridge to the nitrogen of a substituted thiazole ring. In the general structural formula, *A* is any appropriate anion but usually chloride (see structure below). In addition, ammonium salts may be formed with the amine substituent on the pyrimidine ring. The common nomenclature is confusing, but in general, the term mono, as in thiamine mononitrate or thiamine monophosphate, designates the thiazolium type salt. Thiamine chloride hydrochloride is the ammonium salt formed by reacting thiamine chloride with hydrochloric acid.



Thiamine compounds are usually readily soluble in water or in alcohol but insoluble in fat solvents. They are stable in acid solution and may be heated without decomposition but are unstable in neutral or alkaline solution. At neutral or alkaline pH, splitting occurs at the methylene bridge upon heating in the presence of moisture. Splitting of the molecule takes place quantitatively in the presence of bisulfite ions, a reaction that is made use of in preparing dietary constituents free of thiamine for bioassay purposes.

Thiamine is oxidized in alkaline solution to thiochrome, a biologically inactive, highly fluorescent substance. This reaction is the basis for the chemical method of estimating thiamine. The pure vitamin is not readily oxidized in air.

An alternate commercial form of vitamin B_1, widely used because of its greater stability than the hydrochloride, is the mononitrate.

The activity of the vitamin is expressed in milligrams of the chemically pure substance, and a USP Reference Standard Thiamine Hydrochloride is available.

The determination of thiamine in food, biological materials, and pharmaceutical products is done almost exclusively by the thiochrome fluorometric method. On oxidation with ferricyanide in alkaline solution, thiamine is transformed into thiochrome, which has a strong blue fluorescence. It is a very sensitive method and correlates well with bioassay results. The sequence in the determination involves extraction of the vitamin, enzyme hydrolysis, adsorption, elution, and oxidation to thiochrome, which is extracted with isobutanol and determined fluorometrically.

Before the development of suitable physicochemical methods, thiamine was determined in a typical rat-growth assay that is based on the growth response of young thiamine-depleted rats to supplemental doses of a reference standard and to the test material either fed in or separate from the diet or injected parenterally.

Metabolic Functions—In a phosphorylated form, thiamine (thiamine pyrophosphate; cocarboxylase) serves as the prosthetic group of enzyme systems that are concerned with the decarboxylation of α-ketoacids. For example, pyruvic acid is decarboxylated to form a two-carbon residue. This process of decarboxylation is catalyzed by the pyruvic acid decarboxylase enzyme system, which consists of a specific protein, manganese ions, and diphosphothiamin. An α-hydroxyethyl group (the *acetaldehyde* residue of the decarboxylated pyruvic acid) attaches to the 2-carbon of the thiazole ring. The hydroxyethyl group (active *acetate,* active *acetaldehyde,* or two-carbon fragment) attaches to one of the sulfur atoms of lipoamide, from which it is removed by coenzyme A. Pyrophosphorylated thiamine is effective in the decarboxylation of other α-ketoacids as well. Some decarboxylation processes are reversible, so synthesis (condensation) may be achieved; thus, thiamine also is important to the biosynthesis of keto-acids. It is involved in transketolase reactions.

Thiamine is absorbed readily in aqueous solution from both the small and large intestine and then is carried to the liver by the portal circulation. In the liver, as well as in all living cells, it normally combines with phosphate to form cocarboxylase. It may be stored in the liver in this form or it may combine further with manganese and specific proteins to become active enzymes known as carboxylases.

Thiamine is excreted in the urine in amounts that reflect the amount taken in and the amounts stored in the tissues. Measurement of the urinary excretion of thiamine after giving a small dose of thiamine is useful in determining whether body stores are adequate or deficient.

Dietary Requirement and Food Sources—Polyneuritis (dysfunctioning of the nervous system) or beriberi is the frank disease associated with thiamine deficiency in humans. Peripheral neuritis is a pathological condition of the nerves of the extremities; usually both legs are affected and sometimes the arms as well. The symptoms include loss of sensation, muscle weakness, and paralysis. In beriberi this condition also is associated with edema and abnormal electrocardiogram patterns.

Severe cases of beriberi are commonly found among people whose diets consist principally of milled or polished rice, from which the vitamin, contained in the bran and germ of the cereal, is largely removed during the milling process. American diets generally furnish sufficient thiamine to meet requirements, and with the use of a varied diet, including whole-grain cereals or enriched bread or flour, the adequacy of thiamine in most instances is beyond question. Symptoms of thiamine deficiency have been observed among chronic alcoholics, who use alcohol in place of food as a source of energy. Deficiency also occurs in cases of chronic diarrhea, in which absorption is interfered with over a period of time, and during pregnancy complicated with anorexia and nausea.

In the diagnosis of thiamine deficiency, symptoms to be noted in particular are anorexia, fatigue, loss of weight, sensation of burning in the soles of the feet, tenderness in calf muscles, muscle cramps, and general muscular weakness. Such signs are not in themselves specific, however, without supplementary laboratory findings that indicate a reduced thiamine content in blood and urine.

For treatment of beriberi or thiamine deficiency in humans, the first requisite is a nutritionally complete, well-balanced diet. Good diet is essential, because beriberi in most instances results from a complex or multiple deficiency, and administration of thiamine alone may precipitate a condition resulting from a lack of other water-soluble factors. Doses of 10 to 100 mg of thiamine have been used in severe cases to bring about a cure, but evidence of superiority of the larger doses is lacking. As size of the dose is increased, the proportion of thiamine retained rapidly decreases, the excess being excreted rapidly in the urine. Frequent small doses are to be preferred to a single large daily dose. Only in the most severe cases or in patients with impaired intestinal absorption does parenteral administration appear advantageous. Pharmaceutical preparations of many types and potencies are available commercially.

It is generally assumed that thiamine need is related to caloric need, particularly calories derived from carbohydrate. The Food and Nutrition Board considers that 0.5 mg/1000 kcal will maintain satisfactory thiamine nutriture under normal conditions in the US. As the caloric allowance varies with age, so does the recommended dietary allowance for thiamine, as can be seen in Table 92-5.

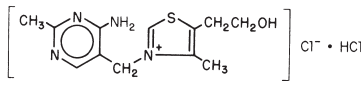
Thiamine is found widely distributed in foods. Thiamine is found in all plants and is synthesized by some microorganisms, particularly yeasts. No one food can be considered of particular importance above all others, although the cereal grains, milk, legumes, nuts, eggs, and pork probably furnish the larger proportion of thiamine in diets used in the US. Sophistication and processing of foods generally tend to reduce the thiamine supply. For example, in the preparation of wheat flour, separation of the bran coat and germ removes 3/4 or more of the thiamine present in the whole wheat. This is true for other cereal grains as well. Much of the white flour, corn grits, and rice used in this country is enriched to approximate the whole-grain level. Because of the lability of thiamine to heat, cooking and baking processes reduce the raw food content of the vitamin.

The loss of thiamine in home cooking is not considered excessive, except with foods cooked in large amounts of water that then is discarded. Because of its solubility, the thiamine content of the cooking water is always appreciable.

THIAMINE DERIVATIVES

THIAMINE HYDROCHLORIDE

Thiazolium, 3-(4-amino-2-methyl-5-pyrimidinyl)methyl-5-(2-hydroxyethyl)-4-methyl-, chloride, monohydrochloride; Vitamin B_1 Hydrochloride; Aneurine Hydrochloride

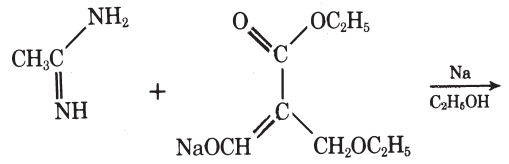


[67-03-8] $C_{12}H_{17}ClN_4OS.HCl$ (337.27).

Preparation—This vitamin consists of two ring systems, a pyrimidine portion and a thiazole portion joined by a methylene bridge. The *pyrimidine* may be prepared by several processes, one of which is as follows: Ethyl acrylate [$CH_2{=}CHCOOC_2H_5$] is heated with ethyl alcohol, forming β-ethoxypropionic ester [$C_2H_5OCH_2CH_2COOC_2H_5$], which is

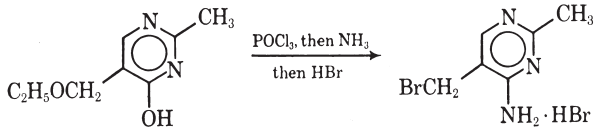
condensed in the presence of sodium metal with formic acid to form ethyl sodioformyl-β-ethoxypropionate, I. This then is condensed with acetamidine, yielding 2-methyl-5-ethoxymethyl-5-hydroxypyrimidine, II. This compound is treated with phosphorus oxychloride, thereby replacing the OH on carbon 6 with Cl, and by reacting the resulting chloro derivative with ammonia, the Cl is replaced by NH_2. Finally, on treating the latter product with HBr, 2-methyl-5-bromomethyl-6-aminopyrimidine hydrobromide, III, is produced.

The *thiazole* portion of the thiamine molecule may be built up in the following matter: Ethyl acetoacetate (IV) is treated with ethylene oxide [C_2H_4O] and the resulting acetyl-butyryl lactone, when reacted with sulfuryl chloride, yields chloroacetyl butyrolactone. This compound is decarboxylated when heated with HCl, splitting off CO_2 and forming 3-chloro-5-hydroxy-2-pentanone, V. The latter, when condensed with thioformamide yields the thiazole, 4-methyl-5-hydroxyethylthiazole, VI.

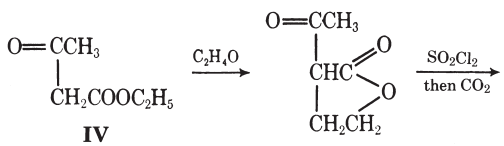


Acetamidine **Enol form of Ethyl Sodioformyl-β-ethoxypropionate**

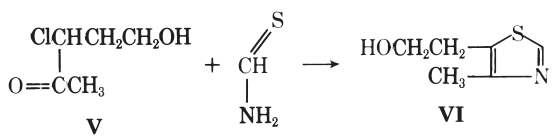
I



II **III**



IV



V **VI**

III + VI $\xrightarrow[\text{then AgCl}]{\text{Condense}}$ **Product**

The final step in this process is the combination of the pyrimidine and the thiazole to form a thiazolium halide. Since this is a simple addition of an alkyl halide, the (bromomethyl) pyrimidine, to a tertiary amine, the thiazole, it is readily effected by bringing the two components together in a suitable solvent. The vitamin-bromohydrobromide so obtained is transformed into the corresponding chlorine compound, thiamine, with freshly precipitated silver chloride. The silver combines with the bromine to form the less soluble silver bromide, and the chloride from the silver chloride replaces the bromine.

Description—Small white crystals or a crystalline powder usually with a slight, characteristic odor; when exposed to air, the anhydrous product rapidly absorbs about 4% water; solutions are acid to litmus paper; pH (1 in 100 solution) between 2.7 and 3.4; melts, with some decomposition, at about 248°.

Solubility—1 g in about 1 mL water or about 170 mL alcohol; soluble in glycerin; insoluble in ether or benzene.

Incompatibilities—In the dry state, it is stable. Acidic solutions having a pH below 5.5, preferably from 5 to 3.5, are also relatively stable. *Alkalies* destroy it. It is precipitated from solution by several of the *alkaloidal reagents* such as *mercuric chloride, iodine, picric acid, tannin,* and *Mayer's reagent*. It is sensitive to both *oxidizing* and *reducing agents*.

Elixirs of thiamine hydrochloride are necessarily acid in reaction and are, therefore, incompatible with any acid-neutralizing substance. *Phenobarbital sodium* has been an occasional offender in this respect, the result frequently being such as to cause precipitation of the phenobarbital as well as a partial lowering of the acidity of the mixture, with consequent deterioration of the vitamin. Phenobarbital, not the sodium derivative, may be dispensed in such an instance, provided that sufficient alcohol is present to keep it in solution. If a part of the elixir is replaced with alcohol for this purpose, an amount of thiamine hydrochloride equivalent to that contained in the volume so replaced must be added to the product.

Comments—To treat *beriberi* and also *general B-vitamin deficiency*. The fact that it cures the neuropathologies of beriberi has given rise to a widespread use of the vitamin in nearly any type of neuropathology. Although such indiscriminate use can do no organic harm to the patient, it constitutes an unnecessary expense; the promotion of the vitamin for such promiscuous use constitutes an abuse. For additional information see the general statement on *Thiamine*.

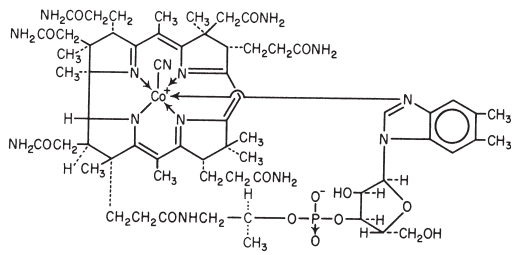
Thiamine Mononitrate Thiazolium, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methyl-, nitrate (salt); Thiamine Nitrate; Vitamin B_1 Mononitrate; thiamine nitrate [532-43-4] $C_{12}H_{17}N_5O_4S$ (327.36).

Preparation: In one method thiamine hydrochloride is reacted with sufficient NaOH to remove the HCl and replace the chloride ion by OH, and the resulting thiamine hydroxide is neutralized with nitric acid. *Description:* White crystals or crystalline powder, usually with a slight, characteristic odor; pH (1 in 50 solution) 6 to 7.5. *Solubility:* 1 g in about 44 mL water; slightly soluble in alcohol or chloroform. *Comments:* More stable than the hydrochloride; solutions of the nitrate are practically neutral, while those of the hydrochloride are acid. Its vitaminergic actions and uses are identical to those of the hydrochloride. See *Thiamine Hydrochloride*.

Vitamin B_{12}

Vitamin B_{12}, the most recently discovered of the B group, was isolated from liver fractions in crystalline form in 1948 and was soon after shown to be specific for the treatment of Addisonian pernicious anemia. It was established that vitamin B_{12} is the active principle in extracts of liver, employed for more than 30 years in the control of pernicious anemia. Liver continues to be an important dietary source of the vitamin, but liver injection is no longer used in the treatment of pernicious anemia, because of the ready availability of crystalline forms of the vitamin.

Chemistry and Assay—Vitamin B_{12} is a complex water-soluble compound that crystallizes as small red needles that have a specific rotation in dilute aqueous solution of −59°. Characteristic absorption maxima occur at 278, 361, and 550 nm. The crystalline substance blackens without melting at 300°. The compound is a cobalt coordination complex, in which the cobalt is trivalent and has a coordination number of six. The complex is neutral. Vitamin B_{12} is composed of two heterocyclic systems, a benzimidazole and a modified porphyrin nucleus, with the following structure:



Cyanocobalamin

Actually, the cyanide group coordinated to the cobalt is not a part of the true vitamin but rather is an artifact caused by isolation of the vitamin on charcoal; in the liver the ligand is the 5′-deoxyadenosyl anion. Nevertheless, by strict organic chemical definition and by virtue of the fact that the cyanide was the first form of the vitamin to be isolated, cyanocobalamin *is* vitamin B_{12}. When the ligand is hydroxide instead of cyanide, the compound is hydroxocobalamin (*vitamin B12a)* ; when it is water, the substance is aquocobalamin (*vitamin B12b)*; when it is nitro, the compound is *vitamin B12c ; the 5′-deoxyadenosyl form is coenzyme B12*; if the ligand is methyl, the compound is *methyl B12*. Sulfito- and thiocyanatocobalamins also are known. In practice, all of these compounds are vitamin B_{12}. A similar situation obtains with respect to the name *cobalamin,* which strictly is synonymous with cyanocobalamin but in loose practice applies to any active compound containing the α-(5,6-dimethylbenzimidazoyl) corrin nucleus. *Cobamides* is a generic term that has been used for these compounds.

Vitamin B_{12} (cyanocobalamin) in an atmosphere of hydrogen with a platinum catalyst is reduced to a red crystalline compound with slightly changed UV-absorption maxima, and a reduced stability to heat. Vitamin B_{12a} results from such reduction. Vitamin B_{12b}, another reduced form, occurs in natural sources.

Commercially, vitamin B_{12} is obtained from fermentation by *Streptomyces griseus*. The vitamin is precipitated from aqueous solutions saturated with ammonium sulfate by 1-butanol. Purification is achieved by chromatography, using bentonite or aluminum silicate as the adsorbent. Sharply defined red bands are formed during the development of the chromatograms, indicating the location of the vitamin. The red band is separated mechanically and eluted with water. The concentrated water solution on addition of acetone gives the crystalline vitamin, which can be purified further by recrystallization from aqueous acetone.

The USP provides a Reference Standard Cyanocobalamin for use in assay of the vitamin. A physicochemical method for determining vitamin B_{12} involves measurement of light absorbance at certain specific wavelengths characteristic for cyanocobalamin. This method is only applicable to relatively concentrated solutions of the compound, such as pharmaceutical preparations. Vitamin B_{12} also can be determined with high-performance liquid chromatography.

Vitamin B_{12} is one of the most active biological factors known; its activity for bacteria is measured in terms of millimicrograms. Because of this sensitivity of some bacteria to such low levels of the vitamin and the fact that foods contain exceptionally low concentrations of the vitamin, microbiological methods (using *Lactobacillus leichmannii, Ochramonas malhamensis,* and *Euglenia gracilis*) were widely used until newer radioligand binding assays were introduced.

Metabolic Functions, Dietary Requirement, and Food Sources—The vitamin is essential for the normal functioning of all cells, but particularly for cells of the bone marrow, the nervous system, and the GI tract. It appears to facilitate reduction reactions and participate in the transfer of methyl groups. Evidence exists that vitamin B_{12} is involved in protein, carbohydrate, and fat metabolism, but its chief importance in mammalian tissues seems to be, together with folic acid, in the anabolism of deoxyribonucleic acid in all cells. Coenzyme forms of vitamin B_{12}, in which the vitamin is linked to adenine and a sugar, which catalyze specific reactions in intermediary metabolism, have been isolated from bacterial cultures and probably have similar vitamin roles in mammalian cells.

The biochemical fault in pernicious anemia, a condition caused by a prolonged deficiency of vitamin B_{12}, is a failure of elaboration of the intrinsic factor, normally secreted by the parietal cells of the stomach mucosa. This intrinsic factor, which is essential for the absorption of the vitamin through the intestinal wall, forms a complex with vitamin B_{12}. Intrinsic factor is a glycoprotein of 45,000 daltons.

Vitamin B_{12} is a requisite for normal blood formation, and certain macrocytic anemias respond to its administration. In pernicious anemia, unless accompanied by intrinsic factor, the vitamin is not absorbed orally in effective amounts and must be administered parenterally in microgram quantities. Vitamin B_{12} deficits not associated with intrinsic factor pathology may be managed orally. Preparations containing vitamin B_{12} and intrinsic factor concentrate are now available for oral use and have been shown for short-term use at least to be equivalent in value to the injections. Clinical studies indicate that if milligram amounts of the vitamin are administered orally in the absence of intrinsic factor, enough of the vitamin passes through the intestinal wall to be effective in maintaining the pernicious anemia patient. However, the injectable form of vitamin B_{12} continues to be the drug of choice because of the desirability of regular attention of a physician to the condition of the patient.

The evidence indicating that vitamin B_{12} is the antipernicious anemia factor is complete. In treating pernicious anemia, vitamin B_{12} administered intramuscularly produces a maximal reticulocyte response in 4 to 9 days and a restoration of red- and white-cell counts in 4 to 6 weeks. The change in bone marrow from a megaloblastic to a normoblastic state is dramatic and occurs within a few hours after the injection of as little as 1 μg of the vitamin. Vitamin B_{12} is considered to be the extrinsic factor of Castle, the absorption of which from the intestinal tract is facilitated by the intrinsic factor present in normal gastric juice. The biochemical defect in pernicious anemia, then, is a failure of elaboration of the intrinsic factor. Because of this relationship, vitamin B_{12} given orally is much less effective in the pernicious anemia patient and entirely ineffective if there is complete absence of intrinsic factor.

The vitamin is effective in preventing the occurrence of neurological changes common to pernicious anemia. These symptoms are observed more frequently among the elderly because absorption of vitamin B_{12} has been shown to decrease among this population. However, it is not uncommon to identify women with neurological changes caused by vitamin B_{12} deficiency in their mid-thirties to late thirties. Acute symptoms of combined-system disease have been found to disappear rather promptly after B_{12} administration, but recovery appears to depend more on the chronicity of the disease than on the extent of neurological involvement, and conditions of long standing are less apt to show recovery. Osteoblast activity probably also depends upon vitamin B_{12}.

A simple nutritional concept of pernicious anemia that seems valid is that of essentially an uncomplicated deficiency of vitamin B_{12} conditioned by the lack of intrinsic factor and, hence, the inability to absorb the vitamin from ingested food. This validation rests on several types of evidence; particularly convincing is the comparison of the clinical development of vitamin B_{12} deficiency in vegans, in patients who had total gastrectomy (resulting in removal of intrinsic factor and interference with absorption of the vitamin), and the relapse following withholding of therapy from previously adequately treated patients with pernicious anemia. Simple experimental dietary deficiency of vitamin B_{12} has not yet been produced in the adult human under conditions of careful continuous observation. It seems probable that the requirements for parenterally administered (or absorbed) vitamin B_{12} by the patient with pernicious anemia or gastrectomy are similar to the requirements of the normal subject. The recommended daily dietary allowance of the Food and Nutrition Board is provided in Table 92-5.

Vitamin B_{12} occurs in meat and dairy products but is not present to any measurable extent in plants or cereal grains. It is probable that indigenous bacteria in plant foods synthesize sufficient vitamin B_{12} to meet the requirement of those individuals whose dietary habits preclude the use of animal food sources.

VITAMIN B_{12} PREPARATIONS

CYANOCOBALAMIN

α-5,6-Dimethylbenzimidazolylcobamide cyanide; Vitamin B_{12}

Vitamin B_{12} [68-19-9] $C_{63}H_{88}CoN_{14}O_{14}P$ (1355.38).

Preparation—Vitamin B_{12} can be isolated from aqueous liver extracts and from *Streptomyces griseus* fermentation. Commercially, it is obtained from the latter source.

Description—Dark red, hygroscopic crystals or amorphous or crystalline powder; when the anhydrous compound is exposed to air it may absorb about 12% water.

Solubility—1 g in 80 mL water; soluble in alcohol; insoluble in acetone, chloroform, or ether.

Comments—This and other forms of vitamin B_{12} are used to treat various megaloblastic anemias, especially *pernicious anemia* and other anemias in which the secretion of the intrinsic factor is impaired, as in *gastric cancer, gastric atrophy, total* or even *subtotal gastrectomy*. It also may be used to treat the megaloblastic anemias of *tropical sprue, idiopathic steatorrhea, gluten-induced enteropathy, regional ileitis, ileal resection, malignancies, granulomas, strictures or other structural disorders of the ileum* in which vitamin B_{12} absorption is impaired; in most of these folic acid deficiency is even more severe, and combined therapy is indicated. Its deficiencies untreated for periods of more than 3 months may result in permanent degenerative spinal cord lesions. The megaloblastic anemia associated with *fish tapeworm infestation* also responds to the vitamin. The megaloblastic anemias of pregnancy, infancy, alcoholism, and poverty usually are due to folic acid deficiency and only infrequently respond to it. The vitamin is *not useful* in the treatment of infectious hepatitis, multiple sclerosis, trigeminal neuralgia, anorexia, miscellaneous neuropathies, thyrotoxicosis, retarded growth, aging, and various psychiatric disorders, and claims to the contrary and promotion therefore represent misuse without support from clinical trials. It should not be administered intravenously and is contraindicated in patients who are sensitive to it or cobalt. Patients with Leber's disease have been found to suffer severe and rapid opticatrophy when treated with it. Either cyanocobalamin or hydroxocobalamin may be used for a loading dose in the Schilling test for malabsorption of the vitamin in diseases that affect the lower bowel, such as *sprue*.

A nasal spray has been developed that is said to provide significant absorption in the nasal mucosa and may supplant the parenteral dosage forms.

In addition to intrinsic factor, GI absorption requires an alkaline pH. In the presence of pancreatic disease it may be necessary to administer the oral vitamin with bicarbonate or give the vitamin parenterally.

For additional information about cyanocobalamin see the general statement on *Vitamin B12*.

HYDROXOCOBALAMIN

Cobinamide, dihydroxide, dihydrogen phosphate (ester), mono(inner salt), 3′-ester with 5,6-dimethyl-1-α-D-ribofuranosyl-1*H*-benzimidazole; Vitamin B_{12a}

Cobinamide dihydroxide dihydrogen phosphate (ester), mono(inner salt), 3′-ester with 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole

[13422-51-0] $C_{62}H_{89}CoN_{13}O_{15}P$ (1346.37); an analog of *Cyanocobalamin* in which a hydroxyl radical has replaced the cyano radical.

Preparation—Cyanocobalamin in solution is hydrogenated at room temperature with the aid of Raney nickel. The solution then is exposed to air and diluted with acetone. Oxidation takes place, and upon standing, the hydroxocobalamin crystallizes.

Description—Dark red crystals or red crystalline powder; odorless or has no more than a slight acetone odor; anhydrous form is very hygroscopic; pH (2 in 100 solution) between 8 and 10.

Solubility—1 g in 50 mL water, 100 mL alcohol, 10,000 mL chloroform, or 10,000 mL ether. It is preferable to make aqueous solutions in acetate buffer at a pH between 3.5 and 4.5 in which 1 g dissolves in about 100 mL water.

Comments—See *Cyanocobalamin*.

MULTIVITAMIN PREPARATIONS

In the preceding text and in various monographs, attention was called in several instances to the fact that it is desirable at times to administer more than one vitamin for what appear to be the symptoms of a single deficiency. The quotation "In the shadow of pellagra walks beriberi" has considerable substance in fact. Diets deficient in niacin are frequently also deficient in thiamine and certain other B vitamins of similar dietary source. The same relationship holds frequently for folate and vitamin B_{12}. Malabsorption syndromes affect the assimilation of several vitamins. Furthermore, the repair of a deficiency of one vitamin may increase the requirement for another; for example, repletion of thiamine increases the need for riboflavin. Diseases in which there is increased metabolism, such as thyrotoxicosis, increase the need for more of the vitamins, as do periods of hard physical work, stress, pregnancy, and lactation. Therefore, multivitamin therapy is often rational. Multivitamin therapy also is recommended for individuals who are on restricted diets for weight control or lack vitality, those who are debilitated, and those working in hazardous environments. Use of multivitamin supplements for infants and preschool children should be done on the advice of a pediatrician. For patients unable to consume an oral diet, injectable multivitamin products containing 13 vitamins are available to be administered diluted in parenteral fluid or in parenteral nutrition admixtures.

OTHER PREPARATIONS

Levocarnitine, L-Carnitine [L-(3-Carboxy-2-hydroxypropyl)trimethylammonium hydroxide inner salt; [461-06-3] Vitamin B_T; $C_7H_{15}NO_3$ (161.20); Carnitor]—*Preparation:* It may be isolated from meat extracts or prepared synthetically. *Description and Solubility:* White, very hygroscopic solid melting at about 197°. Readily soluble in water or hot alcohol; practically insoluble in most organic solvents. *Comments:* Required in mammalian energy metabolism and has been shown to facilitate long-chain fatty acid entry into cellular mitochondria, therefore providing the substrate for β-oxidation and subsequent production of energy. It is synthesized in the liver from lysine. Deficiency may occur from impaired hepatic synthesis or transport from liver to muscle. Carnitine deficiency may lead to elevated triglyceride and free fatty acid concentrations, diminished ketogenesis, and lipid infiltration of muscle and liver.

Betaine (anhydrous) {107-43-7]1-Carboxy-*N,N,N*-trimethylmethanaminium inner salt; trimethyl glycine; $C_5H_{11}NO_2$ (117.15) Cystadane. *Description and Solubility*—White, granular, hygroscopic powder; very soluble in water, soluble in methanol and in ethanol, sparingly soluble in ether. *Comments*—A methyl group donor used in the management of inborn errors of metabolism that result in homocystinuria. The orphan drug product is administered as a solution prepared from an anhydrous powder form.

MINERALS

Minerals can be further differentiated as macro-minerals and micro-minerals. The micro-minerals are also referred to as trace elements and will be presented in the next section. Macro-minerals are found in larger quantities in the human body and as such have higher requirements for intake. Those with adequate data supporting dietary recommendations are listed in Table 92-6. Dietary and supplementary intake of minerals is often in a salt form. These minerals can be found in dissociated ionic form in physiologic fluids in which case they are referred to as electrolytes. These electrolytes can each be administered intravenously as part of an admixture to maintain or replete total body stores of the electrolyte when the gastrointestinal route cannot be used.

SODIUM—(See *Blood, Fluids, Electrolytes, and Hematologic Drugs*).
POTASSIUM—(See *Blood, Fluids, Electrolytes, and Hematologic Drugs*).
CALCIUM—(See *Blood, Fluids, Electrolytes, and Hematologic Drugs*).
PHOSPHATE—(See *Blood, Fluids, Electrolytes, and Hematologic Drugs*).
MAGNESIUM—(See *Gastrointestinal Drugs*).

TRACE ELEMENTS

The trace elements, or micro-minerals, are inorganic nutrients found in small quantities in the human body and have intake requirements in the mg or μg range. The essentiality of several trace elements was established for humans during the 1930s. Those with adequate data supporting dietary recommendations are listed in Table 92-6. Fourteen elements now are thought to be essential, although dietary requirements have been established for only nine (Table 92-6). Some elements, notably manganese and chromium, can exist in several oxidation states; however, only one or two are compatible with a biological environment and function. Evidence to support required functions in humans is still incomplete for nickel, silicon, tin, and vanadium. There also is some evidence that boron may be essential. Although based on limited data, dietary intake of the remaining trace elements is about 15-160 μg cobalt, 100-150 μg nickel, 1.5-3.5 mg tin, and 10-20 μg vanadium.

Information on trace-element distribution in foods is presented in Table 92-7. This is an attempt to indicate important sources of the elements or the level, particularly if low, in important foods. This table is of rather limited usefulness because it is based on so little information. At present, too little is known about the effect of agricultural practices and manufacturing processes on trace-element content.

Our understanding of trace-element function in humans is less complete than that of vitamins. Study of a deficiency syndrome in animals often precedes recognition of deficiency or metabolic problems in humans, particularly as related to a disease. Notable exceptions have been reports of deficiency in patients receiving parenteral nutrition not providing a particular element. For this reason, deficiency syndromes in animals are described for each element known to be essential.

Similarly, our knowledge of trace-element toxicity in humans is limited, and we must rely on animal data. Two problems must be considered. One is the effect of long-term supplementation with a *moderate* excess above requirement. It is important to consider not only the amount of a single trace element, but also the balance among all required elements. This area requires periodic review as knowledge increases. The other toxicity problem relates to short-term intake of multiple recommended doses, either accidentally or purposefully. This must be regarded as undesirable, depending on the excess intake level. It is well known to be very serious in the case of infants swallowing capsules containing ferrous sulfate.

Inorganic elements are very different from the various organic nutrients in that they cannot be destroyed or converted

Table 92-6. Dietary Reference Intakes – Minerals

LIFE STAGE GROUP	Ca (mg/d)	P (mg/d)	Mg (mg/d)	F (mg/d)	Se (μg/d)	Cr (μg/d)	Cu (μg/d)	I (μg/d)	Fe (mg/d)	Mn (mg/d)	Mb (μg/d)	Zn (mg/d)
Infants												
0-6 months	210*	100*	30*	0.01*	15*	0.2*	200*	110*	0.27*	0.003*	2*	2*
7-12 months	270*	275*	75*	0.5*	20*	5.5*	220*	130*	11	0.6*	3*	3
Children												
1-3 years	500*	460	80	0.7*	20	11*	340	90	7	1.2*	17	3
4-8 years	800*	500	130	1*	30	15*	440	90	10	1.5*	22	5
Males												
9-13 years	1300*	1250	240	2*	40	25*	700	120	8	1.9*	34	8
14-18 years	1300*	1250	410	3*	55	35*	890	150	11	2.2*	43	11
19-30 years	1000*	700	400	4*	55	35*	900	150	8	2.3*	45	11
31-50 years	1000*	700	420	4*	55	35*	900	150	8	2.3*	45	11
51-70 years	1200*	700	420	4*	55	30*	900	150	8	2.3*	45	11
>70 years	1200*	700	420	4*	55	30*	900	150	8	2.3*	45	11
Females												
9-13 years	1300*	1250	240	2*	40	21*	700	120	8	1.6*	34	8
14-18 years	1300*	1250	360	3*	55	24*	890	150	15	1.6*	43	9
19-30 years	1000*	700	310	3*	55	25*	900	150	18	1.8*	45	8
31-50 years	1000*	700	320	3*	55	25*	900	150	18	1.8*	45	8
51-70 years	1200*	700	320	3*	55	20*	900	150	8	1.8*	45	8
>70 years	1200*	700	320	3*	55	20*	900	150	8	1.8*	45	8
Pregnancy												
≤18 years	1300*	1250	400	3*	60	29*	1000	220	27	2*	50	13
19-30 years	1000*	700	350	3*	60	30*	1000	220	27	2*	50	11
31-50 years	1000*	700	360	3*	60	30*	1000	220	27	2*	50	11
Lactation												
>18 years	1300*	1250	360	3*	70	44*	1300	290	10	2.6*	50	14
19-30 years	1000*	700	310	3*	70	45*	1300	290	9	2.6*	50	12
31-50 years	1000*	700	320	3*	70	45*	1300	290	9	2.6*	50	12

* Adequate Intake Level, otherwise values represent Recommended Dietary Allowances.

Table 92-7. Distribution of Essential Trace Elements in Foods[a]

	FOOD SOURCE AND CONTENT	
ELEMENT	AVERAGE TO HIGH	LOW
Chromium	Dried brewers' yeast, bran and germ of cereal grains, molasses, liver Refined cereals, refined sugar	
Cobalt	Leafy vegetables	Milk, refined cereals
Copper	Liver, kidney, shellfish, nuts, dry legumes, whole-grain cereals	Milk, muscle meat, eggs, fruit, vegetables
Fluorine[b]	Seafish, red meat, eggs, tea	Milk
Iodine[b]	Seafish, shellfish, iodized salt, milk	
Iron	Liver, kidney, shellfish, muscle meats, poultry, heart, egg yolk, dried legumes, cane molasses, nuts	Milk, refined sugar
Manganese	Whole-grain cereals, dried legumes, tubers, fruits, nonleafy vegetables Milk, poultry, fish	
Molybdenum	Liver, kidney, dried legumes, whole-grain cereals, leafy vegetables Fruits, root and stem vegetables, muscle meats, milk	
Nickel	Whole-grain cereals, vegetables	Muscle meats, fats, eggs, milk
Selenium	Liver, kidney	
Silicon	Whole-grain cereals, chicken skin, beer	Animal foods
Tin[d]	Cereals, muscle meats Milk	
Vanadium[b]	Liver, muscle meats, fish, bread, some cereal grains, nuts, a few root vegetables, oils from corn and soybeans	Milk, most vegetables
Zinc	Meat, egg yolk, whole-grain cereals, oysters, fowl, milk Fruits, fish, vegetables	

[a] Bioavailability is not taken into consideration; see text for individual elements.
[b] Most foods are highly variable.
[c] Selenium content is markedly affected by available selenium during growth of the plant or animal food. Cooking losses can occur.
[d] The tin content is markedly increased by exposure to tin-plated containers.

into another substance by the metabolic processes. In most cases the trace elements are bound to an organic ligand. This is the means for effecting elemental transport and function and minimizing toxicity. The binding may be very loose or very firm. Many of the elements are part of metalloenzymes. Nucleic acids also bind metal ions in a consistent pattern. Other mechanisms of function are described for individual elements below.

Many pairs or groups of essential elements may have chemical properties that are closely similar. This can result in competition for binding sites that may alter transport, storage, excretion, and function. In other words setting the stage for mineral-mineral interactions.

There are many elements in biological systems that have no known essential function but that have some chemical properties similar to those of required elements. These elements can become a health threat when they are present in sufficient quantity to replace a required element or to bind excessively to some organic ligand and cause a physiological aberration. Modern industrial technology has effected translocation of large quantities of many minerals from their native stores in the ground to the air, the water, and ultimately the food supply. Three elements that have caused concern and some isolated severe problems for humans are mercury, cadmium, and lead. The nutritional status of an exposed person can modify the severity of adverse response to a toxic level of an element. A deficiency of certain nutrients can result in a more severe adverse effect, while a moderate excess of other nutrients can afford some protection. The possibility must be kept in mind that elements now regarded only as toxic may at some future time have an essential function described for them at a very low level of intake.

Analysis of trace elements can be accomplished by both chemical and physical techniques. Current techniques such as induction coupled plasma, atomic absorption spectrometry, and neutron activation analysis provide rapid, accurate, and low-cost measurements.

CHROMIUM

Function and Deficiency Syndrome—For biological activity, chromium must be trivalent. The most active form of chromium is that which is incorporated into a low-molecular-weight organic molecule that occurs in many foods. Its structure is not known yet. This compound has been designated GTF (glucose tolerance factor). From a variety of biochemical studies, it appears that the presence of insulin is required for all functions of chromium. GTF is the only one of many compounds tested that passed through the rat placenta into the fetus.

The principal defect in chromium deficiency is an impairment of glucose utilization downstream from the insulin receptor; however, disturbances in protein and lipid metabolism also have been observed. In the young animal, growth rate may be reduced. Corneal lesions have been observed in rats deficient in both chromium and protein; no lesions have been seen with either single deficiency.

Impaired glucose utilization occurs in many middle-aged and elderly human beings. In experimental studies, significant numbers of such persons have shown improvement in their glucose utilization after treatment with chromium. There also have been improvements in diabetic children and infants with kwashiorkor.

Metabolism and Bioavailability—Chromium is transported by transferrin in the plasma and competes with iron for binding sites. The main excretory route is through the urine; however, some chromium is excreted in the bile and by the small intestine. The newborn animal has large stores of chromium that decline with age.

Toxicity—In animals, a wide margin of safety separates toxicity from the nutritional requirement of chromium (III). Hexavalent chromium is considered to be toxic.

COBALT

Function, Metabolism, and Deficiency Syndrome—The only known essential function of cobalt is as a component of vitamin B_{12}.

Cobalt salts are absorbed poorly. Excretion is via the bile and through the intestinal wall. Cobalt is widely distributed in the body, with the highest concentrations in the liver, kidney, and bone.

Toxicity—High levels of cobalt can produce a polycythemia in many species, an effect that is unrelated to vitamin B_{12}. Cobalt usually is considered relatively nontoxic; however, severe cardiac failure and some deaths in humans have resulted from consumption of large amounts of beer containing 1.2 to 1.5 ppm of cobalt. The element was added to the beer to promote optimal foam stabilization.

COPPER

Function and Deficiency Syndrome—Several copper-containing metalloproteins have been isolated from animal tissues, including tyrosinase, ascorbic acid oxidase, laccase, cytochrome oxidase, urate oxidase, monoamine oxidase, δ-aminolevulinic acid dehydrase, and dopamine-β-hydroxylase. Copper functions in the absorption and utilization of iron, electron transport, connective tissue metabolism, phospholipid formation, purine metabolism, and development of the nervous system. Ferroxidase I (ceruloplasmin), a copper-containing enzyme, effects the oxidation of Fe (II) to Fe (III), a required step for mobilization of stored iron. There is evidence that a copper-containing enzyme is responsible for the oxidative deamination of the epsilon amino group of lysine to produce desmosine and isodesmosine, the cross-links of elastin. In copper-deficient animals the arterial elastin is weaker, and dissecting aneurysms may occur.

The most common defect observed in copper-deficient animals is anemia. Other abnormalities include growth depression, skeletal defects, demyelination and degeneration of the nervous system, ataxia, defects in pigmentation and structure of hair or wool, reproductive failure, and cardiovascular lesions, including dissecting aneurysms. Copper deficiency occurs very infrequently in human beings. Deficiency has been observed in some patients receiving nutrition support regimens deficient in copper.

Metabolism and Bioavailability—Copper is absorbed from the small intestine. Most of the copper in the plasma is in ceruloplasmin; however, significant amounts are loosely bound to albumin, and this fraction is important in transport. The plasma copper level increases in acute infections, in pregnancy, and in women taking oral contraceptives. Small amounts of copper are excreted in the urine, but the major excretory pathway is via bile and feces.

Copper is present in high concentrations in the brain, liver, heart, and kidney, with the highest levels occurring at birth. It is important that pregnant women receive adequate copper during pregnancy, so that the infant will have adequate stores of copper at birth.

The chemical form of copper in food is largely unknown. A variety of salts of copper have been used in animal studies and may vary in bioavailability. These salts include the sulfate, nitrate, chloride, carbonate, hydroxide, iodide, glutamate, glycerophosphate, aspartate, citrate, nucleinate, and pyrophosphate. Elemental copper, copper sulfide and oxide are utilized poorly. The absorption of copper can be decreased by large amounts of phytic acid, ascorbic acid, calcium, and zinc.

Toxicity—Wilson's disease, a genetic disease in humans, leads to excess copper accumulation in the brain, liver, and kidney, which results in mental and neurological abnormalities. The disease is treated by administration of a chelating agent, penicillamine (β,β- dimethylcysteine), which removes excess copper from the tissues and results in its excretion.

FLUORINE

Function and Deficiency Syndrome—The most important relationship of fluoride to health is that of preventing dental caries. Fluoride has been shown to enter the hydroxyapatite of teeth to form a more perfect crystal that resists acid attack more effectively. In areas where the fluoride content of the drinking water is unusually high, osteoporosis and calcification of the aorta of elderly persons are less than in control population groups not receiving high fluoride. In these areas the effective fluoride concentration is high enough to cause mottling of the tooth enamel in young children.

Metabolism and Bioavailability—The absorption of fluoride from the GI tract is rapid and complete. Even the water-insoluble forms are absorbed fairly well. Fluoride can cross membranes easily, and it passes readily from the plasma into the tissues; however, the mammary gland and the placenta offer some resistance to transport. Excess fluoride is excreted in the urine.

Bones typically have high concentrations of fluoride, which gradually increase throughout life to about age 55 years. Fluoride supplementation increases bone density but is reported to increase brittleness. Of the soft tissues, the kidney is highest in fluoride. Calcium and aluminum can decrease the absorption of fluoride, and sodium chloride can depress the skeletal uptake of fluoride.

Toxicity—Toxic doses of fluoride cause loss of appetite and body weight, muscular weakness, clonic convulsions, pulmonary congestion, and respiratory and cardiac failure.

Chronic exposure to fluoride most often comes through consumption of drinking water, usually from deep wells drilled through or near fluoride-containing rocks. Levels of fluoride around 2 ppm or higher produce a permanent brownish mottling of tooth enamel when the exposure is during the time of tooth formation.

IODINE

Function, Metabolism, and Deficiency Syndrome—The only known function of iodine is for the production of the thyroid hormones, which regulate cellular oxidation.

The absorption of iodide can occur at all levels of the GI tract. Iodinated amino acids can be absorbed as such but less efficiently than iodide. Excretion of iodine is primarily via the urine, and the amount is a reasonably good indicator of thyroid status. Iodine in saliva is reabsorbed.

The iodine-deficiency disease is goiter. In iodine-deficient young, growth is depressed and sexual development is delayed, the skin and hair are typically rough, and the hair becomes thin. Cretinism, feeblemindedness and deaf-mutism occur in a severe deficiency. There is reproductive failure in the female and decreased fertility in the male.

Goiter has been observed in human beings in many areas of the world, with incidence in women and children usually higher than in the adult male. As a public-health measure, use of iodized salt has markedly reduced the incidence of goiter. Goitrogens, including those found in food, also can cause goiter.

IRON

Function and Deficiency Syndrome—Iron is an essential component of several important metalloproteins. These include hemoglobin, myoglobin and many oxidation-reduction enzymes. In iron deficiency, there may be reduced concentrations of some of the iron-containing enzymes, such as cytochrome c in liver, kidney, and skeletal muscle and succinic dehydrogenase in the kidney and heart.

Hypochromic microcytic anemia is the characteristic end result of iron deficiency. Depending on the severity, the anemia is accompanied by listlessness and tiredness, palpitation on exertion, sore tongue, angular stomatitis, dysphagia, and koilonychia.

Metabolism—Iron is absorbed from the small intestine by a complex but incompletely understood mechanism. Heme iron is more readily absorbed than non-heme iron. The proportion of dietary iron absorbed is greater in iron-deficient anemic individuals. Iron is transported via the blood, in which it is bound to transferrin, a β_1-globulin.

The iron from deteriorated red blood cells is reused. Under normal circumstances, the loss of iron from the body is very small, about 1 mg a day for men and an additional average daily loss of 0.5 mg a day by menstruating women. Iron is stored in the bone marrow, intestinal wall, liver, and spleen, with the latter organs containing the largest amounts.

Bioavailability—The recognition of anemia as a major public-health problem for menstruating women and young children throughout the world has focused on the need for more-extensive and better fortification of foods. This has stimulated a great deal of research on the availability of iron from foods and inorganic sources. Iron compounds that are utilized readily by experimental animals and humans are ferric ammonium citrate, ferrous sulfate, ferrous gluconate, ferrous fumarate, and ferrous ammonium sulfate. Average to poor sources of iron are reduced iron, ferric chloride, and ferric pyrophosphate. Very poor sources are ferric oxide, ferrous carbonate, sodium iron pyrophosphate, and ferric orthophosphate. The availability of iron from foods can vary also.

Several dietary components can affect the availability of iron from many sources. Phytic acid and antacids can decrease iron absorption. The availability of dietary iron is increased by a variety of reducing compounds such as ascorbic acid and molecules with sulfhydryl groups, as well as histidine and lysine. The smaller the particle size of elemental iron, the greater is the intestinal absorption and use. Heme iron is absorbed as such. High intakes of zinc, copper, manganese, and cadmium can decrease the absorption of iron. Many additional studies are needed to evaluate adequately the availability of iron as influenced by composition of the diet and method of food preparation beyond single test meals.

Toxicity—Because iron absorption is regulated by the body, moderate excess above the RDA was considered harmless. Some individuals have a metabolic defect such that their iron absorption is not carefully controlled, and even a normal iron intake can lead to excess tissue accumulation. A disease known as hemochromatosis results. It usually can be controlled by phlebotomy at periodic intervals; however death can result if the disease is not treated. Epidemiological data suggest that continued high intake of iron may raise the risk for chronic disease occurrence, especially in susceptible individuals, particularly those diseases that are increased with free radical formations. Deaths have occurred, however, in children who swallowed capsules or tablets containing a readily available source of iron, such as ferrous sulfate. Acute effects include vomiting, hematemesis, hepatic damage, tachycardia, and peripheral vascular collapse.

MANGANESE

Function and Deficiency Syndrome—Manganese is required for the synthesis of mucopolysaccharides of cartilage and for the conversion of mevalonic acid to squalene. Glucose utilization is impaired in manganese deficiency. Pyruvate carboxylase is a manganese metalloenzyme. It also participates in superoxide dismutase.

Manganese deficiency has been produced experimentally in many animals. Characteristics of the deficiency include growth depression of the young animal, skeletal abnormalities (ranging from mild rarefaction to crippling deformities), mortality of the young, perosis (slipping of the Achilles tendon and accompanying joint deformity) in birds, depressed reproduction of both males and females, nutritional chondrodystrophy of the chick embryo, and ataxia in newborn mammals, with head retraction, tremor, abnormal otoliths, and semicircular canals in the ears. Newborn manganese-deficient guinea pigs have aplasia or marked hypoplasia of the pancreas. Manganese deficiency has not been well recognized in humans.

Metabolism and Bioavailability—The homeostatic mechanism for regulating the concentration of manganese in the body is very precise. Manganese is absorbed from the small intestine and then is transported via the blood in the trivalent form bound to a β_1-globulin, transmanganin. Manganese is excreted in the bile and through the intestinal wall. The latter constitutes the principal mechanism for regulating the amounts of manganese in the tissues. With a high manganese intake, the element also is excreted in the pancreatic juice. The amount excreted in the urine is very small.

High levels of manganese occur in bone, liver, kidney, pancreas, and the pituitary, whereas the concentration in the skeletal muscle is very low. The manganese in bone cannot be mobilized to meet a need. The stores of manganese, in the order of their importance, are found in the liver, skin, and skeletal muscle. There is not a special store in the newborn.

Bioavailability of manganese from various salts (oxide, carbonate, sulfate, and chloride) has not been well evaluated. High dietary intakes of calcium and phosphorus can decrease manganese absorption.

Toxicity—Miners exposed to manganese oxide dust for long periods of time develop psychiatric abnormalities that resemble schizophrenia. This is followed by crippling neurological disorders similar to those found in Parkinson's disease.

MOLYBDENUM

Function, Metabolism, and Deficiency Syndrome—Xanthine oxidase is an important molybdenum-containing enzyme. Due to a variety of indirect evidence and the importance of xanthine oxidase, molybdenum is considered to be an essential trace mineral for humans, required in very small amounts.

Molybdenum supplied by water-soluble salts is absorbed readily. The element crosses the mammary gland easily. Excretion is into both urine and feces. The liver and kidney have the highest soft-tissue concentrations of molybdenum. Changes in level of dietary intake can be reflected in the concentrations in liver, kidney, skin, bones, and hair. The newborn does not have special stores of the element. Sulfate can affect the absorption, tissue distribution, and excretion of molybdenum. The content of molybdenum in erythrocytes decreases in many types of anemia. Adverse effects due to simple deficiency of molybdenum in healthy humans and in experimental animals have not been observed.

Toxicity—The tolerance of animals to high intakes of molybdenum varies with species, age, and the level of numerous other dietary components. The toxicity is decreased by copper, inorganic sulfate, and the sulfur amino acids.

NICKEL

Evidence that nickel is an essential element is based on abnormalities produced in chicks and rats fed diets containing 3 to 4 ppb of nickel. Lipid metabolism was affected. Rats maintained through successive generations on the nickel-deficient diet had increased fetal mortality.

Absorption of nickel is small from ordinary diets. Excretion is primarily through the feces; however, significant amounts can be lost in sweat. Phytate can form a very stable complex with nickel, so it is possible that phytate may decrease absorption of nickel. Further studies are required to establish clearly the essentiality of nickel and its significance to human health.

A low level of toxicity has been established for nickel in rats, mice, monkeys, and chicks.

SELENIUM

Function and Deficiency Syndrome—Selenium is an essential component of several enzymes including glutathione peroxidase. This provides a link between the antioxidant properties of vitamin E and the biological function of selenium in preventing most of the same selenium-deficiency problems. Animal studies have indicated that selenium may be useful as a chemoprevention agent, but studies in humans have not been accomplished. Experimentally, selenium has been shown to provide protection to pulmonary oxygen toxicity similar to that observed for vitamin E.

Depending on species, age, and specific diet composition, a deficiency

of selenium can lead to one or more of the following abnormalities: growth depression, muscular dystrophy, degeneration of the myocardium, neurological lesions, liver necrosis, pancreatic fibrosis, exudative diathesis, ceroid-pigment deposition in adipose tissue, and death. Deficiency occurs in domestic animals with intakes below 0.02 to 0.05 ppm. Deficiency in humans has been demonstrated in China, where extremely low intake causes a cardiomyopathy in children (Keshan disease Other geographic areas with low selenium soil content also exist. Most deficiency syndromes responsive to selenium also respond favorably to vitamin E. An exception is pancreatic fibrosis, which occurs only in selenium deficiency.

Metabolism—Selenium is absorbed from the duodenum. It can be metabolized to a variety of compounds and lost from the body via the bile, pancreatic and intestinal secretions, and ultimately through the feces, urine, and expired air. Selenium can replace sulfur in the normal sulfur amino acids, and selenite also can bind to sulfur amino acids. It also is incorporated into selenonucleosides and may be involved in genetic translation. The highest tissue concentrations of selenium occur in the kidney, pancreas, pituitary, and liver.

Toxicity—Acute selenium toxicity is characterized by abdominal pain, excess salivation, grating of the teeth, paralysis, and blindness. Eventually, disturbed respiration leads to death.

Selenium is one of the most toxic of the essential nutrients, and the quantitative separation of required and chronic toxic levels is not very large. The source of selenium has a significant impact on the level that will cause toxicity to develop. Organic compounds containing selenium enhance absorption and, therefore, are toxic at lower levels. For domestic animals, the requirement is about 0.1 to 0.2 ppm, and 3 to 4 ppm in the diet are beginning levels for chronic toxicity. Intakes above 500 μg for long periods of time are considered to present a risk of toxicity in man. The upper tolerable intake level set by the Food and Nutrition Board is 400 μg daily for adults. A reported carcinogenicity for selenium is an elusive association that has not been clarified finally.

SILICON

With highly purified diets it has been possible to produce a deficiency of silicon in chicks and rats. The deficiency affected growth rate, bones, and integumental tissues. The primary biochemical lesion in the deficient animals was an effect on the cartilage matrix.

Silicon (as silicates) is absorbed easily from the intestinal tract and excreted readily in the urine, in part as SiO_2. Silicon is distributed widely in soil, plants, and animal tissues. It is relatively nontoxic; however, siliceous kidney stones have been reported in persons who live in regions with water high in silicate concentration or who chronically ingest magnesium trisilicate antacids.

TIN

Through rigid exclusion of environmental and dietary tin, it has been possible to produce growth retardation responsive to this element in rats. A maximal growth effect was obtained with 1 ppm of tin in the diet, a level similar to that found in many foods.

Tin is absorbed poorly and most of that in the diet is excreted in the feces. Tin has a low order of toxicity.

VANADIUM

Chicks and rats fed a diet containing less than 10 ppb of vanadium had slow growth, defective bones, and altered lipid metabolism. At low doses the element may influence glycemic control. Vanadium is a rather toxic element. The addition of 25 to 50 ppm of vanadium to the diet of rats causes diarrhea and mortality.

ZINC

Function and Deficiency Syndrome—Zinc is known to occur in many important metalloenzymes. These include carbonic anhydrase, carboxypeptidases A and B, alcohol dehydrogenase, glutamic dehydrogenase, D-glyceraldehyde-3-phosphate dehydrogenase, lactic dehydrogenase, malic dehydrogenase, alkaline phosphatase, aldolase, and others. Impaired synthesis of nucleic acids and proteins has been observed in zinc deficiency. There is some evidence that zinc may be involved in the secretion of insulin and in the function of the hormone. It appears to be a modulator of neurohumoral transmission.

Zinc is required for growth of every animal species studied; therefore, growth depression of young animals is invariably observed if the zinc deprivation is severe enough. Other characteristics of deficiency include skin lesions, alopecia, abnormal feathering in birds, deformed and poorly mineralized bones, hyperkeratinization of the esophagus, reduced numbers of circulating lymphocytes, impaired reproduction in males and females, fetal abnormalities, and decreased learning ability. Persons with impaired taste acuity and discrimination and delayed healing of wounds and burns have responded favorably to therapeutic doses of zinc in some cases.

Nutritional dwarfism has been studied extensively in the Middle East. The syndrome includes delayed sexual development, reduced height and weight, hepatosplenomegaly, spoon nails, and usually anemia. Although the subjects were deficient to some degree in several nutrients, zinc was required to correct the hypogonadism and growth depression. The syndrome occurs in both males and females. Indolent ulcers and delayed wound healing in patients with low plasma zinc levels have been reported, and both systemic and topical administration of zinc compounds are followed by accelerated healing. There is limited evidence that some young children and elderly persons in the United States do not receive adequate zinc.

Metabolism and Bioavailability—Zinc can bind readily to sulfhydryl groups, amino groups, and imidazole groups of proteins, amino acids, and other organic molecules.

Zinc is absorbed primarily from the duodenum. It binds to all proteins of the plasma; however, it is bound most loosely to albumin, and this may be important for transport to and from tissues. The concentration of zinc in plasma decreases rapidly when a low-zinc diet is fed, and it is reduced in pregnancy and in women taking oral contraceptives. The principal route of excretion is via the feces. Small amounts of zinc are excreted daily in the urine; these increase when there is tissue catabolism such as occurs in burns and in fasting. Significant losses of zinc also can occur in the sweat.

Zinc is present in all tissues, with very high concentrations in the prostate and choroid of the eye. Generally, tissue concentrations are not affected greatly by zinc deficiency. The stores of zinc in the body are thought to be small.

Zinc bioavailability may vary with the wide variety of inorganic salts as well as metallic zinc. Phytic acid can markedly decrease absorption of zinc, particularly in the presence of large amounts of calcium. Consumption of whole-wheat bread, which contains phytic acid, has been shown to be primarily responsible for the zinc-deficiency dwarfism observed in the Middle East. The toxic effects of cadmium are probably partially related to interference with the normal physiological pathways and functions of zinc.

Toxicity—The taste threshold for a soluble salt of zinc in water is 15 ppm of zinc, whereas 40 ppm have a very definite taste. A dose of 225 to 450 mg of zinc has an emetic effect in an adult man. Acute toxicity of zinc is characterized by dehydration, electrolytic imbalance, stomach pain, lethargy, dizziness, muscular incoordination, and renal failure. High zinc intakes are known to lower copper absorption; therefore zinc supplements should be taken only with adequate intakes of copper. Zinc has been used successfully to treat Wilson's disease.

ZINC SULFATE—see RPS-19, page 1271.

ASSOCIATED DIETARY SUBSTANCES

A large number of substances, predominantly from plant sources (ie, phytochemicals), are found in the human diet. An understanding of these compounds and their potential impact on health and disease risk are only beginning to be described. Whether they will constitute a new class or classes of nutrients will depend on the essentiality to health of each individual class. Those undergoing the most scrutiny include the carotenoids, flavonoids and phenolic acids, as well as phytosterols, organosulfurics, indoles and isothiocyanates, lignans, stilbenes, terpenes, and tannins. Recent food composition databases contain estimates of carotenoid and flavonoid content of foods commonly consumed.

CAROTENOIDS

There are an estimated 600 or more different carotenoids found naturally, of which several dozen are consumed in the human diet, a number of which can be routinely assayed in humans. Circulating concentrations of carotenoids are biological mark-

Table 92-8. Common Dietary Phenolic Compounds

CLASS	COMPOUNDS	FOOD SOURCES
Flavonoids		
• Flavones	Apigenin, luteolin	Parsley, peppers
• Flavonols	Kaempferol, quercetin	Apples, onions
• Flavanones	Hesperetin, naringenin	Citrus fruit, prunes
• Flavanols	Catechins, theaflavins	Cocoa, tea
• Anthocyanidins	Cyanidin, malvidin	Cherries, grapes
• Isoflavones	Daidzein, genistein	Soybeans, legumes
Phenolic acids	Caffeic acid, curcumin, ferulic acid	Apples, tomato, turmeric, wheat bran
Organosulfurics	Allylic sulfides, glucosinolates	Garlic, onions, leeks, cruciferous vegetables
Indoles	Indole-3-carbinol	Cruciferous vegetables
Lignan	Enterodiol, enterolactone	Grains, flax meal
Stilbenes	Resveratrol	Wine, grapes, peanuts
Triterpenes	Limonin, nomilin	Citrus fruit, spices

ers for fruit and vegetable consumption; and increased intakes are associated with lower risk of chronic disease. Most naturally occurring carotenoids exist in the all-trans configuration, and they serve to protect plants against photosensitization, but may possess antioxidant and other health-related activity. While a small number of them are known to be precursors to retinol (vitamin A), most are not. The carotenoids α-carotene, β-carotene, and β-cryptoxanthin are known to be pro-vitamin-A compounds that may be partially converted to retinol at the gastrointestinal mucosa. This is the only currently recognized nutrient function of carotenoids in humans. Other widely recognized carotenoids include lycopene, lutein, and zeaxanthin. Data on the absorption, metabolism, and excretion of carotenoids continue to be generated. Carotenoid bioavailability varies considerably with the food matrix it is part of and compounds it is administered with, as well as with the specific carotenoid. Lipoproteins serve as the route of transport for carotenoids. The recent DRIs provided no quantitative recommendations for carotenoid intake because data is insufficient to establish requirements; beyond consuming a wide variety of fruits and vegetables. It is known that the average dietary intake of carotenoids includes about 8 mg of lycopene, 2 mg of β-carotene, 1.7 mg of lutein and zeaxanthin, 400 μg of α-carotene, and about 100 μg of β-cryptoxanthin daily. Several carotenoids have been included in dietary supplement products. A valid method for assaying β-carotene and other carotenoids found in these products is currently being explored.

FLAVONOIDS

A large number of phenolic compounds are consumed in the human diet. These range from simple phenolic molecules (ie, phenolic acids) to high molecular weight, highly polymerized polyphenols (ie, tannins). These phytochemicals have been classified into groups that include flavonoids, and phenolic acids (Table 92-8). The flavonoids, once referred to as "vitamin P," are the largest class of polyphenols containing several thousand compounds, and are further broken down into a number of subclasses. The most common subclasses of flavonoids are the flavones, flavonols, flavanones, flavanols, anthocyanidins, and the isoflavones. Except for the flavanols, which exist in free form or as gallic esters, most of the other compounds exist in glycosylated forms. Flavonoids in plants are produced as a result of stressors that include climate, ultraviolet radiation, herbivores, and pathogens. These secondary metabolites are involved in plant communication and defense. As such the flavonoid content of foods can be quite variable depending on conditions of development and growth. Antioxidant, free-radical scavenging, enzyme inhibiting and other activities of the flavonoids are being explored. Select flavonoids have been added as ingredients to dietary supplement products, although the data do not currently support this pharmacological use of individual flavonoids.

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CHAPTER 93

Pesticides

Mark G Robson, PhD, MPH
Ara H DerMarderosian, PhD

Pesticides may be defined simply as chemical agents used to control pests. In its broadest sense it includes insecticides, rodenticides, fungicides, and herbicides. These substances represent big business, with the US once being the largest producer in the world.

For the US, the Environmental Protection Agency (EPA) reports that pesticide use has remained stable, with year-to-year variations resulting from changes in acreages planted and weather conditions. In the most recent report, *Pesticide Industry Sales and Usage—1998 and 1999 Market Estimates,* released in August 2002, the EPA reported that the use of herbicides to control weeds has increased slightly over the previous 3 years. An average of $4200 per farm was expended in 1995 on pesticides. Conventional pesticides account for 27% of all pesticides used annually in the US and total an estimated 1.2 billion pounds. Wood preservatives account for 16% of all pesticides used and total about 0.72 billion pounds; speciality biocides, such as those used to control bacterial growth in cooling towers, are about 6% and total 0.26 billion pounds; and chlorine/hypochlorites, used in water-purifying plants and swimming pools represent 51% of all pesticides used and total 2.32 billion pounds.

The specific results of the National Home and Garden survey revealed that

In households without children under 5 years old, about 75% had at least one pesticide stored less than 4 feet off the ground and not locked in a cabinet (ie, within reach of children).

In homes with children under 5 years of age, about 47% stored at least one pesticide within reach of children. Overall, an estimated 85% of all households have at least one pesticide in storage and around the home.

Most families have between one and five pesticide products stored, and slightly over 27% of single family households have over six products stored.

Some 76% of all households used pesticides in their homes themselves, while about 20% hired a commercial applicator to treat such pests as roaches, fleas, or ants (termites are not included in these estimates).

Less than 25% could recall receiving written notification about the pesticides used in their home or any safety precautions to follow.

About 15% of households had pesticides applied in or around their homes by someone outside the household. Only half of these people recall receiving written information regarding the pesticides used and safety precautions to be followed.

In the households that dispose of concentrated pesticides, 67% use regular trash, 16% use special collections, and 17% give it away or pour it down the toilet or sink, on the street, in the gutter or sewer, or on the ground.

Some 44% of all households identified at least one insect that was considered a major problem.

Some 25% of all households were treated for cockroaches in 1990. It appears that cockroaches are the most common pest problem for households living in multifamily dwellings. For households in single-family dwellings, ants are the most common problem.

The most difficult pest to control was identified as fleas.

One of the most interesting reports on this scientific random sampling was an amazing response rate of 85%. The executive summaries of this 400-page National Home and Garden Pesticide Use Survey are available and may be obtained from the Communications Branch of EPA's Pesticide Programs (telephone: 703-305-5017).

Pharmacies throughout the US stock a myriad of consumer pesticide products used for these purposes. This represents an important area in which pharmacists can exercise their knowledge and skills, particularly for proper use, handling, and disposal of pesticides.

The EPA published the *Status of Pesticides in Registration and Special Review* (Rainbow report) that contains a general management directory, a chemical review manager directory, and a general information section that covers purpose, timing, comments, additional information, and electronic access (see EPA website, www.epa.gov, for the latest information).

Chapter 2 is entitled *Special Review* and is organized so that the first section explains the special review process including the criteria that EPA uses to initiate a special review, the steps it takes to conduct a Special Review, and the risk-reduction alternatives to the conventional Special Review process.

The following section gives an *At a Glance* summary of the dates when Special Review decision documents were published in the *Federal Register*.

The third section provides a comprehensive reference list of all chemicals that have been or are currently in the Special Review program. The various chemicals are listed in alphabetical order.

The final section lists the chemicals in identical sequence and additionally, gives the details of Special Review criteria met or exceeded as well as the outcomes of the reviews. The entire report is 377 pages long and lists almost 1500 compounds.

Further, the EPA lists numerous solvents, surfactants, stabilizers, and similar substances. Various economic, political, and toxicological considerations that crop up routinely in the pesticide business preclude any more-accurate figures within a given year.

For those who question the use of pesticides at all it is important to know something about what damage pests can do on a worldwide basis. First it should be understood that plants are the world's major source of food. These plants are susceptible to 80,000 to 100,000 diseases caused by everything from viruses to bacteria, fungi, algae, and even other higher plants. Food plants have to compete with some 30,000 different species of

weeds worldwide, of which at least 1800 species are capable of causing serious economic losses. Various higher organisms such as nematodes and insects also devastate crops routinely around the world.

It has been estimated that about one-third of the food crops of the world is destroyed by these various pests at various stages, *viz,* growth, harvest, and storage. The rates of destruction often are higher in less developed nations. The Food and Agriculture Organization (FAO) estimates that one-half of cotton production in developing countries would be lost to pests without the use of pesticides. Even in the US, crop devastation due to pests is estimated to be about 30% ($20 billion annually) even though pesticides are used widely here. Several studies have shown that this country could not survive as a nation without pesticides. Without herbicides alone, at least 10% to 12% of the US population would be working on our farms instead of the current 3%.

Another important consideration of recent origin is the concept of minimum or reduced tillage. In this relatively new farming practice, herbicides help promote energy savings and soil conservation by reducing plowing and cultivation drastically. Now, farmers till only enough to plant new crops. Previous crop debris and weeds are left on the soil, and insects and weeds are controlled chemically rather than mechanically through unnecessary plowing. This method of control requires some 80% less energy.

There have been many who have argued for the return of what is called *organic* farming. Generally, organic farmers prefer to avoid the use of synthetic chemical products at all. They prefer naturally occurring chemicals such as rock phosphate and limestone and the manure of domestic animals. Also, leguminous plants are used as a nitrogen source as well as other plants that contain natural pesticidal compounds. While these are laudable practices, they generally result in higher prices because of the costs of these less available materials and the higher costs involved in the more labor-intensive practices of organic farming. In addition, more land with lower yielding capability would have to be farmed to make up for the lower efficiency of organic farming.

From a scientific point of view all natural materials are not necessarily organic, and organic substances are not necessarily natural. All things on earth are made up of chemicals, and plants do not really differentiate between what is made by man or nature. However, organic farming practices are sensible for the smaller farmer who wishes to avoid excess use of unnecessary chemicals and does not mind the use of extra labor practices to save money on materials.

According to a study by the Natural Resources Defense Council entitled "Harvest of Hope," alternative farming techniques could reduce pesticide applications 25% to 80% on nine crops grown in California and Iowa. The study showed that over 580 million pounds of pesticide-active ingredients were sold in California in 1987, and 57 million pounds of herbicide per year were used by Iowa farmers.

The study further stated that many ill effects have resulted from use of all of these, including pesticide contamination of the food supply, farm worker illness, ecosystem degradation, and water pollution. The council study calls on the federal government to redirect its agricultural research to make development of alternative farming systems a priority and to adopt alternative farming systems, including crop rotations, without incurring financial penalties. In addition, it promotes the concept that federal and state governments should levy fees on fertilizers and pesticides to help finance alternative agricultural research. At the same time that alternative ways of controlling pests are being sought, there are efforts to develop new chemicals with greater specificity to a particular pest and less toxicity to nontarget species. Proponents claim that having different chemical pesticides on hand with varying mechanisms of action allows rotation of these to limit development of resistance.

The first of this type developed is *imidacloprid*. Its uses are limited to sucking insects such as aphids and whiteflies, and it is less effective against chewing insects (worms, caterpillar larvae, butterflies). Imidacloprid works to bind to one type of receptor for the neurotransmitter acetylcholine, causing the nerves of an insect to fire uncontrollably, leading to muscle paralysis and death. Other new pesticides under development include fiproles and pyrroles.

Perhaps the major reason for use of pesticides has been the long world history of mass destruction of crops by disease and insects. One constantly is reminded that it would not take long to return to a primitive agriculture status by the numerous reports of crop devastation and disease that appear in various underdeveloped countries. Some of the relatively recent examples of pest effects include the destruction of 3 million tons of wheat by stem rust in western Canada in 1954, the continuous problem of arthropod-borne encephalitides that caused an average of 205 human cases in the US annually between 1964 and 1973, and the reduction of the annual death rate of malaria through the use of pesticides. The death rate in 1939 was 6 million, compared with 1996 estimates of 1.5 to 2.7 million. There are at least 24 common diseases (eg, encephalitis, typhus, anthrax, and dysentery) still of concern to man that are transmitted by a myriad of insects, ticks, or mites.

As with all substances used by modern man, pesticides offer a risk-benefit ratio that must be assessed for each application. A modern, concerned society should always advocate very specific, carefully planned usage of pesticides, well-integrated with other control practices. This approach has become quite popular today and is referred to as Integrated Pest Management (IPM). It consists of determining a workable combination of the best parts of all possible control procedures and applying them to a specific problem. The concept is to keep pests at a controllable level within the confines of sound ecological principles so that economic injury to plants or man is avoided. Overall, while mistakes have been made (eg, DDT), pesticides have contributed significantly to the increased productivity of the US farmer.

According to the American Crop Protection Association, less than 2% of Americans are farmers, compared with 30% in 1920. According to the US Department of Agriculture, in 1950 one farmer in the US fed 27 people; in 1970, 73; and in 1992, 129.

In recent years, there is a new trend in pesticide chemistry and application technology. For example, a 1-lb bottle of a new rice herbicide can control 10 acres of weeds; 5 years ago this area would have required 20 lb of pesticide.

EPA requires a new pesticide product to undergo rigorous registration requirements. Up to 120 safety, health, and environmental tests are required for registration. Typically it takes 10 years for a product to move from discovery to market, with an average cost of $35 to 50 million.

PESTICIDES AND LAW

In the US, numerous federal laws protect the user of pesticides as well as the consumers. Many of these laws are quite old and have been amended from time to time for obvious reasons. Since they are all complex and change with time, a brief summary is presented here so the pharmacist will be aware of who is responsible for which laws and what the current status of pesticide registration is.

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as amended (EPA, Oct 1996) is administered by the EPA. These new amendments require a substantial acceleration of the reregistration process for previously registered (licensed) pesticides and authorize the collection of fees to support reregistration activities. This law also changes EPA's responsibilities and funding requirements for the storage and disposal of suspended and cancelled pesticides and the indemnification of holders of remaining stocks of such canceled pesticides. Hence, un-

der FIFRA, all pesticides have to be registered with the EPA before they may be sold or distributed in commerce in the US.

This agency establishes an overall risk-benefit standard for pesticide registration, requiring that pesticides show efficacy when employed according to label instructions and show no unreasonable risk of adverse effects on human health or the environment. Laws require that EPA take into account the economic, social, and environmental costs and benefits of pesticide uses.

Because FIFRA was originally enacted in 1947, there has been developed since literally thousands of pesticides registered for use. However, over time, the standards of use obviously have changed and evolved in tandem with general advances in science and public policy. Specifically, for example, test-data requirements for pesticides have become increasingly stringent in the light of modern advances in analytical chemistry and toxicology. So now, more than ever, companies that hold pesticide registrations are responsible for providing all test data needed to satisfy EPA's registration requirements. To be sure all of these things are done, FIFRA requires the review and *reregistration* of all existing pesticides.

The Food Quality Protection Act of 1996 (PL 104-170) amends both the Federal Food, Drug, and Cosmetic (FD&C) Act and FIFRA to provide a comprehensive and protective regulatory scheme for pesticides.

Highlights of the new laws are

FD&C ACT PROVISIONS

Health-Based Safety Standard for Pesticide Residues in Food—Establishes a strong, health-based safety standard for pesticide residues in all foods. It uses "a reasonable certainty of no harm" as the general safety standard, the same approach used in the Administration's 1994 bill.

1. Eliminates longstanding problems posed by multiple standards for pesticides in raw and processed foods with a single health-based standard.
2. Requires the EPA to consider all non-occupational sources of exposure, including drinking water, and exposure to other pesticides with a common mechanism of toxicity when setting tolerances.

Special Provisions for Infants and Children—Incorporates language virtually identical to the Administration's 1994 bill to implement key recommendations of the National Academy of Sciences report, "Pesticides in the Diets of Infants and Children."

1. Requires an explicit determination that tolerances are safe for children.
2. Includes an additional safety factor of up to 10-fold, if necessary, to account for uncertainty in data relative to children.
3. Requires consideration of children's special sensitivity and exposure to pesticide chemicals.

Limitations on Benefits Considerations—Places specific limits on benefits considerations, unlike previous law, which contained an open-ended provision for the consideration of pesticide benefits when setting tolerances.

1. Applies only to non-threshold effects of pesticides (eg, carcinogenic effects); benefits cannot be taken into account for reproductive or other threshold effects.
2. Limits further by three *backstops* on the level of risk that could be offset by benefits considerations: a limitation (1) on the acceptable risk in any 1 year, which greatly reduces the risks; (2) on the lifetime risk, which would allow the EPA to remove tolerances after specific phaseout periods; and (3) on not allowing benefits to be used to override the health-based standard for children.

Tolerance Reevaluation—Requires that all existing tolerances be reviewed within 10 years to make sure they meet the requirements of the new health-based safety standard.

Endocrine Disruptors—Incorporates provisions for endocrine testing and also provides new authority to require that chemical manufacturers provide data on their products, including data on potential endocrine effects.

Enforcement—Includes enhanced enforcement of pesticide residue standards by allowing the FDA to impose civil penalties for tolerance violations.

Right-to-Know—Requires distribution of a brochure in grocery stores on the health effects of pesticides, how to avoid risks, and which foods have tolerances for pesticide residues based on benefits considerations. Specifically recognizes a state's right to require warnings or labeling of food that has been treated with pesticides, such as California's Proposition 65.

Uniformity of Tolerances—Prohibits states from setting tolerance levels that differ from national levels unless the state petitions the EPA for an exception, based on state-specific situations. National uniformity, however, would not apply to tolerances that included benefits considerations.

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT PROVISIONS (FIFRA)

Pesticide Reregistration Program—Reauthorizes and increases (from $14 to 16 million per year) user fees necessary to complete the review of older pesticides to ensure that they meet current standards. Requires tolerances to be reassessed as part of the reregistration program.

Pesticide Registration Renewal—Requires the EPA to review pesticide registrations periodically, with a goal of establishing a 15-year cycle, to ensure that all pesticides meet updated safety standards.

Registration of Safer Pesticides—Expedites review of safer pesticides to help them reach the market sooner and replace older and potentially more risky chemicals.

Minor-Use Pesticides—

1. Establishes minor-use programs within the EPA and USDA to foster coordination on minor-use regulations and policy and provides for a revolving grant fund to support development of data necessary to register minor-use pesticides.
2. Encourages minor-use registrations through extensions for submitting pesticide residue data, extensions for exclusive use of data, and flexibility to waive certain data requirements and requires the EPA to expedite review of minor-use applications. These incentives are coupled with safeguards to protect the environment.

Antimicrobial Pesticides—Establishes new requirements to expedite the review and registration of antimicrobial pesticides and ends regulatory overlap in jurisdiction over liquid chemical sterilants. Office of Prevention, Pesticides and Toxic Substances (7506C) (August 1996)

Readers are advised to write or call the Special Review and Reregistration Div (H-7508W), Office of Pesticide Programs, US EPA, Washington, DC 20460; telephone: 703-308-8000.

For similar reasons it has not been possible to provide the exact status of every pesticide mentioned in this chapter. For completeness, however, the longstanding status and general properties of many *classically* used pesticides have been retained.

THE ENVIRONMENTAL PROTECTION AGENCY RESPONSIBILITIES. Interpret its laws and implement its provisions.

Established, by regulation, 10 categories of certification for commercial applicators. These include (1) agricultural pest control (plant and animal); (2) forest pest control; (3) ornamental and turf pest control; (4) seed treatment; (5) aquatic pest control; (6) right-of-way pest control; (7) industrial, institutional, structural, and health-related pest control; (8) public health pest control; (9) regulatory pest control; and (10) demonstration and research pest control.

Set general standards of knowledge for all categories of certified commercial applicators of pesticides. In each state, the certification is carried out by an appropriate regulatory agency, usually the state department of agriculture. Pesticide applicators are trained through the various cooperative extension services of the state.

The US Food and Drug Administration, Center for Food Safety and Applied Nutrition has published and put on its web sites (FDA/CFSAN Pesticides, Metals, and Industrial Chemicals; http://www.cfsan.fda.gov/~lrd/pestadd.html) several pesticide-related topics including various guidance articles, certain residue monitoring reports, and at least five technical references of the past 2 to 3 years. Other related web sites (http://www.cfsan.fda.gov/~dms/pes93rep.html and http://www.cfsan.fda.gov/~dms/pesrpts.html) provide over 30 pages on the FDA Pesticide Program residue monitoring from 1993 to 2001 These cover the FDA monitoring program, regulatory monitoring, analytical methods, FDA–state cooperation, animal feeds, international activities, incidence level monitoring, total diet studies, and results and discussions.

STATE REGULATION

Since these vary considerably for each state there is little room to include them in this chapter. For the most part, these laws are similar to the federal regulations. Refer to local state agricultural agencies for specific information.

Pesticides and the Law

At the international level, the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations continue to press for wider use of certain pesticides to help raise the level of efficiency in agriculture. Recent WHO literature relates international concern on safe use of pesticides and pesticide residues in food.

Interest in pesticides extends beyond their use simply to increase crop yields, specifically to their use in the control of pests as vectors of disease. For example, it is well-known that insects such as chiggers, itch mites, and ticks transport disease to humans directly or via foodstuffs, and that mosquitos, tsetse flies, rat fleas, and others are capable of directly injecting disease organisms into the bloodstream. Pest control also enters into areas where livestock must be protected against predatory animals such as coyotes, wolves, and bobcats.

It should be stated at the outset that the various pesticides discussed in this chapter are subject to numerous constraints under new and continually changing rulings. For this reason it is suggested that reference be made directly to the EPA for definitive information on specific pesticides and their registered uses. Each state also publishes its own set of pesticide recommendations.

Last updated in August 1997, the EPA has published a list of banned and severely restricted pesticides.

A *banned* pesticide is a pesticide for which all registered uses have been prohibited by final government action or for which all requests for registration or equivalent action for all uses have, for health or environmental reasons, not been granted.

BANNED PESTICIDES

1. Aldrin
2. Benzene hexachloride [BHC]
3. 2,3,4,5-Bis(2-butylene) tetrahydro2-furaldehyde [Repellent-11]
4. Bromoxynil butyrate
5. Cadmium compounds
6. Calcium arsenate
7. Captafol
8. Carbon tetrachloride
9. Chloranil
10. Chlordane
11. Chlordimeform
12. Chlorinated camphene [Toxaphene]
13. Chlorobenzilate
14. Chloromethoxypropyl-mercuric acetate [CPMA]
15. Copper arsenate
16. Cyhexatin
17. DBCP
18. Decachlorooctahydro-1,3,4-metheno-2*H*-cyclo-buta(cd) pentalen-2-one [chlordecone]
19. DDT
20. Dieldrin
21. Dinoseb and salts
22. Di(phenylmercury) dodecenylsuccinate [PMDS]
23. EDB
24. Endrin
25. EPN
26. Ethyl hexyleneglycol [6–12]
27. Hexachlorobenzene [HCB]
28. Lead arsenate
29. Leptophos
30. Mercurous chloride
31. Mercuric chloride
32. Mevinphos
33. Mirex
34. Monocrotophos
35. Nitrofen (TOK)
36. OMPA (octamethyl-pyrophosphoramide)
37. Phenylmercury acetate [PMA]
38. Phenylmercuric oleate [PMO]
39. Potassium 2,4,5-trichloro-phenate [2,4,5-TCP]
40. Pyriminil [Vacor]
41. Safrole
42. Silvex
43. Sodium arsenite
44. TDE
45. Terpene polychlorinates [Strobane]
46. Thallium sulfate
47. 2,4,5-Trichlorophenoxy-acetic acid [2,4,5-T]
48. Vinyl chloride

A *severely restricted* pesticide is a pesticide for which virtually all registered uses have been prohibited by final government regulatory action but for which certain specific registered use or uses remain authorized.

SEVERELY RESTRICTED PESTICIDES

1. Arsenic trioxide
2. Carbofuran
3. Daminozide
4. Heptachlor
5. Sodium arsenate
6. Tributyltin compounds

Although it is difficult to classify all pesticides chemically or biologically, it is useful to list some of the major categories, with a few examples in each class. Some of the examples provided are considered restricted-use pesticides.

Insecticides

Stomach Poison or Protective Insecticides—Chlorinated hydrocarbons (methoxychlor); miscellaneous (carbaryl).

Contact Insecticides—Botanicals (pyrethrum, rotenone); organic phosphorus compounds (parathion, malathion); miscellaneous (carbaryl).

Fumigants—Gaseous materials used in tightly closed spaces such as warehouses, ship holds, mills, grain elevators, boxcars, and vaults and in the soil; these include methyl bromide and paradichlorobenzene.

Acaricides (Miticides)—Phosphate insecticides.

Fungicides—Chemicals and formulations used to control fungi and bacteria on living and nonliving plants and plant parts, as well as on or in all materials and surfaces but *excluding* all uses on living humans or animals and all uses on or in processed foods, beverages, or pharmaceuticals. A *localized fungicide* is dodine; examples of *complete fungicides* are benomyl and thiabendazole.

Nematicides—Chemicals and formulations used to control nematodes (roundworms) inhabiting soil and water that are associated with damage to plants or plant parts. A *postplanting nematicide* is VC-13; a *systemic nematicide* is aldicarb.

Herbicides

Selective—Dalapon, siduron, 2,4-D.

Nonselective—Bromacil.

Contact—Cacodylic acid, paraquat.

Translocated—2,4-DB, MCPA.

Plant Regulators—All preparations intended to alter the behavior or products of plants through physiological action, such as gibberellic acid and maleic hydrazide.

Defoliants and Desiccants—Preparations intended to cause leaves or foliage of plants to drop prematurely and usually used to aid harvesting of certain crops such as cotton. Endothall, arsenic acid, and sodium chlorate are in this class.

Rodenticides—Strychnine, zinc phosphide, warfarin, chlorophacinone.

Sex Pheromones—Chemical substances produced and released by one sex of an insect (usually the female) that elicit a sexual response in an individual of the opposite sex. *cis*-7,8-Epoxy-2-methyloctadecane (Disparlure) is a gypsy moth lure.

Juvenile Hormones (Insect Growth Regulators)—A relatively new type of pest control agent that regulates insect growth. Isopropyl-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate (generic name, methoprene; brand name, Altosid) is used to arrest mosquito development at the pupal stage.

Attractants—These are insect sexual pheromones that are used to attract specific pests to traps where they may be destroyed. Examples include boll weevil sex attractant and muscalure (Z-9-tricosene), a sex and aggregation pheromone for the common fly *(Musca domestica)*.

Many of the chemical names given to pesticides are contractions of longer systematic nomenclature that usually serve as nonproprietary names. As with drugs, many proprietary names are featured. Many pesticides are put into proprietary formulations that include the active ingredients often coupled with some adjuvant such as abscission agents, acidifying agents, buffering agents, antifoaming agents, antitranspirants, colors and dyes, compatibility agents, crop oil concentrates, surfactants, deposition agents, dispersants, drift control agents, foam-markers, gustatory/feeding stimulants, harvest aids, spreaders, penetrants, wetting agents, stickers, extenders, adhesive agents, and suspension and gelling agents.

According to the major purpose for which pesticides are used, they may be classified as

Acaricides—Control ticks or mites.

Algicides—Destroy algae and other aquatic vegetation.

Antiseptics—Protect objects from damage by microorganisms.
Arboricides—Defoliate and/or destroy trees or shrubby vegetation.
Bactericides—Control bacterial infection in plants.
Fungicides—Control fungal infection in plants.
Herbicides—Control weeds or undesirable species of plants.
Insecticides—Control harmful insects. Several specific terms named for the insect group have been coined; eg, aphicides—agents that control aphids.
Larvicides—Control larval stages of insects.
Limacides or Molluscicides—Control mollusks, including gastropods.
Nematicides—Control roundworms (nematodes).
Predacides—Control predatory mammals or birds.
Zoocides—Control rodents (rodenticides).

GENERAL SUGGESTIONS TO PHARMACISTS

The pharmacy is a logical source to obtain pesticide and pest-control information. However, pharmacists who desire to handle pesticides and build a permanent patronage should acquaint themselves with the common pest problems, with chemicals recommended, and how such materials should be used. In particular, they should be acquainted with the classification of pesticides since they will be handling and selling the *general-use* type and not the *restricted-use* group.

Pharmacists should keep abreast of new laws that influence the ways in which chemicals may be used legally. Particular attention should be placed on becoming familiar with the Pesticide Chemicals Amendment to the FD&C Act dealing with the safety determination needed on the residue of pesticides on raw agricultural commodities. This amendment is known commonly as the *Miller Bill* and was passed in 1954.

The pharmacist should study the Chemical Additives Amendment to that same Act passed in 1958 and fully effective in 1960. An annual updating of federal and state pesticide legislation may be obtained through the most recent edition of the *Farm Chemicals Handbook,* published by Meister Publ Co, 37733 Euclid Ave, Willoughby, OH 44094. This reference features a buyer's guide, application equipment, fertilizer, tradenames and dictionary, and a pesticide dictionary. Particularly noteworthy in this edition is description of crop chemicals, toxicity class, and handling and storage cautions. The current regulatory file is an important new supplement and incorporates information on regulatory action at both the federal and state level in the US affecting pesticides. Further information is included on the Endangered Species Act, Superfund Amendment and Reauthorization Act (SARA), the OSHA Hazard Communication Standard, and California's Proposition 65.

The following are some websites that the authors consider beneficial. The authors and the publisher make no claims as to the accuracy and quality of this information.

http://www.igc.apc.org/panna—The Pesticide Action Network North America Regional Center (PANNA) is a nonprofit organization working to advance ecological alternatives to pesticides. This website provides many links to various sources of information on pesticides.

http://chemfinder.camsoft.com—The CambridgeSoft Corp is a distributor of information supplied by third parties. The ChemFinder webserver will search by CAS number, molecular weight, formula, or name. It will search by chemical name or tradename and provides links to other websites for more information about the specific chemical searched.

http://www.cdpr.ca.gov—The California Environmental Protection Agency, Dept of Pesticide Regulations, provides access to general consumer fact sheets for safe pesticide handling and precautions. It also provides pesticide-related links and database resources.

http://pmep.cce.cornell.edu—The Pesticide Management Education Program at Cornell Univ promotes the safe use of pesticides and provides information such as chemical information on active ingredients and external links to other websites. Chemical information is sorted by type, eg, herbicides, then alphabetically. It does not have a search engine for chemical or tradename.

http://www.epa.gov/pesticides—The US EPA, Office of Pesticide Programs, offers a broad range of information.

http://ace.ace.orst.edu/info/extoxnet—EXTOXNET, the Extension Toxicology Network, is a cooperative effort of the Univ of California-Davis, Oregon State Univ, Michigan State Univ, and Cornell Univ. The *Global Search and Browse* page will search by chemical and tradename and yields detailed information about the specific pesticide searched.

http://hammock.ifas.ufl.edu—The Florida Agricultural Information Retrieval System (Univ of Florida) website has information on pesticide poisoning, listed under the heading *Pesticide Management Topics*. It provides several vehicles for searching for the pesticide of interest and includes signs/symptoms of poisoning as well as treatment methods.

http://atsdr1.atsdr.cdc.gov:8080—The Agency for Toxic Substances and Disease Registry (DHHS) lists ToxFAQs for Hazardous Substance Fact Sheets. The number of pesticides is limited.

http://www.acpa.org—The American Crop Protection Assoc provides scientific and regulatory information in the form of downloadable files. Other information on agriculture industry issues is available. This website does not allow searching by chemical or tradename. Information is focused on agricultural applications.

http://www.state.*XX*.us—To search for state and local information about pesticides, enter the two-letter state abbreviation for *XX*. This provides access to the state's homepage that links to state government health, environment, and agricultural departments. The quality of information and hyperlinks vary.

The entomologist and plant physiologist of the state agricultural experiment station and the county agent of the state's cooperative extension service should be consulted for identification of insects and up-to-date information about plant diseases. Publications on weed, insect, and plant disease control may be obtained from the state experiment station. Also, the Office of Information, USDA, Washington, DC, supplies on request a publications list from which those needed for a personal reference library may be selected for ordering. To learn about applicator certification, contact the local state department of agriculture.

Meetings of insecticide dealers, held annually in many states, also can be important sources of knowledge of new developments in the field of insecticides. Information about the scheduling of such meetings may be obtained from the local county agricultural agent. Each year the cooperative extension service in each state publishes recommendations on pesticides.

Since there are many dependable sources of pesticides, pharmacists generally will find it advantageous to stock packaged materials for their sales. To aid in contacting wholesalers, the guide known as ENTOMA, prepared and distributed by the Entomological Society of America, 4603 Calvert Rd, College Park, MD 20740, is invaluable.

Guidance on methods of rodent and predatory animal control may be obtained from the US Fish and Wildlife Service, Dept of the Interior, Washington, DC 20240.

Authority for promulgating regulations establishing tolerances for pesticide chemicals in or on raw agricultural commodities or exempting any pesticide chemical from the necessity of such a tolerance is vested in the administrator of the EPA, according to the Miller Amendment (Sec 408) of the FD&C Act. It should be emphasized that both FEPCA and state laws require that pesticides be used according to label directions. Failure to do so can result in civil and criminal penalties.

Since garden insecticides are of fair importance in suburban areas, pharmacists should be aware of the numerous inexpensive publications that are available from the Superintendent of Documents, US Government Printing Office, Washington, DC 20402. These include discussion of such topics as diseases and pests of garden and ornamental plants.

Finally, it has been noted that pharmacists frequently are consulted on venereal diseases, which have increased dramatically in recent years. Beyond the usual recommendation to consult a physician, the pharmacist may be of direct service in recommending agents for body lice infestation.

CONTROL OF INSECTS

Insects may be controlled through proper application of chemicals by means of suitable techniques.

CLASSIFICATION OF INSECT CONTROL CHEMICALS

Insect control chemicals may be classified as insecticides, fumigants, repellents, or attractants.

INSECTICIDES—Insecticides often are classified according to the type of action that results in destruction of the insect. Three broad categories, namely stomach poisons, contact insecticides, and fumigants, are recognized generally. Among older insecticides such classification was rather distinct. However, with the new synthetic organic compounds, a single material often produces insecticidal action in several ways. Certain materials often are selected and used, however, in such a manner as to accomplish control primarily by stomach, contact, or fumigating action.

Stomach Poisons—For control of insects by this method it usually is necessary to apply the insecticide to the food that they consume. Stomach poisons are used widely to control leaf-feeding insects or other pests of plants that will result in consumption of the surface-contaminated material. Stomach poisons also are used in specially prepared baits for controlling a variety of insects. With the rapid advances in employing systemic insecticides it is now feasible to destroy by stomach action certain insects that feed on plant juices or blood and tissues of animals, which in the past were considered vulnerable only to contact insecticides.

Systemic insecticides are those chemicals that move in plants and animals from one location where applied to another location where the insect may be feeding. Some of the more widely used systemic insecticides include *O,O*-diethyl-*O*(and *S*)-2-(ethylthio)ethylphosphorothioates), *Meta Systox R,* and *dimethoate,* (*O,O*-dimethyl *S*-methylcarbamoylmethyl- phosphorodithioate). Stomach poisons include a variety of organic *arsenicals, fluosilicates, rotenone,* various *chlorinated hydrocarbons,* and the *organic phosphates* and *carbamates*.

Contact Insecticides—Most of the insecticides in use today depend largely on contact action to destroy insects. *Pyrethrum, rotenone, oil emulsions, nicotine,* and *soaps* have been used for this purpose for many years. The chlorinated hydrocarbon insecticides (eg, lindane), the organic phosphates (eg, malathion), and the carbamates (eg, carbaryl) have been employed extensively for many years. Some have restricted use for specific purposes as stated in the EPA's banned and severely restricted pesticide list of Aug 1997. Contact insecticides are employed against chewing as well as sucking insects.

Often insecticides appear on the market with added compounds called synergists, which may enhance the effects of the insecticides considerably. Some, like piperonyl butoxide, help block metabolic degradation of the insecticide by the insect.

Fumigants—These are gases or vapors used for the control of insects, usually in enclosed spaces. The fumigants include *ethylene dichloride, methyl bromide, chloropicrin,* and many others. A number of the *chlorinated hydrocarbon* and *organic phosphorus* insecticides have sufficiently high vapor toxicity to cause marked fumigating action against insects, particularly in enclosed spaces and in soils, but many of these, like lindane, have been cancelled for use in vaporizers.

REPELLENTS—A variety of insect control chemicals possess repellent action. *Citronella* and *creosote* are examples of older materials. *Ethohexadiol* and *diethyltoluamide* are examples of materials more recently developed. Such materials often cause insects to avoid contact with treated surfaces. Repellancy in a strict sense might vary greatly in mode of action. Some insecticides, such as pyrethrum, have little or no repellent action except on contact. However, the action of *pyrethrum* is so rapid that the spraying of animals may cause flies and mosquitos to leave after alighting and before biting.

ATTRACTANTS—The use of attractants to lure insects to poisons or traps has been employed as a means of control for many years. The attractants employed are usually favorite foods for the particular insect involved, such as *molasses, sugar,* or *milk* for houseflies; *sugar* or *grease* for ants; *bran* for cutworms; *bananas* for cockroaches; decaying *meats* for blowflies; and *protein hydrolysate materials* for tropical fruit flies such as the Mediterranean fruit fly. In some cases specific chemicals prove highly attractive. Notable examples are *methyl eugenol* for attracting males of the Oriental fruitfly, a serious pest of fruits in some tropical areas, and many synthetic substitutes such as 10-dodecadienol, the codling moth sex attractant, and *cis*-7,8-epoxy-2-methyloctadecane *(Disparlure),* the gypsy moth sex attractant.

A new trap for Japanese beetles, now on the market, combines a controlled-release strip containing a furanone sex attractant and a eugenol odor attractant.

QUALIFICATIONS OF SUPPLIERS OF INSECTICIDES

Mere stocking of insecticides is not enough to establish a professionally recognized and economically successful enterprise as a supplier of insecticides, for three basic services must be provided in addition to physical supplies. These services, principally of information, are

Recognition of the type of insect causing the damage, from examination of either the insect or the injury it produces.

Recommendation of a remedy, based on knowledge of the action of various insecticides or other insect-control chemicals and of the life history, habits, and structure of the insect responsible.

Familiarity with methods of application of the remedy, for which the user is largely responsible but who may need instruction in such methods.

Pharmacists will find the following specific information useful in developing the aforementioned services:

An understanding of the relative importance of different insects and the relation of the cost of treatment to the increase in value resulting therefrom to the product injured is necessary. Not infrequently, the cost will exceed the damage that might be done. If the value of the product is small, the insect may not cause appreciable loss, even though it may be conspicuously evident. Again, the damage may have been done before its recognition, and the delayed treatment will not affect the insect or aid in preventing the damage.

A knowledge of the life history and habits of the common insects is desirable, as all insect control methods are based on a knowledge of these things.

The ability to recognize the common insects is a great aid, as it is the first step in providing suitable control. The county agents, federal entomologists, and the members of the staff of the respective state agricultural experiment stations are usually available to aid in the identification of insect pests.

A knowledge of how insecticides kill, of the relation of types of mouthparts to the kind of insecticide to use, and when and how the material should be applied is useful.

A knowledge of the usual insect problems of a community will enable the supplier to carry in stock the insecticides likely to be needed. This will eliminate surplus stock and will provide the materials that so often fill emergency needs.

A knowledge of the toxicity of an insecticide to warm-blooded animals, persistence of residues on plants or in animal tissues, hazard of the materials to bees or fish and wildlife is important so that advice can be given on precautions that should be taken in the use of certain chemicals. A wide variety of chemicals is in use today. They vary in their toxicity and hazards to different organisms. The degree of dan-

ger is governed not only by the inherent toxicity to higher animals and beneficial organisms in a lower category but also by the manner of use and extent of exposure. A highly toxic material properly applied in small amounts may be less hazardous than a material low in toxicity that is applied in larger amounts.

The variety of insect control chemicals is clearly apparent by mentioning some of the materials in wide use today. They include some organic arsenicals, nicotine compounds, a few chlorinated hydrocarbon insecticides (methoxychlor, lindane), and the insecticides grouped as *organic phosphates,* which at present include *parathion, malathion, dipterex, diazinon, dursban, imidan,* and the newer carbamates, which include *Sevin* (carbaryl, 1-naphthyl-*N*-methylcarbamate) and others. Several pamphlets are available from the EPA that deal with pesticide disposal, pesticide dust-avoidance respirators, and diagnosis and treatment of poisoning by pesticides. These should be kept on hand for reference by pharmacists providing poison control information on pesticides.

It is important to follow the recommendations for each locality. An insecticide effective in one region may not be in others.

It is essential to understand the labels on tradenamed preparations and follow the directions very carefully.

A knowledge of the essentials of a good insecticide, its effect on insects, and its availability and cost, is important.

Those manufacturing and offering preparations such as insecticides and rodenticides for sale on the open market must familiarize themselves with the various regulations of the individual states where the products are being manufactured or are to be sold. If such products are shipped in interstate commerce, these preparations also must comply with the various federal regulations, especially the FEPCA of 1972 and subsequent EPA amendments.

Many states require dealers in pesticides to be licensed. Some require the dealer to pass a written test to obtain the license. The test usually focuses on pesticide laws and regulations.

MOUTHPARTS AND THEIR RELATIONSHIP TO INSECT CONTROL—In general, pests have two kinds of mouthparts: chewing and sucking. An understanding of the mouthparts and how they relate to the use of different chemical insecticides often will aid in recommending a satisfactory insecticide treatment.

Chewing insects include the *grasshoppers, cockroaches, crickets, bird lice, beetles, slugs,* and *caterpillars*. Such insects have mandibles or jaws that enable them to cut off solid tissue and take it into their stomachs. Consequently, an insecticide can be used that kills when taken into the stomach with food eaten by the insect. Most of the newer insecticides, however, are active both as contact and stomach poisons.

Sucking insects include *plant bugs, leafhoppers, scale insects, aphids, fleas, mosquitos, flies,* and *sucking lice* on animals. Such an insect punctures the plant or animal but does not take any of the surface tissue into its stomach; consequently, stomach poisons that have no contact action will be ineffective when applied to the surface.

Recently, however, a variety of compounds has been found that are absorbed through the roots, stems, or leaves and transported to various parts of the plant where the chemical is available to sucking or chewing insects that feed inside or on the plant or fruit. These compounds are referred to as systemics. Insecticides having systemic action offer great promise for controlling insects, and a number of such compounds now are being employed on both plants and animals.

Plants that have been attacked by chewing pests frequently are recognized by the appearance of the eaten areas. Some plant feeders eat the entire tissue, as do *potato beetles;* others eat holes in leaves, as do *flea beetles;* while some chewing insects skeletonize the leaves, as do *slugs* and the *Mexican bean beetle*.

Sucking insects injure plants in different ways, and it is often difficult to determine the kind of insect responsible for the damage unless specimens are available. Sucking insects or mites may remove the sap and cause the plant to "stand still," wilt, or drop its foliage; or they may deform the plant, causing the leaves or shoots to curl and become deformed. Some sucking insects, such as the *potato leafhopper,* the *tarnished plant bug,* and *plant lice (aphids),* inject toxic secretions at the time of feeding, causing the death of plant cells, while others, such as *plant lice, leafhoppers,* and *striped cucumber beetles,* may injure plants directly by feeding as well as through the transmission of plant diseases. Sucking insects also may affect animals by removing the blood, injecting toxic secretions, causing swelling and irritation, or carrying disease organisms.

LIFE HISTORY AND HABITS OF INSECTS—In general, there are two types of metamorphosis or development among insects: incomplete and complete. Those with incomplete metamorphosis, such as aphids, grasshoppers, plant bugs, and scale insects, have only three stages in development: the *egg* or *embryo,* the *nymph,* and the *adult* or *imago*. Insects with complete metamorphosis, such as beetles, butterflies, moths, flies, bees, ants, and wasps, have four stages in development. In this type, the larva hatching from the egg has no resemblance to the adult, there being also an intermediate resting stage known as the *pupa,* during which remarkable changes in structure take place.

The interrelation of insects, where they hibernate, when they are actively feeding, where they lay their eggs, if they have natural enemies that feed on destructive pests, all have an important bearing on controls. The ant is essential to the life of the corn root aphid, and cultural practices that eliminate the ant likewise will eliminate the aphid; the fact that *Anopheles* mosquitos often rest in homes and other sheltered areas explains the great success of residual sprays such as malathion and baytex for controlling malaria, which such mosquitos transmit; a knowledge of the preferred oviposition sites for grasshoppers permits surveys of egg abundance or abundance of newly hatched nymphs to forecast impending outbreaks of grasshoppers.

METHODS OF INSECT CONTROL

For convenience, insect controls can be grouped as follows.

NATURAL CONTROLS—Those that are usually present and that normally tend to hold insects in check.

Natural Enemies—Parasitic and predacious insects. Every insect is more or less hindered in its increase by other insects as well as by predacious birds, mammals, and other animal life. Although insect-eating birds and certain mammals are important, the insect parasites, predators, and insect diseases are usually the most important factors in natural insect control. In fact, it is probable that outbreaks of insects, such as the army worm, often are due not so much to favorable conditions for the pests as to unfavorable conditions for the insect parasites and predators that normally hold them in check. The use of a specific insecticide against a major pest on a crop might lead to a serious outbreak of a secondary pest because of the destruction of natural enemies that normally keep it in check, particularly if the pesticide chosen was largely ineffective against the secondary pest. Such an upset in the balance between destructive and useful insects is a problem of increasing concern in developing insect control chemicals.

Weather and Topographic Influences—Summer and winter temperatures, rainfall, soil, and atmospheric humidity plus all similar natural factors have their effect on insects and their hosts. No definite statement can be made concerning the effect of these factors on all insects. A severe winter may be harmful to some insects such as those that winter in an exposed condition; on the other hand, such conditions may have little effect on insects that are well-protected. Similarly, a severe winter may weaken trees and make them more susceptible to insect attack, or it may kill the fruit buds and deprive fruit-infesting insects of their food. However, it should be remembered that insects have a high reproductive capacity, and the seasonal conditions, especially spring and early summer conditions, may aid insects in becoming destructively abundant, even though they pass the winter few in numbers. On the other hand, an insect overwintering in large numbers may not be important the following season if the weather is not favorable for increase.

In tropical, temperate, and frigid climates there are to be found insect pests peculiar to these areas because of their adaptation to prevailing weather and topographic influences. Topographic features, such as mountain ranges, act as rather effective barriers to insect migration. However, the great increase in the amount and speed of national and international travel and commerce during the last few decades has provided greater opportunities for hitchhiking insect species to overcome such barriers.

ARTIFICIAL CONTROLS—Those that are scientific developments of man.

Farm Practices—Many of our most effective aids to insect control are those called farm practices. These include rotations, cultivation, time of planting, time of harvesting, sanitation, good seed, good fertility, good planting conditions, and drainage. In general, it may be said that the practices recognized as the best garden, agronomic, orchard, greenhouse, or other farm practices are likewise the best for holding insects in check. Certain insect problems are intensified, however, because of changes in practices such as irrigation and prolonged fruiting periods. It generally is recognized, for example, that supplemental irrigation, increased use of fertilizers, and the planting of higher- yielding varieties of cotton have increased the boll weevil problem.

Mechanical Devices—Aside from devices for applying insecticides, there are mechanical devices of value in fighting insect pests. The house screens, fly swatters, insect-proof packages for cereals, and other contrivances may be included in this classification.

Insecticides—An insecticide may include any material used for the purpose of killing insects or of protecting crops, animals, or other property against insect attack. Insect repellents, fumigants, and attractants are considered insecticides in a broad sense. It is important to note that some insecticides may destroy only certain insect pests and are not effective against all insects.

Parasiticides—These substances kill animal parasites such as itch mites and ticks.

Sterilizing Agents—The release of large numbers of insects treated by radioisotopes or chemicals to interfere with reproduction has produced high degrees of control of native populations with whom the sterilized individuals mate, particularly when the insect may mate only one time. Intensive research to extend this insect control concept is under way.

Bioinsecticides—In the 1920s, entomologists experimenting with moths and butterflies found that there were natural chemicals internal to the insects that controlled their development. The release of these natural chemicals was controlled by the brain. These findings encouraged the development of so-called insect growth regulator (IGR) pesticides. Further work in the 1970s showed that synthetic analogs could react similarly. For example, methoprene can prevent adult moth emergence from pupae. Thus, insect larvae grow larger and molt repeatedly, never pupate into reproductive adults, and eventually die. Because these IGRs are unique to insects and their relatives, they are very specific in their toxicity and are among the safest pesticides known. They have been found to be useful in many areas, eg, they can have an effective life of up to 4 years in controlling stored product pests like beetles in tobacco.

MISCELLANEOUS CONTROLS—Some of the other natural insecticides are those of botanical origin. These include pyrethrins, nicotine, and rotenone. They work mainly as nerve-type poisons. Pyrethrins are the most common botanical insecticides and are extracted from the flower heads of a chrysanthemum relative grown mainly in South America and Africa. The pyrethrins have been synthesized, and many derivatives with specific advantages (eg, longer lasting) have been used in recent years.

Some of the inorganic pesticides act in a natural manner because of their desiccant or drying properties. They include boric acid, silica gel, or sulfur.

Another approach of a natural nature has been the use of microbials. These kill by causing a fatal disease in insects via specifically introduced bacteria or viruses. Among the two most common microbials in use today are *Bacillus thuringiensis,* which kills only larvae (caterpillars) of butterflies and moths, and *B popilliae,* which kills the grubs of Japanese beetles. *B thuringiensis* var *israelensis* is a newly developed variety that affects mosquito larvae. While microbials act slowly, they are very specific and only attack certain groups of insects. Microbials, therefore, are generally quite safe to use, because they will not harm people, pets, or nontargeted organisms.

For a more complete list of the biocontrol agents, please refer to the list provided in the *Farm Chemicals Handbook* (see Bibliography). They list over 500 different, biologically derived pest-control agents. These include semiochemicals (pheromones, allomones, kairomones), plant regulators, hormones, and enzymes, either naturally occurring or identical to a natural product, that attract, retard, destroy, or otherwise exert a pesticidal activity.

The microbial agents include viruses, bacteria, fungi, and protozoa. Beneficial biological control agents include predators, parasites, and weed-feeding invertebrates, living organisms used for controlling the population or biological activities of another life form considered to be a pest. The EPA refers to all of these as biorational pesticides. This list also includes traps and lures.

APPLICATION OF INSECTICIDES

HOW INSECTICIDES KILL—An understanding of how insecticides affect insects will assist in explaining methods and timing of applications.

Stomach poisons kill by being taken into the stomach where they are acted upon by the digestive juices, absorbed through the stomach walls, and assimilated by the blood. Details of the mode of action that leads to the death of the insect are not too well-known, even for our most common insecticides. However, much information is being obtained on the general nature of toxic action.

Contact insecticides kill by direct or indirect contact with the insect. Sometimes the insecticide may penetrate directly through the body integument; in other cases it causes oxidation and suffocates the insect, dissolves the insect covering, or may prevent settling of the young, as in scale insects, when lime-sulfur has been used. Some contact insecticides are effective only when applied in the presence of the insect, a fact that explains the necessity for the proper timing of applications as well as the importance of directing the spray or dust to the insect itself. Other contact insecticides of the residual type may persist on the treated surfaces where insects rest, such as barn walls and leaves of plants, and kill pests that contact the insecticide deposit.

An important contact insecticide is amorphous silica gel. It has an adsorbing action on the wax coating or cuticle of insects, preventing entrance and exit of water, which leads ultimately to dehydration and death.

Fumigants can be applied only in enclosed spaces. Fumigants surround the insect and, being in a gaseous state, readily enter the breathing pores of the insect. The systemic insecticides such as the phosphates are taken up by the plants. These kill insects, which in turn can cause a residual phosphate problem.

ESSENTIALS OF A GOOD INSECTICIDE—There are certain important factors that have a definite bearing on the practicability of insecticides.

Insecticidal or killing properties
Effect on the plant or animal or environment being treated under varying conditions
Physical properties, such as color, odor, staining properties, adhesiveness, spreading properties, stability under varying seasonal and storage conditions, reaction with other insecticides or with fungicides, consistency, and cost of preparing suitable formulations
Availability
Cost
Safety in the hands of the user
Safety and palatability of food products exposed to the insecticide
Ease of application
Flammability or explosive character

All of these factors must be kept in mind by those interested in insect control by the use of insecticides, whether researcher, manufacturer, dealer, or user.

INSECTICIDE FORMULATIONS—Most of the contact and stomach insecticides cannot be used for insect control as manufactured. They must be compounded in forms that will permit the user to apply them directly or in a manner that requires simple mixing with water or some other diluent before application. Many insect repellents, however, are applied to the skin or clothing without being formulated. The fumigants also are used without special preparation before use.

Insecticides generally are employed in three ways—as dusts, sprays, or baits.

Dust Preparations—Prepared dusts ready for use may contain 1 to 20% of the active insecticide in a carrier such as talc, bentonite, or pyrophyllite. When the insecticide compound is a crystalline material, it usually has to be ground to a fine state

so that the finished product will flow readily from the dusting equipment and disperse readily. In dusts made from insecticide chemicals that are liquid, such as parathion, the concentration of the active material seldom can exceed 5% and still have good dusting qualities.

Special conditioning agents may be necessary, and special equipment might be required to make a satisfactory dust product. For this reason the ultimate users are seldom in a position to make their own insecticidal dusts from the manufactured insecticide chemical. Dusts are used mainly for home purposes.

Insecticide dusts are used for controlling pests on agricultural crops, in homes, on man, or on animals.

In some instances when it is desired to limit the drift of dust particles and prevent particles from adhering to vegetation, dry preparations are prepared so that the particles are about the size of sugar granules. Such preparations, called granular insecticides, are used for treating soils for soil-inhabiting pests and certain other pests such as the European cornborer, when the granules collect in whorls or leaf axilla and destroy the young larvae before they bore into the stalk. They also are employed to some extent for controlling mosquito larvae, sand-fly larvae, and other insects affecting man. In general, however, dusts and granular insecticides are not used as extensively as are sprays.

Spray Preparations—Insecticidal sprays are formulated in three ways—as solutions, emulsions, or suspensions.

In preparing *solutions* the material may be dissolved in a suitable solvent such as crude or refined kerosene. The solutions are then ready for use. Many insecticide preparations containing pyrethrum, malathion, lindane, methoxychlor, etc, for household use are distributed in solution form ready for application. Ultralow-volume (ULV) spraying by airplanes makes use of some of these.

When employed as emulsions, the chemical is dissolved in a solvent in combination with an emulsifying agent. It is usually highly concentrated. Such a concentrate is intended for dilution with water before use. Emulsion concentrates, eg, may contain 40% to 50% carbaryl, 45% to 50% xylene, and 10% oil-soluble emulsifying agent. Depending on the intended use, this concentrate is added to water at rates varying from 1 part of concentrate to 4 or as much as 100 parts of water. Emulsion sprays are used widely in the agricultural field for controlling both plant and animal pests and for controlling household and industrial pests.

Suspensions are prepared in dry form similar to dusts but contain a wetting agent that makes it possible to prepare suspensions in water. These preparations in concentrate form usually are called wettable powders. They may contain 15% to 75% active ingredient, depending on the insecticide formulated.

Wettable-powder concentrates (25–85%) are added to water for application at concentrations of 0.1% to 2.5% active ingredient. Wettable-powder sprays are used on crops and livestock and as barn sprays. Such sprays are particularly useful for application to plants that might be sensitive to the oils employed for emulsions or solutions.

Bait Preparation—Many of the active ingredients have been formulated into insect baits. Baygon bait is an effective example. In very restrictive areas, Amdro (amidinohydrazone) has been packaged as a bait inside a self-contained, stick-on bait station. These can be effective in restaurant kitchen ceilings and similar areas.

Other Insecticide Preparations—Insecticides are employed in several other ways. Heat can be used to produce vapors or smokes for dispensing insecticides. This method also can be employed for treating greenhouses with insecticides to control insects and mites.

One of the most widely used methods of dispensing insecticides is the aerosol form. The *aerosol bomb,* developed just prior to and during World War II and employed by the military services, has gained general favor by civilians. Millions of the aerosol bombs, now referred to as *pressure packs,* are sold annually for dispensing insecticides in homes and industrial establishments to control flies, mosquitos, and other household pests. Pyrethrum, allethrin, organic thiocyanates, and methoxychlor in various formulations are used most frequently as the insecticides.

The insecticides are dissolved in a liquefied gas, such as butane or propane, plus a suitable solvent under pressure in the container. Producers are substituting the fluorocarbon propellants with hydrocarbons (butane or propane) because of concerns about the effect of fluorocarbons on the ozone layer in the atmosphere. When applied, the gas volatilizes instantly, leaving the insecticide and nonvolatile solvent suspended in the air as minute droplets that contact the insects present. Aerosols also are employed for applying insecticides in greenhouses.

The liquefied gas propellant also is used to apply *wet aerosols* or so-called *self-propelled* sprays. These water droplets are larger than those usually obtained with aerosol propellants. The amount of nonvolatile solvent is increased so that the droplets are larger and will readily wet the surface treated. Such wet aerosol sprays are used for applying insect repellents to the skin or clothing or for applying insecticides as residual sprays for controlling various household insects.

The development of systemic insecticides for controlling plant and animal pests has led to other special methods of use. For control of cattle grubs in cattle, boluses containing the insecticide are administered orally. With plant systemics, the treatment of soils prior to planting with a slurry of the insecticides or insecticide granules is one method.

Insecticidal strips of polymer impregnated with DDVP *(Vapona)* emit vapors for long periods of time. In areas of little human or animal activity these can be effective. Mosquito *coils,* which are burned to release pesticides, are also important control measures. Flytraps are still available and catch these insects by sticky material (flypaper) or by attracting them into a device that resembles an inverted funnel, from which they are unable to emerge.

EQUIPMENT FOR APPLYING INSECTICIDES— Often, failure to obtain satisfactory results with insecticide preparations is due to improper equipment for their application. A knowledge of the type of equipment to employ is therefore important to the supplier of insecticides. Equipment might vary from small hand sprayers, or even paint brushes for use in homes, to large power sprayers for treating livestock, field crops, or fruit or large shade trees. The use of airplanes and helicopters for insecticide dispersal is increasing steadily. The manufacturers of equipment, also county agents, entomologists, and agricultural engineers with state and federal governments, as well as suppliers of insecticides, are in a position to give advice on insect control equipment to the potential user.

Control of Household Pests and Insects Attacking Man

Pharmacists often are asked to provide materials or advise on the control of insects, ticks, and mites affecting man or those that are pests in homes or industrial establishments. Suggestions for the control of such arthropods are presented below.

GENERAL CONSIDERATIONS

The most important measure to follow in minimizing insect problems in the home or on the person is to practice *sanitation* and *good housekeeping*. Many of the pests in homes and industrial establishments, including mice, rats, cockroaches, ants, and silverfish, depend on exposed foods or scraps of food for their existence. Cleanliness, therefore, will go a long way toward reducing the insect problem within homes, restaurants, and other buildings.

Pantry pests, such as grain moths and weevils of various kinds, develop in flour, corn meal, dog biscuits, and many other food products. An open container of oatmeal or dog biscuits hidden away in a pantry for several months can produce hundreds of moths or other pests that may continue to emerge over a period of weeks or months. Obviously, the simplest and best solu-

tion for such a problem is to destroy the source of the infestation rather than to use insecticides repeatedly.

A homeowner might be alarmed, and rightly so, when an infestation of fleas is detected in the home. In most modern dwellings the odds are great that the source of the fleas is the cat or dog that has not had proper care. The householder can minimize the danger of flying pests such as mosquitos and flies getting into the premises by maintaining screen doors and windows in proper condition and by closing any openings into the home. Poorly cared-for garbage containers can be responsible for serious fly problems by attracting adult flies and by providing places for fly breeding. A few tin cans or tire casings that catch rainwater can provide the moisture essential for mosquito breeding on the premises.

The four general control measures for the prevention of insect and mite damage without chemicals are physical, mechanical, cultural, and biological.

Physical control simply involves direct action by hand, eg, removal of insect nests or egg masses.

Mechanical control involves the use of equipment specifically designed to control insects, eg, applying sticky bands around tree trunks to trap tent caterpillars and frequent hosing of foliage to prevent red spider mites and mealybugs from taking hold.

Cultural control is based on knowledge of the life history and habit pattern of insects and controlling these in various ways, eg, cultivating the soil when many insects are in the pupal stage, breeding insect-resistant plants or interplanting. Interplanting marigolds, which discourage nematode growth, with tomatoes is an example.

Biological control involves, eg, the use of the praying mantis, which devours insects.

It is recognized, however, that in spite of proper precautions, every homeowner is likely to be faced with insect problems that must be solved by applying insect-control chemicals. In some cases, however, the solution is not simple. It may require knowledge of the habits of the pest, a thorough survey of the problem, and know-how to control the pest involved. Often, it is not practical for the owner to attempt to do the job himself. In such circumstances the services of a licensed pest control operator (listed in the yellow pages of telephone directories) should be sought. The National Pest Control Association is in a position to advise on qualified pest-control firms in almost every city. County agents and entomologists in state experiment stations and with the federal government are prepared to give advice and furnish publications that will be helpful in many cases.

For insect control in living quarters, in food-handling establishments, and on the person, the factor of safety in handling and applying toxic chemicals must be considered fully. Fortunately, a number of efficient insecticides have low levels of hazard to man and animals, although no insecticide can be considered completely harmless. The petroleum oil solvent most commonly used as the carrier in household sprays is in itself sufficiently hazardous to cause toxic effects if the operator is careless in use and permits overexposure to it.

Foods and food utensils should not be left uncovered while insecticides are being used. All food preparation surfaces, utensils, and food serving areas should be cleaned thoroughly before the next use, to avoid contamination by pesticide residues. Care is needed in handling and applying pesticides to avoid excessive inhalation or skin contact. All poisons should be stored so that they are inaccessible to children and unauthorized people or where they cannot be mistaken for food. It also must be kept in mind that many preparations containing petroleum oil are flammable, or the vapors are explosive.

While stressing necessary precautions, it must be kept in mind that the proper use of insecticides should not be discouraged. Many pests in and around homes are capable of transmitting diseases, and experience has shown that the disease hazard may be far greater than that of the chemicals needed to control the insects responsible for propagating an epidemic.

ANTS—Several species of ants are pests in the home or around the premises. In the past, poison baits of various kinds were used to destroy them. Such methods are still effective under certain conditions, but the use of newer sprays or dusts provides more effective and more rapid results.

Efforts should be made to locate the colony and destroy it if possible, although inside buildings the colony often cannot be found or may be inaccessible for treatment. The use of dusts and suitable sprays applied to the point of runoff on runways and other surfaces where ants have been seen, and along baseboards, borders of floors, window frames, doorsills, and similar places usually will give satisfactory control, although followup treatments may be necessary. In general, the procedure for poisoning ants is similar to that for controlling roaches.

For ant control on lawns or in gardens, the best procedure is to locate the ant colony and apply Baygon, Dursban, Ficam, or one of the other pyrethrin derivatives. Baygon, a carbamate insecticide, and Dursban, an organic phosphate insecticide, have become popular for this use. These currently are formulated at higher concentrations for use by professional applicators only. The material may be applied with a sprinkling can, sprayer, or any other convenient method, being sure to follow product labels, particularly on those allowed for lawn use only. A concentration of 0.25% of these insecticides is suggested for treating individual mounds. The amount to apply varies with the size of the colony. A quart may be sufficient for small colonies and up to 3 gal may be necessary for large fire ant colonies 1 ft high and 2 to 3 ft in diameter at the base. The surface of the mound or soil should be disturbed by raking, and the material poured on and around the nest.

Children and pets should not be permitted to play on the lawns until the area has been watered or rained on and allowed to dry. It is advised that the insecticide be washed off vegetation, into the ground, by sprinkling; this will not reduce the efficacy of the treatment.

Chlorpyrifos *(Dursban),* and synergized pyrethrum sprays, may be employed for ant control in homes.

Bedbugs are controlled effectively by thorough spraying of the bed frame, springs, and edges and ticking of mattresses with 1% to 3% malathion by a professional applicator. Cracks, crevices, and surfaces behind objects near a wall also should be treated. Bedbugs stay well hidden in such places. Spraying the bed and other hiding places to the point of running off of the solution will provide long-lasting control. The treated mattress should be aired well before use.

Chiggers or red bugs cause severe annoyance to many people. These mites are most common in southern and midwestern areas. Some individuals are particularly susceptible to chigger bites, especially if they have not previously been exposed to them.

The insect repellents dimethyl phthalate, dimethyl carbate, diethyltoluamide, 2-ethyl-1,3-hexanediol, and benzyl benzoate, when applied to clothing, are excellent in preventing attack by chiggers. The repellents may be applied by hand to socks, inside cuffs of trousers and sleeves, and on the edges of any other openings in the clothing. Additional application of the repellent to the skin on the legs and forearms and base of neck will increase the probability of complete protection. Chiggers seldom attack the exposed portion of the body and are killed or repelled while crawling over treated clothing or exposed skin.

Clothing may be made repellent by light spraying, by drawing the mouth of the bottle along the parts of cloth to be treated (eg, cuffs and fly), or by complete impregnation of the cloth.

Although the repellents are highly effective in providing protection against chigger attack, persons often become exposed in areas where they do not expect chiggers to be present. After chiggers attack, there is no known treatment of the bites that will destroy the toxic substance that causes the irritation, although certain local anesthetics such as benzocaine will provide relief for several hours. A thorough, soapy bath as soon as chigger irritation is noted, which may be within a few hours after exposure, will reveal those attached and thus allow removal and subsequent reduction of irritation.

COCKROACHES—The German, American, and brown-banded are the most common cockroach species found in homes

and industrial establishments. Although the efficacy of different insecticides varies with the species, those in common use can be employed effectively in most instances. The German roach accounts for 98% of the problem in the US.

Most aerosol formulas contain pyrethrum, allethrin, or resmethrin. Although intended primarily for flying insects, the aerosols can be used fairly effectively for roach control if applied in considerable amounts directly into the hiding places or released in high concentration in closed rooms. A thorough spray or dust treatment is considered more effective and longer-lasting. Many purchasers of aerosols expect roach control in the home by a light treatment. Such treatment, although satisfactory for flies, mosquitos, and similar pests, is inadequate for good roach control.

Boric acid and *borax* in finely powdered form, applied to hiding places and runways, are used for roach control, although they are less effective and slower to produce results than most other insecticides. The materials also are used in tablet form mixed with food baits that the roaches must eat. When well-distributed in office buildings or rooms where there is little food for roaches, they often provide satisfactory control.

Dursban (chlorpyrifos) sprays and dusts are widely used insecticides for roach control. The sprays, either oil-based or prepared from an emulsifiable concentrate, should contain about 2% and dusts about 5% of the insecticide as described on the label.

During the day, roaches usually remain well hidden in cracks and crevices and behind objects. It is important to know where the roaches hide and where they run. The coarse, wet insecticide sprays are applied into these runways and hiding places. A few puffs of a mist spray will not provide satisfactory control. A paint brush may be used to apply the solution instead of a sprayer, if label directions allow it. A dust should be blown directly into hiding places and placed along runways. Dursban *O,O*-diethyl-*O*-(3,5,6-trichloro-2-pyridyl)phosphorothionate may be recommended as a first-use agent.

Ficam (2,2-dimethyl-1,3-benzodioxol-4-yl), or bendiocarb (generic name), also is useful and is popular as a highly effective broad-spectrum carbamate insecticide for control of at least six species of cockroach.

Pyrethrum sprays or dusts usually will provide satisfactory roach control. It is necessary, however, to treat with pyrethrum often to obtain and maintain control. The use of synergists with this insecticide has made it more effective.

When chlorinated hydrocarbon resistance is encountered in roaches, malathion as a 1 to 2% spray has proved to be an effective substitute. *Diazinon* *O,O*-diethyl-*O*-(2-isopropyl-4-methyl-6-pyrimidinyl)phosphorothioate also has proved useful when roach resistance has been a problem. The residual life of malathion is generally less than that obtained with methoxychlor prior to the appearance of insecticide-resistant strains.

Fleas often are pests in homes and even in lawns in some areas. Infestations usually are associated with the presence of cats, dogs, rats, or other animals. To prevent recurrence of fleas, the source of the trouble should be treated. For dogs, powders containing 1% lindane, pyrethrum, or rotenone are used per label directions. For cats, only rotenone or pyrethrum insecticides are recommended, because these animals are very susceptible to the toxic effects of chlorinated hydrocarbons. If the source of the fleas is rats, the host animals should be eliminated by following suitable rodent-control measures.

Actual flea control in homes is usually not difficult. Bedding where dogs sleep should be removed, and the area thoroughly cleaned. Ordinary household sprays containing pyrethrum also may be used, although several repeat treatments may be required. Certain volatile organophosphate insecticides are the active ingredients of *flea collars* for dogs and cats. A new insect growth regulator, *methoprene,* is giving effective indoor flea control. This agent interferes with the life cycle of insects undergoing complete metamorphosis.

Finally, attention must be given to the pesticide label precautions. Some dogs and many cats are allergic to collars. Malathion and Sevin (carbaryl) are excellent materials for the control of fleas in the home or in infested yards.

FLIES—For most homes or industrial establishments flies can be eliminated by using ordinary household sprays or aerosols. The most common ones consist of deodorized kerosene, about 0.1% pyrethrins or allethrin, and 0.75% of a synergist such as piperonyl butoxide or sulfoxide. Many variations in percentages of such insecticides are included in different formulations. Aerosol formulas often contain 0.25% to 0.6% pyrethrins or allethrin, 0.8% to 1% synergist, and 1% to 2% methoxychlor. The method of using the sprays or aerosols generally is known and usually well-described on the labels.

If flies are a serious problem on the premises, other methods of control must be followed. Recently, the use of poison baits has become more widespread.

Malathion and Diazinon sprays as residual treatments outdoors around homes, in livestock buildings (including inside dairy barns), and similar places have come into use. When used according to label directions, these materials often provide good fly control up to several weeks after application. Flytraps (paper) and mechanical devices for trapping are still available and popular.

ITCH MITE—Many preparations have been employed for controlling the itch mite, or scabies. One of the most successful was the NBIN emulsion employed for head-louse control. It is important to treat all portions of the body and to delay a bath for about 12 hr after treatment. A second treatment may be needed after 1 week, although one thorough treatment will usually eliminate the infestation.

LICE—Three kinds of lice attack man: the *body louse, head louse,* and *crab (pubic) louse*. In the US, head louse and pubic louse infestations are more common than those of the body louse.

Body louse infestations can be controlled by regular changes of clothing and sterilization of all wearing apparel and bedding. Synergized pyrethrum dusts are also highly effective for body louse control. It also has been found that allethrin is about as effective as pyrethrins in such formulations. The material most commonly used today for head and body louse treatment is synergized pyrethrum (eg, the OTC product RID).

Head louse infestations are controlled readily with benzyl benzoate followed by a thorough shampoo the next morning. Weekly treatments may be needed. Since eggs are not destroyed easily, treatments should be repeated. One treatment applied to the hair on the head before bedtime will kill all motile stages of the lice, which may be brushed or washed out of the hair in the morning.

Crab louse infestations are controlled effectively with any of the preparations discussed under head louse. It is important that all hairy portions of the body be treated.

Mosquitos that occasionally enter homes can be killed easily with the type of space sprays and aerosols discussed in connection with fly control. Mosquitos often breed in areas several miles from the places where they are serious nuisances. Community mosquito control programs are the only real solution to this problem. The problem of achieving satisfactory mosquito control in a community is usually so complex and extensive that the help and advice of specialists are necessary.

Persons exposed to mosquitos, biting gnats, and flies outdoors in connection with work or recreation can obtain relief by applying skin repellents. The most common individual repellents available on the market are *diethyltoluamide, dimethyl phthalate, ethohexadiol,* and *dimethyl carbamate.* Various combinations of these also are available. All of these materials used as directed on container labels will provide transient relief from insect attack.

In some circumstances treatment of the exposed skin alone is inadequate because the mosquitos also may bite through clothing. The application of repellents to clothing by impregnation, by light spraying, or by hand will prevent the attack. The same repellent materials intended for skin application may be used. Most of the repellents are plasticizers. They should not be applied to rayons and similar synthetic clothing.

MOTHS AND CARPET BEETLES—Every homeowner is likely to encounter damage due to clothes moths or carpet

beetles, often called *buffalo* moths. The damage caused by these insects to woolens and other items such as furs, materials made of animal hair, or feathers is very great.

For many years the fumigants naphthalene and paradichlorobenzene were the chief means of control. It takes a high concentration of vapor to kill clothes moths or carpet beetles, however. Many pounds of these fumigants are needed to eliminate infestations in closets that are not tight or where the doors are opened too often to permit sufficient concentration of vapor. In using these fumigants add crystals, flakes, or balls at the rate of 1 lb/100 ft^3, and make closets tight by sealing cracks and edges of doors. Since the gas is considerably heavier than air, the fumigant should be placed high in the closet. For protecting clothing, furs, etc in trunks and other storage spaces for long periods, about 1 lb suffices for an average-size trunk.

Moth infestations are destroyed and woolen items effectively protected against subsequent infestations by treating with paradichlorobenzene, naphthalene, or DDVP (dichlorvos).

SILVERFISH—For the control of silverfish, use carefully applied residual insecticide sprays and dusts such as bendiocarb, diazinon, propoxur, and silica gel. Silverfish may be found in many places in the home—basement, attic, around books, and behind wall paper. They feed on the starchy material used as glues or for sizing paper.

Ticks are serious pests in some areas. If the infested areas must be used, it is possible to kill the ticks by following the procedures suggested for area chigger control. Protection of individuals from tick attack, however, is fairly effective if clothing is thoroughly impregnated with certain repellents. Emulsions of dimethyl phthalate and diethyltoluamide may be used for such treatment.

Insecticides, Fumigants, and Repellents

The number of insecticides and repellents currently in use has increased greatly during the past 30 years. New synthetic compounds have come into use for many pests for which practical chemical control methods were unknown, and in some cases have largely replaced certain inorganic compounds and insecticides of plant origin. However, some of the more recently developed chemicals are being replaced by even newer materials because of development of resistance by various insects to insecticides. This is a problem of major significance in insect control. The housefly, for example, became resistant to DDT and other chlorinated hydrocarbon insecticides within 5 to 10 years after they came into extensive use.

Organic phosphorus insecticides were developed as substitutes, but within a few years evidence of resistance to them became apparent. A wide variety of insects affecting man, livestock, fruits, vegetables, and cotton are resistant to one or more of the newer insecticides. Currently, the resistant strains still are restricted generally to certain localities. However, authorities in insect control generally are agreed that such local resistance problems are likely to become more widespread with continued use of the materials. The use of piperonyl butoxide as a mixed-function oxidase inhibitor and an inducer of cytochrome P-450 has led to the reduction of resistance to many insecticides by many insects.

The more widely employed insect control chemicals and their areas of use are discussed briefly. The extensive literature on the many insecticides may be consulted for further details, and the US Dept of Agriculture, state experiment stations, the US Public Health Service, and manufacturers of specific insecticides are prepared to provide more-detailed information. The EPA should be consulted for the latest information about a particular pesticide, since its status may change at any time. A chart for emergency treatment of acute pesticide poisoning is available from the US Navy Disease Vector Ecology and Control Center, Jacksonville, FL 32212.

COMMON INSECTICIDES

Allethrin (*dl*-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one esterified with a mixture of *cis* and *trans dl*-chrysanthemum monocarboxylic acids)—This synthetic pyrethrin-like compound has been developed as the result of basic studies on the complex composition of the active principles in pyrethrum insecticides. It has many of the desirable features of pyrethrum—high insecticidal activity with low toxicity to warm-blooded animals. In general, allethrin is effective against the same insects as pyrethrum. For some species such as the *housefly* and the *body louse* it is equally effective, but against others it is less effective than pyrethrum. At present it can be produced commercially at a cost somewhat lower than the cost of the pyrethrins (principal active ingredients in pyrethrum). This advantage in practical use is offset, however, because the insecticidal activity of allethrin is not increased to the same degree as that of the pyrethrins when combined with synergists available at present.

The development of allethrin is of great significance however. It is now used in household sprays and aerosols as a substitute for pyrethrins or to supplement the pyrethrins. The Dept of Defense uses the insecticide in sprays and aerosols supplied to troops. Research has shown that allethrin is highly efficient for the control of lice affecting man. The availability of allethrin ensures a supply of a pyrethrum-like insecticide in the event our source of supply of pyrethrum is cut off or greatly reduced as during World War II.

Arsenicals—These are among the older insecticides and are still employed to a very limited extent. Many compounds, such as lead arsenate and calcium arsenate, have been canceled voluntarily for use by the manufacturers. Due to the development and availability of many new insecticides equally effective and often less hazardous to plants and animals, the arsenicals have been replaced largely by other insecticides.

Lime-Sulfur (Calcium Polysulfides)—Originally used as a *sheep dip* for the control of *mites* and *ticks,* lime-sulfur in liquid and dry form is now better known as a dormant spray for the control of *scale insects* and as a summer spray for the control of certain *plant diseases*. For the methods of using the lime-sulfur liquid concentrate, follow the recommendations on the container. It generally is used to control apple scab and powdery skin irritation mildews.

Oil Sprays—Oils made from petroleum are among the insecticides that have been used for many years, chiefly as contact insecticides for *scale insects* and *mites* attacking plants. They are very important today. Oils will destroy other insects however, including *aphids, thrips, and leafhoppers,* and *eggs* of certain *Lepidopterous* spp.

There are two classes of oils used as insecticides: the *dormant oils* and *summer oils*. The dormant oils are applied to hardier trees during the dormant period. The summer oils are used on fruit and vegetable crops during the growing season. The chief differences between the two types are the degree of refinement and their heaviness or viscosity, which determine in part the degree of phytotoxicity. The oils are applied as emulsions that permit dilution with water and more-uniform distribution on the plants. The concentration of oil in the finished spray for citrus usually is 1.66% to 2.0%. Small amounts of insecticides such as parathion added to the oil sprays increase their efficacy against various insects.

Pyrethrum—Pyrethrum flowers, the first widely used insecticide, possess unusually fast contact action against many insects, causing paralysis in a few minutes. Their low mammalian toxicity and rapid toxic action against many pests are features that are not present in the newer materials.

The active substances, pyrethrins I and II, occur in the oleoresin secretion of certain floral parts (achenes) of the closed or partially open flowers. A maximum of about 1.4% pyrethrins has been adopted by the foremost manufacturers of pyrethrum insecticides.

Formerly, pyrethrum insecticides were prepared as dusts by using the finely ground flowers or were prepared and used as liquids by extracting the active ingredients from the flowers with special fractions of light petroleum oil, preferably odorless kerosene. Today, manufacturers extract and concentrate the active ingredients in products containing about 20% pyrethrins. This concentrate is used to prepare the various preparations employed by the public including dusts, petroleum oil solutions, emulsion concentrates, wettable powders, and aerosol formulations.

Pyrethrum still is used as an ingredient in most household sprays and aerosols, chiefly for its *knockdown* effects against insects. It also is used in dusts and liquid preparations for controlling a variety of garden pests and *fleas, lice,* and *ticks* on pets.

The continued prominent place of pyrethrum as an insecticide has been maintained chiefly because of the development of chemicals that, when combined with pyrethrum, have the remarkable property of increasing the insecticidal activity of the insecticide even though the material added alone has little or no insecticidal properties. This cooperative potentiation is known as *synergism*.

These compounds include piperonyl butoxide, sulfoxide, and others and are called *synergists*. The development of these synergists has increased the range of activity of pyrethrins and at the same time permits reduction in the cost of formulas containing it.

Synergized pyrethrum combinations, although not so long-lasting as the chlorinated hydrocarbon insecticides, are used chiefly in household

sprays and aerosols for *flies, mosquitos,* and other *household pests,* in liquid and dust preparations for controlling *external parasites* on pets, as sprays for flies on dairy cattle, and as dusts and sprays for controlling certain *vegetable pests.* Synergized pyrethrum powders and liquids were employed extensively for a time in controlling *lice* attacking man during World War II. Some preparations include pyrelline, pyrenone, and pyrocide. Most of these contain pyrethrins in varying concentrations and other materials such as piperonyl butoxide, rotenone, or ryania. Many pyrethroid synthetics have been found effective and now are registered for use. These include newer allethrin derivatives, resmethrin products, and *S*-bioallethrin.

Rotenone—This is a useful botanical insecticide and represents the chief chemical constituent of derris (*D elliptica* and *D chinensis*) and cube roots (species of *Lonchocarpus*) and other sources. Rotenone ($C_{23}H_{22}O_6$) is commercially available as such or in the form of derris and cube roots, sold with assayed rotenone content, usually 5%.

It is classified incorrectly as a nontoxic insecticide. It can cause skin irritation. Its use for louse control on humans is not recommended, since irritation often is produced, especially in the groin region. On internal administration in moderately large doses, especially in the presence of fatty foods, it is very toxic to higher animals. In general, however, rotenone insecticides are considered low in hazard. The relatively small amounts applied and rapid loss of toxic action results in minor residues on food crops. Rotenone is used mainly to kill unwanted fish in a pond prior to restocking.

Its paralyzing action on insects is slower than that of pyrethrum but more certain, with usually no recoveries. As a dry, crystalline powder, it is odorless and relatively stable. It is soluble in alcohol, oils, chloroform, and carbon tetrachloride (used in the extraction from the crude drug and its quantitative determination). It is slightly soluble in water, but aqueous sprays, particularly in the presence of alkaline soaps, quickly deteriorate and must be prepared fresh before use.

Its dusts at concentrations of 0.75% to 1.0% still are used to control pests such as the *Mexican bean beetle, cabbage worms, leaf hoppers,* and other insects attacking a variety of vegetables. It is especially useful for application to vegetables near the time for harvest, when certain of the effective newer insecticides cannot be used because of potentially excessive residues.

It also is used for controlling insect parasites of animals. It is effective for controlling *cattle grubs* and is employed also for *lice, fleas,* and *ticks* on pets and livestock.

Sulfur is used widely in insecticide preparations. It formerly was used for controlling such insects as *plant mites, fleahoppers* on cotton, *lice* on livestock, and *chiggers*. The new insecticides available today are far more efficient than sulfur for most insects. However, it is still one of the more effective insecticides for certain species of plant mites. Sulfur also is used in combination with many other insecticide dusts as a diluent. It serves a useful purpose in such combinations in controlling or preventing a buildup of mites and for the control of *plant diseases*. It is employed as a spray made from wettable sulfur or is used in wettable powder preparations containing other insecticides.

Other Materials—A number of other insecticides that have been used as pesticides, but for limited purposes, include *pentachlorophenol* ($C_6C_{l5}OH$), widely used as a wood preservative to control termites, other wood-infesting insects, and wood rots (it is under investigation for dioxin contamination and the health ramifications of this contaminant); *Ryania,* a plant product containing alkaloids, used to some extent for controlling corn borers and codling moths on apples; and *sabadilla,* another plant product, which is effective for controlling squash bugs, lygus bugs, and harlequin bugs.

Also of interest in the biopesticide group are the avermectins. These are macrocyclic lactones isolated from the soil organism *Streptomyces avermitilis*. Known by the common name abamectin, it is considered an insecticide as well as a miticide.

Another interesting modern pesticide of biological origin is *neem*. This is a general name given the plant and its products. It is a subtropical shade tree *(Azadirachta indica)* native to the arid regions of India, Pakistan, and parts of Africa. Its most important constituent is a limonoid compound named azadirachtin. The tree has been known for centuries as being free of insects, disease, and nematodes. All parts of the tree, especially the seeds, are resistant. The bark, leaves, and fruit have been used in traditional medicinal remedies, and various extracts have been long used as insect repellents and antifeedants in Asia.

In June 1993 the Clinton administration announced an effort to encourage farmers to reduce their use of pesticides. This was due partly to a National Academy of Sciences report that said that pesticides may have a greater effect on children and that studies should be expanded to determine the possible dangers to children, who may consume more pesticides relative to their body weight.

Leaders in biotechnology are expanding efforts to circumvent the use of pesticides and hope to replace 10% to 20% of the current chemical pesticides in use. Already, biotechnology is being used to develop squash plants that are immune to a killer virus by activating the plant's natural defenses. In a similar way, hybrid corn, using genes from rare species, may allow resistance to corn borer worm.

Opponents are concerned that biotechnology raises ethical questions about tinkering with nature. Of course, this approach will take time and money to see if it will be successful. Until then, the older advice of shopping for fresh vegetables frequently, serving a variety of fruits, and washing and peeling vegetables should be continued to minimize pesticide residue consumption.

CHLORINATED HYDROCARBON INSECTICIDES

The advances in insect control since about 1940 have been phenomenal because of the development and extensive use of a variety of chemical compounds broadly classified as synthetic chlorinated hydrocarbons. The use of this class of insecticides began with DDT, which was employed first in Switzerland, but within a decade a number of new similar insecticides of comparable, or in some instances greater, insecticidal activity came into use. These materials, although effective against similar pests in many instances, vary in their usefulness for controlling insects.

Insect species vary in their susceptibility to the different compounds. In addition, a factor of great significance that limits the practical use of many insecticides is the hazard associated with their use. Some of the insecticides possess long residual action—which may be of great advantage in controlling certain pests—but which is an objectionable feature when applied to food plants consumed by man and animals. Some of the materials are stored in fat or are excreted in milk of animals when the residues are consumed on forage treated for insect control or when the insecticides are applied to the animals for controlling pests. Such residues of some insecticides may persist for months, while others are eliminated within a few days or weeks.

Because of the persistence in the environment, DDT, aldrin, and dieldrin have been canceled by the EPA. Although their uses have been banned or severely restricted, approximately 1 million households still have products containing chlordane, 150,000 households have products containing DDT, and 70,000 have heptachlor.

Obviously, it is not possible in this chapter to discuss in detail the many uses for the various chlorinated hydrocarbon insecticides. The formulation to use, amount to apply, method and time of application, precautions that must be observed in avoiding harmful residues on the harvested crop, and many other aspects must be considered. Discussion is limited to those products whose use is currently approved by the EPA.

Lindane [γ-1,2,3,4,5,6-hexachlorocyclohexane]—This insecticide is used in household sprays and dusts on livestock and other animals and for controlling some pests on fruits and vegetables. When lice resistant to 10% DDT powder appeared in Korea the Dept of Defense substituted a 1% lindane dust to control this insect attacking man. The acute oral toxicity of lindane to animals is somewhat higher than that of DDT, but when absorbed through the skin it is more toxic than DDT. Lindane possesses high insecticidal activity in vapor form. This property has resulted in certain restricted use for the compound in devices that generate vapors with the aid of heat. Lindane has been canceled for use in vaporizers, canceled for indoor use in smoke fumigation devices, and a host of new restrictions were developed for limited use on commercial and homeowner ornamentals, such as hardwood logs and lumber, dog dips, moth sprays, seed treatments, flea collars, etc.

Methoxychlor [1,1,1-trichloro-2,2-bis(*p*-methoxyphenyl)ethane]—This has chemical and physical properties similar to those of DDT. The chief advantage of this over other chlorinated hydrocarbon insecticides is its low hazard to animals. It is satisfactory for controlling *flies* and other *household pests,* including *clothes moths* and *flies* and *lice* on livestock, *Mexican bean beetles,* and a variety of other insects attacking fruit, vegetable, and forage crops. It is available in 25 to 50% concentrations in various application forms.

It is one of the few chlorinated hydrocarbon insecticides that is not readily stored in animal fat or excreted in milk when consumed as residues on forage crops. For this reason it is used for controlling various insects on livestock feeds and forage. It also was used as a spray for controlling flies and lice on dairy cows but is no longer used thus because small amounts of the insecticide occur in milk.

MITICIDES. A variety of synthetic organic insecticides is used for controlling mites on plants, in addition to older insecticides such as sulfur and the organic phosphates discussed in the next section. Among the compounds used are *Ovex* (*p*-chlorophenyl *p*-chlorobenzenesulfonate) and *Kelthane* (1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol), used extensively on fruits and vegetables. These miticides may be used as dusts or sprays, and they often are combined with other insecticide applications or in insecticide-fungicide formulations.

ORGANIC PHOSPHORUS COMPOUNDS

A large variety of organic compounds of phosphorus possesses high insecticidal activity. They often are referred to as organophosphorus compounds. Some of these compounds also have unusually high potency as miticides, and many are also extremely toxic to man and other warm-blooded animals because of their action as irreversible inhibitors of cholinesterase.

A number of human fatalities in the US and other parts of the world have occurred as a result of exposure to phosphate insecticides, and many other persons have suffered ill effects. It is important, therefore, that the more toxic of these insecticides be handled with extreme caution and strictly in accordance with recommendations outlined by the manufacturer and federal and state agencies.

The reputation of the organic phosphorus insecticides is such that to the uninformed, most compounds in this class are regarded as dangerous to use. This is a misconception. The mammalian toxicity of some of the compounds is of a low order, and they can be handled with no more danger than that associated with the use of a number of the synthetic chlorinated hydrocarbon insecticides that are employed without serious toxic reactions.

The organophosphorus compounds will control a wide range of pests and disease carriers. Certain of these compounds possess systemic action, a characteristic that offers great promise for controlling important insect pests of crops as well as livestock.

The organic phosphorus insecticides are used extensively, in many instances replacing in part, at least, some of the chlorinated hydrocarbons and older insecticides such as rotenone. This trend is due to several factors. Resistance to the chlorinated hydrocarbons by a number of pests has necessitated substitute materials possessing a different mode of insecticidal action. Several of the organic phosphorus compounds do not accumulate in meat and milk as readily as do certain chlorinated hydrocarbon insecticides when consumed as residues on forage crops.

The phosphorus insecticides have not been in use as long as the older materials, and relatively few insects have become resistant to them. There is no assurance, however, that many pests will not in time become resistant to the phosphorus materials. A number of species of mites on plants became resistant within a few years, and as already mentioned, the house fly also has developed resistance to certain organic phosphorus compounds. There is some evidence, however, that in some insect species, resistance to the phosphorus insecticides does not develop to the high level of the chlorinated hydrocarbons.

Organic phosphorus insecticides generally destroy a wide range of insect species. Consequently, their use often kills many parasites, predators, and pollinating insects, as well as the destructive pests.

The more widely used organic phosphorus insecticides are described briefly, and some of their more important uses are given.

Ciodrin [3-hydroxycrotonic acid α-methylbenzyl ester dimethyl phosphate; Crotoxyphos]—An insecticide for control of animal parasites and for premises use.

Diazinon [*O,O*-diethyl *O*-(2-isopropyl-4-methyl-6-pyrimidinyl)-phosphorothioate; Spectracide *Knox Out*]—An amber-colored liquid with a somewhat objectionable odor in its technical form; it is an excellent insecticide. It is less toxic than parathion but more so than malathion to warm-blooded animals. It is highly toxic to flies as a contact and residual spray as well as a stomach poison and is in use for controlling these insects both as sprays and in poison baits. It also is effective against aphids, mites, leafhoppers, the codling moth, fruitflies, cabbage worms, mosquitos, roaches, and other insects. Some resistant strains of houseflies have been reported. It also is used as a bait to control scavenger yellowjackets in 11 contiguous Western states.

Dibrom [1,2-dibromo-2,2-dichloroethyl dimethylphosphate; Naled]—A broad-spectrum insecticide for both plant protection and premises use. Not approved for use in grain bins.

Dipterex [*O,O*-dimethyl-2,2,2-trichloro-1-hydroxyethylphosphonate; trichlorofon]—A white, crystalline solid; soluble in water. The material is used in poison baits for controlling flies and for controlling many different species of insects. Its toxicity to warm-blooded animals is reported to be of a low order.

Guthion [*O,O*-dimethyl *S*-(4-oxo-3*H*-1,2,3-benzotriazine-3-methyl) phosphorodithionate; azinphosmethyl]—A crystalline material relatively insoluble in water. It has a wide spectrum of activity as a contact insecticide for the control of insect pests. It is generally more persistent on plants than other commonly used organophosphorus insecticides. The material is employed as a dust or spray.

Although the toxicity of Guthion is somewhat lower than that of parathion, it is in the class of highly toxic materials and must be handled with extreme caution. It is finding wide use for controlling cotton insects, particularly the boll weevil, which has become resistant to chlorinated hydrocarbon insecticides. It is also highly effective for the control of fruit pests such as the plum curculio, codling moth, stink bugs, aphids, and mites. This has proven useful in integrated fruit-pest control.

Malathion—This phosphorus compound, *S*-(1,2-dicarbethoxyethyl)-*O,O*-dimethyldithiophosphate, as produced commercially, is a light-amber liquid, with a sulfur-like odor. It is relatively low in toxicity to most warm-blooded animals and is active against a wide range of insects, although in general it is less effective than parathion or TEPP. The much lower toxicity to warm-blooded animals and rapid loss of residues on plants make it an acceptable insecticide for many uses.

It is used extensively for controlling insects on vegetables, fruits, and cereal and forage crops as well as for controlling insects affecting man and animals. The residues disappear in a few days to 2 weeks, thus permitting application near the harvest period. The compound is available commercially as emulsifiable concentrates, wettable powders, dusts, and for ultra-low-volume spraying. In the US Malathion ULV concentrate is the only grade registered for use on stored grain, recommended for use inside homes, and accepted for use on humans. Over 25 commercial products are marketed in the US that contain this ingredient.

Methyl Parathion—Closely related to parathion, with insecticidal and toxic properties somewhat similar to it. It is employed for controlling mites, aphids, thrips, and other insects, including such pests as the boll weevil. All applications are classified by the EPA as restricted use.

Parathion [*O,O*-diethyl *O*-*p*-nitrophenyl phosphorothioate]—This insecticide is a pale yellow liquid and is highly active against most insects. Its use is restricted because of its high toxicity to humans and animals. Parathion products are available commercially as dusts and as emulsifiable and wettable powder concentrates for mixing sprays. As of December 31, 1991, parathion was voluntarily canceled for use on over 80 crops in the US.

Phorate [*O,O*-diethyl *S*-(ethylthio)methyl phosphorodithioate; Thimet]—A liquid material with an objectionable odor. It is relatively insoluble in water. It is one of the more toxic of the organophosphorus insecticides and must be handled with extreme caution. It is primarily systemic in action and is absorbed readily by the roots of plants when applied to the seeds or when added to the soil. It has had limited use for controlling aphids, spider mites, thrips, leafhoppers, and certain other insects on cotton and sugar beets. It is now classed as an RUP by the EPA.

Phosphamidon [2-chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate]—An organic phosphate, a water-miscible oil, used as a systemic insecticide, with strong stomach action, in small grains, cotton, and other field crops.

CARBAMATE INSECTICIDES

These insecticides, like the organic phosphorus insecticides, inhibit insect cholinesterases. Their mode of action is sufficiently different, however, for them to be considered a separate class of insecticides. The carbamates of interest as insecticides include

Carbaryl [1-naphthyl *N*-methylcarbamate; *Sevin*]—Occurring as crystals, it is slightly soluble in water and highly effective against a wide range of insects, including the *codling moth, Mexican bean beetle, cabbage worms, gypsy moth, boll weevil* and *pink bollworm*. It is not highly effective against most insects of medical importance or against

mites affecting plants. Although the carbamate insecticides are considered to be of moderate to low toxicity to higher animals, carbaryl is highly toxic to the honey bee. It has the greatest range of controlled pests of any insecticide; vegetables, fruits, field crops, ornamentals, and pets. It is classed as a broad-spectrum insecticide.

NEWER METHODS OF INSECT CONTROL

Extensive research continues on new methods of insect control that reduce or avoid the dangers of toxic insecticide residues. Three experimental procedures that illustrate how such control may be achieved are

1. The use of irradiation to destroy the breeding capacity of the insect. Certain insects breed only once, and when the female of such a species is mated with a sterile mate, that female will not produce fertile eggs. Advantage has been taken of this biological fact in controlling the screw worm—a serious pest of cattle in the Southern US. In this operation males are irradiated with controlled doses of radioactive cobalt and then are released in tremendous numbers in the areas to be protected. Preliminary results have been so promising that this procedure is being considered for use against other species of insects with the same biological characteristics.
2. Distribution of the spores of organisms that are pathogenic for certain insect species only. Spores of *Bacillus thuringiensis, Berliner,* var *Kurstaki* have been shown to have value in controlling a small number of insect species and are now commercially available as Bactur, Thuricide, and others. The toxin is referred to as deltaendotoxin. Another is *Bacillus popilliae dutky,* also referred to as Milky Disease Spores.
3. The use of certain of the silica aerogels that act on soft-bodied insects by desiccation. Since the silica aerogels are exceedingly low in toxicity to humans, residues may be insignificant.

Pheromones are potentially important for monitoring insect populations. They are chemical substances produced and released by one sex of an insect (usually the female) that elicit a sexual response in an individual of the opposite sex. The specificity of pheromones makes them valuable for detecting and estimating insect populations before an infestation can enlarge or spread. There are at least 90 different pheromones currently available, eg, the boll weevil *(Grandlure),* coddling moth *(Codlelure),* house fly *(Muscalure),* and Mediterranean fruit fly *(Trimedlure)*.

Insect population suppression also can be achieved by using large numbers of attractant-baited traps (mass-trapping), by disruption of normal communication between sexes *(confusion technique),* and by using a mixture of pheromone and a chemical sterilant.

FUMIGANTS

Fumigants have been, and still are being, used extensively for controlling a wide range of insects. Homes, industrial establishments, ships, and other structures may be fumigated to control household or structural pests. Large amounts of fumigants are employed to control pests in grains and woolens, in soil, and in living plants or plant products such as nursery stock, fruits, and vegetables.

The most common fumigants and their uses are discussed briefly below.

Aluminum Phosphide—A pelletized source of phosphine plus fire retardant. It is used widely in grain fumigation. It is available as *Phostoxin, Alphos, Celphine,* and others.

Carbon Disulfide [CS2]—This is one of the older fumigants. A colorless to slightly yellow liquid with a disagreeable odor. The vapor is about 2.6 times as heavy as air. Its chief disadvantage is its extreme explosiveness. It also is toxic to animals, and lengthy exposure must be avoided. It is not registered for use in fumigating stored beans, cowpeas, or peas. Fumigants are employed most extensively in grain fumigation. *Caution*—It can be toxic on inhalation. It is no longer allowed for home use and is not registered for use in fumigating dry beans, peanuts, or peas.

Chloropicrin, (Trichloronitromethane [CCl_3NO_2])—A colorless liquid that causes intense irritation of the eyes and throat and induces vomiting. It is used chiefly as a *soil fumigant*. It may be injected in the soil in combination with xylene, carbon tetrachloride, or ethylene dichloride to help distribute the gas. It also is used in combination with certain other fumigants for *treating stored products* by sprinkling or spraying the infested materials. Since the gas is only slowly volatilized, thorough airing after use is required. Several products are on the market, eg, *Acquinite*. It is now classed as an RUP by the EPA.

Methyl Bromide (CH_3Br)—A colorless and usually odorless gas at ordinary temperatures, approximately three times as heavy as air. The gas is nonflammable and sometimes is used as a fire extinguisher. It is highly toxic to humans and the absence of odor and slow toxic action are characteristics that increase its hazard. It is among the most widely used fumigants. It destroys a wide range of pests. It is not highly toxic to most plants and leaves no objectionable odor in food. Since the chemical is a gas at ordinary temperatures, it is applied from containers into which it has been compressed as a liquid. It readily vaporizes at temperatures ordinarily encountered in fumigating. It usually is formulated with a small amount of chloropicrin to recognize the presence of this colorless and odorless gas.

Some important uses are for *fumigating warehouses, ships, railroad cars, residences, grains, living plants* shipped under quarantine regulations, *tobacco,* and many other products. The fumigant also is used to destroy *soil pests*. During World War II it was used successfully to *fumigate clothing of refugees and prisoners of war* to control *body lice*. Currently, all applications are classified by the EPA as RUPs. Only the registrant is authorized to refill cylinders.

INSECT REPELLENTS

Repellents are substances used to protect humans, animals, and plants from insects by making the hosts objectionable or unattractive by disguising the characteristic odor of the hosts.

During World War II, troops on many fronts in tropical and semitropical regions employed repellents effectively in the preventive campaign to keep away mosquitos and other annoying and disease-carrying insect pests. The problem here was to use compounds that not only had effective staying and nonirritating properties when applied to the skin of man and animals, but also were without pronounced and penetrating odors that would give the enemy information about patrolling or combat activities and locations of hideouts. During and since World War II more than 10,000 chemicals have been tested for use as insect repellents.

Perhaps the best all-purpose repellent developed since World War II is *diethyltoluamide,* which in various tests has been shown to be the most effective agent against a wide variety of insects.

Repellents, single- or multi-ingredient, generally are compounded in solution, emulsion, cream, or semisolid stick application forms. Most will provide relief from attack from mosquitos, biting flies, and gnats for periods of 30 min to 2 hr or longer.

The volatile oils of citronella, cedarwood, eucalyptus, pennyroyal, bergamot, cassia, clove, wintergreen, and lavender are, to some degree, repellent to mosquitos and other annoying insects but are not nearly as effective as the aforementioned chemicals.

Individuals who are allergic or sensitive to repellents may show various skin reactions, such as burning, itching, and swelling. Most repellents cause smarting when applied to broken skin or mucous membranes, hence care should be exercised when applying them around the eyes or other sensitive areas.

A brief chemical and physical description of the principal repellents follows.

Avitrol [4-Aminopyridine]—An avian repellent. It controls several species of birds, eg, blackbirds, crows, gulls, pigeons, sparrows, starlings, and other birds in and around structures and agriculture (eg, field corn and sunflowers). The odor causes the birds to signal vocal and physical distress that acts as an area repellent to the flock.

***n*-Butyl phthalate [1,2-benzenedicarboxylic acid dibutyl ester; $C_{16}H_{22}O_4$]**—An oily liquid used as an insect repellent for impregnation of clothing.

Diethyltoluamide [*N,N*-diethyl-*m*-toluamide; *N,N*-diethyl-3-methylbenzamide; (*Delphene,* Deet); $C_{12}H_{27}NO$]—A colorless liquid with a faint, pleasant odor; practically insoluble in water, miscible with alcohol. This is a repellent for mosquitos, biting flies, gnats, chiggers, ticks, fleas, and certain other biting insects. Safe for use on human skin.

Ethohexadiol [2-ethyl-1,3-hexanediol; $C_8H_{18}O_2$]—A colorless, oily liquid, odorless or with a slight odor; 1 mL dissolves in about 50 mL water; miscible with alcohol. A common insect repellent used by humans.

Hinder—Ammonium soaps of higher fatty acids. It is used as a deer and rabbit repellent by odor from fruit trees, vegetables, field crops, ornamentals, etc. It is a viscous, brownish, aqueous solution with an ammonia-like odor.

Hot Sauce Animal Repellent—Contains capsaicin, the active irritant principle from hot peppers. It is used on ornamental trees and shrubs, fruit trees, and nursery stock to repel deer, rabbits, and mice.

Methiocarb [3,5-Dimethyl-4-(methylthio)phenyl methylcarbamate]—A nonsystemic insecticide, ascaricide, molluscicide, and bird repellent. It is registered in several US states for bird repellency on blueberries.

Methyl Nonyl Ketone [MGK]—A dog and cat repellent. It is used as a training aid for pets and to prevent damage by stray animals to ornamental plantings.

Thiram [Bis(dimethylthiocarbamoyl)disulfide]—A fungicide, seed protectant, and animal repellent.

CONTROL OF RODENTS

The following compounds are employed commonly to control rodents. They are dangerous and must be handled with caution. Many of the modern rodenticides are now packaged in *bait stations* to minimize larger-animal and human poisonings.

Bromadiolone [3-[3-(4′-bromo[1,1′-biphenyl]-4-yl)-3-hydroxy-1-phenylpropyl]-4-hydroxy-2*H*-1-benzopyran-2-one]—A yellowish powder, rather insoluble, and used in baits or tracking powder for rodent control. It is used in official establishments operating under the federal meat, poultry, shell egg grading, and egg products inspection program. Some applications are classed by the EPA as RUPs.

Brodifacoum—A complex benzopyranone derivative. It is an off-white powder. It is an anticoagulant rodenticide, available in pellets and bait blocks. Single feeding causes death.

Chlorphenacinone *[Rozol]*—An indandione derivative. It is a white crystalline material made in grain bait, water bait, paraffin blocks, and tracking powder. It is registered for use in official establishments operating under the Federal Inspection Program for meat, poultry, shell-egg grading and egg products.

Diphenadione [Diphacinone; 2-diphenylacetyl-1,3-indandione]—The most toxic of the anticoagulants in use at present. While other chemicals in this class usually are used in bait at a concentration of 0.025%, this is effective in 0.005% concentration.

Red Squill *[Dethdiet, Rodine]*—Because of its relative safety for humans, pets, and domestic animals, properly standardized red squill powders and extracts generally were recommended poisons for rats. Red squill contains scilliroside, a cardiac glycoside and strong emetic that causes humans and most species of domestic animals to void the poison promptly. Its specific toxicity is due to the inability of rats to vomit. This allows the absorption of the toxicant. Other animals do vomit, allowing them to survive accidental poisoning. Red squill has never been more than a mediocre rodenticide and is used little in the US today.

Warfarin [*WARF-42, Compound 42;* 3-(α-acetonylbenzyl)-4-hydroxycoumarin]—A chemical relative of dicumarol; it acts by causing loss of clotting power of the blood, and the animals die of exhaustion from multiple hemorrhages. The product was the first successful anticoagulant rodenticide and was unique in that it had to be eaten repeatedly to cause death. For rats, the feeding time is usually 3 to 10 days, and for mice a much longer period of daily feeding is needed. Fantastically low percentages of the poison in food are effective; food baits now on the market contain 0.025 to 0.05%, and concentrates for making solutions of the sodium salt of warfarin containing 0.005% of warfarin equivalent are available. At these levels rats and mice do not detect the material in the baits and will continue to come back to eat or drink until too weak to do so.

Warfarin itself is a highly toxic poison, but the fact that it is needed at such low concentrations in baits and that these must be eaten repeatedly to cause symptoms makes it less likely to injure pets and children than certain other poisons. It has had a good record of safety and is considered one of the less dangerous rat and mouse control materials.

Zinc Phosphide [Zn_3P_2]—A phosphorus preparation that has found a definite place in a specialized rodent control problem in the US. It is blended with a diluent to permit easier use as a dusting powder over cut apples in the preparation of a highly effective orchard mouse bait. Just enough of the perishable bait is made to supply an afternoon's work, and it is placed by uncovering mouse tunnels and making a bait spot of two or three apple sections placed directly in the runway. This is repeated at several points in the trails around each orchard tree, and when properly done is quite effective.

The same zinc phosphide blend can be used on other types of food bait for domestic rat or mouse control. It is dangerous to animals other than rats or mice and should be handled carefully. Some or all applications of several products containing this are classed by the EPA as RUPs.

CONTROL OF FUNGI AND BACTERIA

Fungicides are chemical compounds used to prevent or retard the deleterious action of a varied group of plants called fungi, which for the most part are microscopic, are devoid of green coloring matter, and reproduce by spores.

Fungi are present throughout the world. They attack other living and dead plants, animals, human beings, and such diversified inanimate objects as foodstuffs, cloth, paper, lumber, paint, plastic coverings, and leather, to mention only a few of the substances affected.

Some fungicide materials also are toxic to bacteria, but in general the term is limited to those materials used for protection against fungi. For many years fungicides have been used extensively in agriculture for the protection of crops.

The prevalence of fungi fluctuates with environmental conditions. Early historical and religious writings contain references to the blasting, blighting, rusting, or mildewing of the crops. From the dawn of civilization to the present there has been a constant battle between the agriculturist on one hand and the fungi on the other, with the environmental conditions swinging the balance to one side and then the other.

Prior to 1853 losses resulting from the attacks of fungi were accepted as inevitable, since the true cause was not understood. However, in that year Anton de Bary established the parasitism of the fungi associated with the rust and smut diseases. This discovery, establishing the science of plant pathology, has been followed by an increasing number of investigations into the cause of plant diseases and by the development of a wide variety of materials used for the control of these diseases.

FUNDAMENTAL REQUIREMENTS OF A FUNGICIDE—These materials may be applied in either liquid or powder form. The process of applying substances in liquid form is termed *spraying;* that of applying them in powder form, *dusting*.

Irrespective of the method of application, a fungicide, to be entirely satisfactory, must be

Capable of destroying, controlling, or preventing the growth of the fungus
Relatively noninjurious to the host plant
Easy to apply
Easy to prepare
Reasonable in cost

TYPES OF FUNGICIDAL ACTION—Fungicidal materials are of varied composition, and their exact mode of action against specific organisms is beyond the scope of this discussion. In general, however, all materials fall into two general categories; *protective* and *eradicative*.

In the *protective type* the material does not necessarily kill the fungus spores but does prevent their germination. The various forms of elemental *sulfur* used as spray or dust are protective in their action against the spores of the apple scab fungus *(Venturia inaequalis)* and are used widely by commercial or-

chardists to prevent numerous infections from developing on the apple leaves and fruit. However, the same materials used against certain rust fungi are definitely eradicative in their action upon the rust spores. This diverse effect on different fungi is but one example of the complexity of the problem.

The *eradicative type* of the material kills the fungus and in this way stops the disease either before or soon after initial infection has occurred. The complex *calcium polysulfides* or newer agents like the Captan, Thiram, or Benlate preparations, for example, have a definite eradicative effect on the apple scab fungus. Unfortunately, most of the eradicative materials are rather caustic in their action, and they can be used only under certain conditions, since they are apt to produce injury often more serious in consequence than the disease they are being used to combat. However, whenever it is possible to use an eradicative type of fungicide without serious injury to the plant, this procedure should be adopted, as it produces the most satisfactory control results.

COMMONLY USED FUNGICIDES

It is realized that pharmacists are not expected to have the detailed knowledge of technically trained plant pathologists regarding the use of fungicide materials. However, they are asked frequently for advice, and they should familiarize themselves with directions on pesticide labels and recognize the importance of having their patrons understand and follow the directions; also, they should use the services of state or county extension pathologists when label information is insufficient to deal with specific problems that might arise.

The following list of commonly used materials should enable them to answer intelligently most of the questions with which they are confronted. Requests for information concerning large-scale usage of fungicides should be referred to the state agricultural experiment station, to the USDA, or to the EPA.

Afugan *(Pyrazophos)*—A systemic fungicide used for powdery mildew on apple, cereals, cucumber, grape, melon, ornamentals, pumpkin, squash, strawberry, and watermelon.

Benomyl [Methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate]—A carbamate type of fungicide of broad spectrum, with both protective and curative qualities. It shows local systemic activity within the leaf system and from soil applications where the root system stays within the treated zone. It is registered for use on roses, other ornamentals, turf, stone fruits, melons, beans, cucumbers, grapes, pome fruits, and peanuts. The LD_{50} of a rat oral dose is over 10,000 mg/kg. Avoid contamination of food supplies.

Botran—This tradename and others *(DCNA, Allisan)* refer to *2,6-dichloro-4-nitroaniline,* which was developed in England. This substituted amine is formulated as a yellow, wettable powder used for spraying (75%) and for dipping (50%); it also is used as dust. It generally is used as a soil and foliar fungicide to control *Sclerotinia* mold, *Monilinia* rot, *Rhizopus* rot, and *Sclerotium* and *Botrytus* mold, including storage or transit on vegetables, fruits and ornamentals. It is almost nontoxic to rats but phytotoxic to strawberries, wilted leaf lettuce, asters, petunias and some other greenhouse plants, and some germinating seeds and annual seedlings. It persists on leaf surfaces for 1 to 2 weeks and involves low hazard generally.

Caution—Avoid inhalation of dust and spray mist; occasional cases of contact dermatitis have been reported.

Calcium Hypochlorite [Chloride of lime; bleaching powder]—The activity of this compound as a general disinfectant is based on its ability to release chlorine. Various forms of this are used to sanitize swimming pools. It has fungicidal and bactericidal properties.

Captan [*N*-trichloromethylthio-4-cyclohexene-1,2-dicarboximide]—An organic fungicide used at the rate of 1 to 2 lb/100 gal of water for control of diseases of fruits, vegetables, and ornamental plants. It is excellent for summer spraying of apple trees. It is used extensively on fruits and vegetables and on field and ornamental crops. Do not use with lime or other strong alkali. It is classed as a protectant-eradicant fungicide.

Chloroneb (1,4-dichloro-2,5-dimethoxybenzene)—Used in systemic seed treatment, in-furrow soil treatment, and turf diseases.

Copper 8-Quinolinolate—An organic copper compound (sold under the tradename *Bioquin)* used for the control of *Alternaria* blight, *Botryus* blight, and *powdery mildew* on carnations, chrysanthemums, and roses. It is used as an industrial fungicide for the treatment of wood products.

Copper Sulfate—In addition to being the principal ingredient of Bordeaux mixture, it is the essential component of many commercial copper fungicides. It is a fungicide and algicide.

Diphenyl [biphenyl]—Used as a preservative for citrus in storage and transit. It is used by impregnating citrus fruit wraps.

Dithiocarbamates—This is a mixture of metallic dimethyldithiocarbamates and ethylene bisdithiocarbamate salts. The dithiocarbamates are solids and are insoluble in most common solvents. They decompose under strongly basic or acidic conditions. It is available as an 80% wettable powder and several dusts. Moisture can cause deterioration. It generally is used as blight control on potatoes and tomatoes. It can control apple scab, cedar apple rust, sooty blotch, and fly speck and also is used on ornamentals. It is also useful on certain other vegetables and some field crops. It has no known phytotoxicity and persists on plant surfaces for 10 to 14 days. This agent is compatible with chlorinated hydrocarbons, coppers, sulfurs, and phosphates, except parathion oil sprays. Dinocap or diazinon should be added just before use. It has a low hazard potential; however, some or all applications are classified by the EPA as RUP.

Dodine [*N*-dodecylguanidine acetate; *Melprex, Doquadine*]—A fairly stable fungicide formulated as a 65% wettable powder and a protectant and eradicant fungicide, particularly for apple and pecan scab, cherry leaf spot, sycamore anthracnose, and other tree diseases. It may cause foliage or fruit injury, particularly if applied at freezing or near-freezing temperatures. *Caution*—It may produce eye and skin irritation. If exposed, flush eyes for at least 15 min.

Ferbam—An iron organic compound, *ferric dimethyldithiocarbamate,* used extensively as a substitute for sulfur and copper compounds in the control of fungus diseases of fruit trees. It is employed as a specific for the control of apple cedar rust. In the Pacific Northwest it is used instead of sulfur for the control of pear scab, since it does not russet the fruit. Likewise, it is used for the control of the fungi causing apple scab, apple blotch, and bitter rot, since it reduces the risk of spray injury and at the same time gives satisfactory control of these fungi.

It also is used for the control of tomato anthracnose and is especially effective for the control of anthracnose leaf blight, downy mildew, and fruit rot of cucumbers and melons. It causes less leaf injury than copper compounds on tomatoes, cucumbers, and melons.

Caution—Ferbam is a flammable material and must not be mixed near an open flame. In mixing sprays the operator should avoid inhaling it.

Ferric Dimethyldithiocarbamate—See *Ferbam*.

Folpet [(*N*-trichloromethylthio)phthalimide]—Generally used as a protectant-eradicant fungicide for fruit, vegetables, ornamentals, and turf. It is especially good for black spot of rose. It is slightly more phytotoxic than captan. It is not recommended for apples before the fourth cover spray; it may burn grape leaves in hot, dry seasons and also may injure sweet cherry leaves and snapdragons severely. It has a low health hazard. Concentrated solutions may cause skin irritation. Its use is limited to the Western states.

Krenite [fosamine ammonium]—A plant-growth regulator that stops treated plants from refoliating during the next growing season. It is classed as a brush-control agent.

Lime-Sulfur Solution—A widely used spray material consisting of approximately 30% calcium polysulfides prepared by heating sulfur and lime together with appropriate quantities of water. It has proved specially effective for the control of the apple scab fungus and has been used widely for the control of many other plant diseases. The water dilution for use during the growing season varies. For a long time, it has been used during the winter on peach trees for the combined control of *San Jose scale* and the *leaf curl fungus*.

Since the calcium polysulfides are likely to produce spray injury, it is being replaced by less injurious forms of sulfur and various organic materials in large-scale commercial spraying operations. It also has miticidal activity. It has been supplanted largely by newer synthetic fungicides with a milder action on plants.

Mancozeb—A zinc ion and manganese ethylene bisdithiocarbamate compound. It is a broad-spectrum fungicide used on vegetables, fruits, turf, and ornamentals for leafspot, early and late blight, crown rot, damping off, anthracnose, and others. It is one of the most commonly used vegetable fungicides.

Maneb [manganese ethylenebisdithiocarbamate; *Manzate, Dithane M-22, Chem-Neb*]—The manganese salt of dithiocarbamic acid is used for the control of potato, tomato, celery, carrots, and onion diseases. It also has been used to control grape black rot and is used on many fruits and vegetables. It is currently an important fungicide.

Mercaptobenzothiazole *[Niacides]*—Used on apples as a plant fungicide by pesticide formulators in their products.

Nabam [Disodium ethylenebis[dithiocarbamate]—For industrial applications only; not for food crops. It is an algicide in rice.

Pentachloronitrobenzene *[PCNB, Terraclor]*—A nitrobenzene compound used as a soil fungicide effective against many soil pathogens that attack vegetables, turf, and ornamentals. It also is used as foliar spray on young lettuce, cabbage, and cauliflower as well as on fruit trees.

Sulfur—For a long time one of the standard fungicide materials and still used widely to control a wide variety of plant diseases. It is sold as a dry powder ground to varying degrees of fineness, as a paste, or fused with clay (bentonite) and subsequently ground. Many special brands are available, and each manufacturer claims special virtues for his particular product. They all depend for their effectiveness on its inherent toxic property in affecting the growth processes of various fungi. The directions on the packages are a guide to their use. It is one of the cheapest fungicide materials and probably will continue to be used extensively as spray or dust for many years to come.

Combined with lime and water and heated for a considerable period, it forms complex *polysulfides*. This reaction product, called lime-sulfur, was described above under *Lime-Sulfur Solution*. If it is added to slaking stone lime and the only heat supplied is that of the stone lime combining with water, another type of spray called *self-boiled lime-sulfur* results. Properly prepared self-boiled lime-sulfur has a very low calcium polysulfide content and produces very little injury; it can be used with safety on peaches during the growing season, whereas lime-sulfur used at that time would cause excessive injury to the trees.

Yellow Cuprous Oxide—This material, containing 47% metallic copper, is sold under the tradename *Yellow Cuprocide* and may be used as a spray or dust. It is effective against celery blight, *Alternaria* blight of tomato, early and late blights of potato, anthracnose, downy mildew, and other leaf diseases of cucurbits, and is recommended for a variety of vegetable crops whenever a copper spray is needed.

Zineb *[Zinc ethylenebisdithiocarbamate]*—Exceptionally effective in the control of potato and tomato late blight in Florida. It has not been much superior to copper compounds in the more northern tomato-growing sections. It is less injurious to the tomato and potato plants than copper compounds, a factor of considerable importance in the South where numerous spray applications are required during the long growing season.

It also has been used on cucumbers, muskmelons, and watermelons for downy mildew and anthracnose control, especially in Florida. The lack of injury on these plants is a specially valuable feature of this compound, since cucumbers and melons are extremely susceptible to copper injury. For the same reason this compound has proved of value for the control of cabbage and cauliflower diseases and also has many uses on fruits. It sometimes is used to control fire blight on apple and pear trees. It also has been applied as a dust containing 8 to 10% of the fungicide.

Ziram *[Zinc dimethyldithiocarbamate]*—A white powder that does not leave an objectionable residue. It has found extensive use in the control of vegetable diseases (celery leaf blight, downy mildew of cucurbits, bean anthracnose, cabbage downy mildew, and squash black rot). It also has been used for peach brown rot control but is apt to produce leaf injury and fruit russet when used on apples, sour cherries, pears, and several other fruits. It is not an effective material for the control of potato or tomato late blight.

Relatively crude, denatured forms of streptomycin and oxytetracycline are being used to control many bacterial diseases of plants. Cycloheximide is used to control cherry leaf spot and dollar spot of turf.

ANTIBIOTICS

Streptomycin—Marketed as the sulfate or nitrate under the tradenames *Agri-Mycin 17* and *Phytomycin*. It is formulated as a dry, wettable powder (sulfate) and liquid (nitrate). Its salts are very soluble in water. It has general use as an antibacterial against fire blight of apples and pears and similar infections on ornamentals, including woody and herbaceous plants. It persists on plant surfaces for up to 4 months but is considered of low general toxicity. It can produce allergenic reactions such as rashes, conjunctivitis, and bronchial asthma. This agent should not be applied following Bordeaux mixture, and it is incompatible with lime-sulfur, pyrethrane, and aldrin.

Other animal and plant diseases can be controlled with aureomycin and terramycin.

CONTROL OF WEEDS AND PLANTS

Approximately $7.5 billion/year is spent in the US on agricultural pesticides. Herbicides account for about two-thirds of the agricultural expenditures for pesticides. Since 1990 herbicide use has remained relatively stable at 325 to 350 million pounds of active ingredient. High-activity compounds based on new chemistry have been developed that permit significantly lower application rates, employing new modes of action and lower environmental hazards.

Many herbicides are used for weed control, and others are being evaluated experimentally to determine their usefulness. Only those of current general interest and usefulness are described below.

Available information on the degree of toxicity of herbicides is listed in the descriptions of chemicals used for weed control. The symbol LD_{50} (lethal dose that kills 50% of the experimental animals) precedes each number that indicates relative oral toxicity. For example, the single acute oral dose for calcium cyanamide, LD_{50} = 1400 mg/kg, indicates a relatively low oral toxicity. The larger the LD_{50} number, the less poisonous the herbicide.

All LD values listed in this guide are based on a single dose of material orally administered to animals, followed by observation of the treated animals for a definite period of time. However, these findings do not indicate the possible hazards that may arise from skin contact or inhalation of the substance or substances indicated. Likewise, these data do not accurately predict the toxicity of a formulation that may differ depending on the solvent or diluent employed.

Herbicides are materials used mainly for the control of weeds and are used in five general ways:

Preplanting, which means that the herbicides are applied after the soil has been prepared but before seeding of the desired plant.

Preemergence or *contract,* which means that nonresidual dosages of herbicide are used after seeding but before emergence of the crop seedlings.

Preemergence or *residual,* which means that the herbicide is applied at the time of seedling or just prior to crop emergence, so that it kills weed seeds and germinating seedlings.

Postemergence, which refers to herbicide application after emergence of a crop.

Sterilant or *nonselective,* which means that sufficient herbicide is used to effect a complete kill of all treated plant life.

INORGANIC HERBICIDES. The major examples in this class are ammonium sulfamate and copper sulfate.

Copper Sulfate (Pentahydrate) [Basicap]—A blue, water-soluble crystalline material, widely used as a fungicide. However, it is used also as a herbicide, specifically for the control of algae and pond weeds in impounded potable waters. It also is used in irrigation water conveyance systems, root control in sewers, and in rice patties to control algae. *Signal Word:* Danger. *Toxicity Class:* I. *Toxicity:* Acute oral LD_{50}, 470 mg/kg; 1 mg/m^3 for all copper dusts or mists. Toxic to fish.

Antidote/Treatment: See a physician. May be corrosive to mucous membranes, eyes, skin, and gastrointestinal (GI) tract if swallowed. For oral poisoning, give two glasses of milk of magnesia, water, or milk to dilute the chemical, then induce vomiting. This should be repeated until vomitus is clear. *Handling and Storage Cautions:* Avoid direct contact. Do not use excessive amounts in ponds, streams, or lakes as a herbicide. Protective equipment and clothing should be worn during handling. *Formulation:* Numerous crystal forms and sizes, solutions, and powders are available from several manufacturers.

PETROLEUM OILS (90-PAR, VOLCK OILS, WHITE OILS, REFINED GRADES). These long have been used as insecticides, insecticide solvents, and insecticide adjuvants to increase their efficacy. Some are used as herbicides by themselves. They are applied as contact herbicides, being used for general or selective weed control. Petroleum products used as herbicides include Stoddart solvent (petroleum distillate between gasoline and kerosene, known also as mineral spirits) and diesel oil. These should be used with caution and are placed in *Toxicity Class III*. Various physical and chemical properties of the oils are important in determining their final use, eg, sulfonation percentage (indicates degree of refinement), volability, density, and viscosity.

ORGANIC ARSENICALS. This group includes monosodium methanearsonate (MSMA), disodium methanearsonate (DSMA), and cacodylic acid.

Cacodylic Acid [Hydroxydimethylarsine oxide; dimethylarsinic acid]—A nonselective herbicide, cotton defoliant, and silvicide (tree killer) for forestry use. *Toxicity Class:* III; use with caution. *Toxicity:* Acute oral LD_{50} (rat), 700 mg/kg. It also is used in a number of combination products.

Disodium Methanearsonate (DSMA)—Marketed under a variety of tradenames (eg, *Ansor DSMA Liquid, Arsinyl*) and used as a selective postemergence herbicide for cotton and as a directed spray on weeds such as Johnson grass, cocklebur, dallisgrass, watergrass, nutgrass, and goosegrass, particularly in noncrop areas. *Toxicity and Caution:* Similar to MSMA.

Monosodium Methanearsonate (MSMA) *[Ansar, Arsonate Liquid]*—A white, crystalline solid (mp, 132 to 139°C). It is a herbicide used for postemergent control of Johnson grass and other grassy weeds along the banks of ditches, storage yards, rights-of-way, and other noncrop locations; preplant in cotton; bearing citrus (except in Florida); nonbearing orchards; and crabgrass and certain broadleaf control in turf; and as a tree killer. *Toxicity Class:* III; it should be used with caution. *Toxicity:* Acute oral LD_{50} (rat), 700 mg/kg; Arsonate Liquid (51% MSMA); acute oral LD_{50} (rat) 1738 mg/kg; acute dermal LD_{50} (rabbit) 2500 mg/kg; acute inhalation LD_{50} (rat) 20 mg/L. It is mildy irritating to skin and eyes (rabbit). *Antidote/Treatment:* If swallowed, induce vomiting; drink lots of water.

PHENOXY-ALIPHATIC ACIDS. This group incudes many so-called plant hormones and related substances such as 2,4-D, 2,4-DB and MCPA.

2,4-D [(2,4-dichlorophenoxy) acetic acid; *Weed-B-Gon*]—Selective herbicide whose application is for grasses, wheat, barley, oats, sorghum, corn, sugarcane, and rice (Philippines) and noncrop areas for postemergent control of weeds such as Canada thistle, dandelion, annual mustards, ragweed, and lambs-quarters. Certain formulations are registered for pine release, water hyacinth control, and prevention of seed formation, and others for control of wild radish and other broadleaf weeds in cereals. For specific cautions, see the labels of different formulations. The dimethylamine salt form: *Toxicity Class:* I (eyes); EC:III (oral). *Toxicity:* Acute LD_{50} (rat), 375 mg/kg, 700 mg/kg (isopropyl); 666 to 805 mg/kg (sodium salts). At the usual application rates (usually quite dilute), it has no adverse effect on soil microorganisms. Since this compound is active at low concentrations, spray equipment contaminated with it must be cleaned scrupulously before use for any other material. Avoid contamination in irrigation water. When using its preparations, plastic gloves, goggles, aprons, and dust masks are recommended. There are hundreds of commercial formulations and combinations of this agent on the market.

SUBSTITUTED AMINES. The substituted amine herbicides include alachlor, naptalam and propanil.

Alachlor [Chimichlor; 2-chloro-2′,6′-diethyl-*N*-(methoxymethyl) acetanilide]—A preemergence herbicide used to control most annual grasses and certain broadleaf weeds in corn, dry beans, peanuts, and soybeans. Leaves no carryovers residue in soil.

Naptalam [sodium 2-[(1-naphthalenylamino)carbonyl]benzoate]—A herbicide for numerous broadleaf weeds on cucurbits and nursery stock.

Propanil [Prop Job; *N*-(3,4-dichlorophenyl)propionamide]—A postemergence, contact-type herbicide with no residual effect against numerous grasses and broad-leaved weeds in rice.

NITROANILINES. These herbicides include benefin and triflaralin.

Benefin [Benfluralin, *N*-Butyl-*N*-ethyl-α,α,α,-trifluoro-2,6-dinitro-*p*-toluidine; Balan, Quilan]—Selective preemergence herbicides to control annual grasses and broadleaf weeds in seeded alfalfa, direct-seeded lettuce, peanuts, tobacco, and established turf. It may be applied and soil incorporated as much as 10 weeks prior to planting; however, it will not control established weeds. The caution signal word varies with the formulation used. *Toxicity:* Acute oral LD_{50} (rat): over 10,000 mg/kg.

The pure compound is a yellow-orange, crystallline solid that is readily soluble in organic solvents. It has a flashpoint of 25.5° (78°F). These characteristics dictate caution in handling and storage. It should not be frozen, or stored above 4.5° (40°F), particularly near heat or open flame. It is corrosive and has caused severe eye irritation in lab animals. Certain individuals may show skin-sensitization reactions to it. It can be harmful if swallowed, inhaled, or absorbed through the skin. In case of contact, the eyes and skin should be flushed immediately with plenty of water. Protective clothing is recommended during usage. Several formulations and combination products are marketed.

SUBSTITUTED UREAS. These herbicides include baturon, diuron, linuron, and monuron.

Diuron; 3-(3,4-Dichlorophenyl)-1,1-dimethylurea; *N*′-(3,4-dichlorophenyl)-*N*,*N*-dimethylurea; *Cekiuron, Unidron*]—Used at low rates as a selective herbicide to control germinating broadleaf grass weeds in numerous crops such as sugarcane, pineapple, alfalfa, grapes, cotton, and peppermint. At higher rates of application it can be used as a general weed killer. As a soil sterilant, it is more persistent and preferred over monuron on lighter soil and/or in areas of heavy rainfall. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (rat), 3400 mg/kg. *Handling and Storage Cautions:* Similar to those for other herbicides. It is used commonly as a flowable, wettable powder in formulations, and numerous combination products exist.

CARBAMATES

Propham [Isopropyl carbanilate; IPC]—Used primarily as a preemergence and postemergence herbicide. It prevents cell division and acts on meristematic tissue. Major uses include control of weeds in alfalfa, ladino clover, flax, lettuce, safflower, lentils, and peas and on fallow land. *Toxicity Class:* III. *Toxicity:* Generally low toxicity to wildlife and fish; acute oral LD_{50} (rat), 5000 mg/kg. It is available in flowable suspensions, wettable powders, and various combination products.

THIOCARBAMATES. These include pebulate, diallate, and EPTC (*S*-Ethyldipropylthiocarbamate; Alirox).

Pebulate [*S*-Propyl butylethylthiocarbamate; R-2061]—A preplant selective herbicide for the control of both grassy and broadleaf weeds. It has been used for selective weed control in sugar beets, tobacco, and tomatoes. The signal word is *caution*. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (rat), 921 to 1900 mg/kg; acute dermal LD_{50} (rabbit) >4640 mg/kg. Formulations include emulsifiable concentrate (6 lb/gal) and granules (10%).

HETEROCYCLIC NITROGEN COMPOUNDS. These herbicides include amitrole, pyrazon, and picloram.

Amitrole [1*H*-1,2,4-triazol-3-amine; *Amerol, Simazol*]—Used mainly as a nonselective systemic herbicide for control of annual grasses, broadleaf weeds, perennial broadleaf weeds, poison ivy, and certain aquatic weeds in marshes and drainage ditches. All applications are classified by the EPA as restricted use. It is restricted to noncropland use. The signal word is caution. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (male albino rat), up to 10,000 mg/kg caused no death or symptoms of systemic activity. It has an indefinite shelf-life and should be stored at room temperature. It is available in liquid and solid powder formulations as well as pressurized-container products. Numerous combination products are also available.

TRIAZINES. These herbicides include atrazine, simazine, propazine, prometone, and cyanazine. The EPA currently is conducting a special review of triazine herbicides. In 1995 the manufacturers of cyanazine voluntarily withdrew its registration rather than proceed with the special review. Cyanazine, which is identified as a carcinogenic material, is the third most-used herbicide on corn and cotton and is commonly used on sorghum and other crops to control grasses and broadleaf weeds. The manufacturer agreed to stop selling products containing cyanazine in 1999.

Atrazine [2-Chloro-4-ethylamino-6-isopropylamino-1,3,5 triazine]—A selective herbicide used in season-long weed control in corn, sorghum, and certain other crops. It also is used at higher rates of application for nonselective weed control in noncropped areas. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (rat), 1780 mg/kg. It is listed as harmful if swallowed, and contact with eyes and skin should be avoided. Another caution listing states "do not contaminate food, feed or water supplies with the product." The shelf-life is given as 3 years under environmental conditions, provided that the product is stored in its unopened and undamaged original containers, in shaded, possibly well-aired, fresh, and dry storehouse conditions and kept away from sources of heat, free flames, or spark-generating equipment. Formulations include dry flowable powders, flowable liquids, and wettable powders. Numerous combination products are on the market.

URACILS. These herbicides are bromacil and terbacil.

Bromacil [5-Bromo-3-*sec*-butyl-6-methyluracil]—A weed and brush herbicide in noncrop areas, especially for perennial grasses. It also has been used in selective weed control in pineapple and citrus growing. The dry formulations are water-soluble. *Toxicity Class:* III (dry); II (liquid). *Toxicity:* Acute oral LD_{50} (rat), 5200 mg/kg. *Handling and Storage Cautions:* There are several because of its irritant and combustible qualities. Protective clothing is advised for proper handling. The formulations include granular powder, liquid, water-soluble liquid, and wettable powder. Several combination products are available, particularly with various contact and hormone weed killers.

ALIPHATIC ACIDS. These herbicides include *dalapon* and *TCA* (trichloroacetic acid).

Dalapon [2,2-Dichloropropionic acid]—A selective herbicide and growth regulator used for quackgrass, bermudagrass and other perennial and annual grasses as well as cattails and rushes. This herbicide is used commonly as a preplant treatment to control established perennial grasses in cropland, noncropland areas, and irrigation ditch banks in 17 Western states. It acts by being translocated to the roots of most species, where it acts as a growth regulator. *Toxicity Class:* II. *Toxicity:* Acute oral LD_{50} (female rats), 970 mg/kg (tech ai); 7570 mg/kg (sodium salt). The acid is not used directly, and commercial products usually contain 85% sodium salt or mixed sodium and magnesium salts. *Handling and Storage Cautions:* There are several, including the avoidance of skin and eye contact because of irritancy and the avoidance of contamination of water, food, or feed through storage or disposal. It is formulated mainly as a water-soluble powder and in several combination products.

ARYLALIPHATIC ACIDS. The herbicides that belong to this class include dicamba, fenac, 2,3,6-TBA (trichlorobenzoic acid) and DCPA (Dacthal; dimethyl tetrachloroterephthalate).

Dicamba [2-Methoxy-3,6-dichlorobenzoic acid; 3,6-dichloro-*o*-anisic acid]—A herbicide. *Toxicity Class:* II. *Toxicity:* Acute oral LD_{50} (rat), 1707 mg/kg; acute dermal LD_{50} (rabbit), 2000 mg/kg. Formulations of a flowable liquid potassium product (Marksman) and the dimethylamine salt (4 lb/gal) are available. Several combination products are marketed.

PHENOL DERIVATIVES

DNOC [4,6-Dinitro-*o*-cresol; 2-methyl-4,6-dinitrophenol]—Insecticide, fungicide, herbicide, and defoliant properties. It has use as a dormant spray for killing insect eggs and in apple scab control. The triethanolamine salt has promise as a complete dormant apple spray for light infestations of mite and aphid eggs as well as other pests. The sodium salt has been used as a weed killer and on apple and peach trees to thin fruit. The signal word is *Danger. Caution:* Very phytotoxic. *Toxicity Class:* III; I. *Toxicity:* Acute oral LD_{50} (rat), 20 to 50 mg/kg. It should be stored in cool, well-ventilated areas away from heat and foodstuffs. Formulations include the ammonium salt (50%), flakes (98 to 100% free acid), and a flowable, wettable powder.

SUBSTITUTED NITRILES. These herbicides include dichlobenil and bromoxynil.

Dichlobenil [2,6-Dichlorobenzonitrile; Casoron]—For selective weed control in cranberry bogs, ornamentals, nurseries, fruit orchards, vineyards, forest plantations, and public green areas and for total weed control (such as industrial sites, railway lines, etc, under asphalt). It also is used to control aquatic weeds in nonflowing water. It has been recommended for selective weed control in woody perennial crops and for total weed control on industrial sites, car parks, roadsides, railways, and related areas. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (rat), 3160 mg/kg; acute dermal LD_{50} (rabbit), 1350 mg/kg. It is toxic to germinating seeds. It should not be stored with propagative structures such as seeds, bulbs, tubers, or nursery stock or with food or feed products. It is available as granules and wettable powder and in several combinations.

BIPYRIDYLIUMS. These herbicides include diquat and paraquat.

Paraquat [1,1′-Dimethyl-4,4′-bipyridinium ion (present as the dichloride salt); Herboxone]—A contact herbicide used in the desiccation of seed crops and for noncrop and industrial weed control in bearing and nonbearing fruit orchards, shade trees, and ornamentals. Other uses include defoliation and desiccation of cotton; a harvest aid in soybeans, sugarcane, sunflowers; pasture renovation; and eradication of weeds in coffee plantations and similar situations. Some or all applications may be classified by the EPA as RUP. The signal words are *danger* and *poison*. *Toxicity Class:* I. *Toxicity:* Acute oral LD_{50} (rat), 150 mg ion/kg. It can kill if swallowed. Use only with protective clothing, and wash thoroughly after using. Various formulations include soluble dichloride concentrate and various liquid and granular forms. Several combination products are available.

MISCELLANEOUS HERBICIDES. Herbicides in this miscellaneous group include endothall and bensulide.

Endothall [7-Oxabicyclo [2.2.1] heptane-2,3-dicarboxylic acid]; Accelerate]—A pre- and postemergence herbicide, defoliant, desiccant, aquatic algicide and growth regulator. *Toxicity Class:* I. *Toxicity:* Acute oral LD_{50} (rat), 51 mg/kg.

Bensulide [*S*-(*O,O*-Diisopropyl phosphorodithioate) ester of *N*-(2-mercaptoethyl)benzenesulfonamide; Bensumec, Exporsan, Prefar]—For preemergence control of annual grasses and crop use in carrots, cucumbers, peppers, and tomatoes, among others. *Toxicity Class:* III. *Toxicity:* Acute oral LD_{50} (rat), 271 to 1470 mg/kg. Various formulations and combination products exist.

PLANT REGULATORS

A plant-growth regulator is a preparation that in minute amounts alters the behavior of ornamental or crop plants or the products thereof through physiological (hormone) action rather than physical action. It may act to accelerate or retard growth, prolong or break a dormant condition, promote rooting, or act in other ways. A classification of plant-growth regulators usually includes auxins—2,4-D, MCPB, BNOA; gibberillins; cytokinins—kinetin; ethylene generators—ethylene ethephon; inhibitors—benzoic acid, MH; and retardants—A-Rest.

Gibberellic acid is used extensively on seeds to aid in uniform germination and growth and on grapes to increase size. 2-Methyl-4-chlorophenoxyacetic acid (MCPA) and a number of related chemicals are used to thin blossoms, stop the premature drop of fruits or vegetables before harvest, increase the uniformity of ripening, and a wide variety of other purposes. For example, when applied properly, 2,4-D will increase the red color in potatoes, and other chemicals will produce pineapples of more uniform shape than untreated ones. This field of chemical usage is expanding and appears to have a future limited only by the necessity to prove that the uses are safe, from both the toxicological and nutritional viewpoints. Also, 2,4-D is used on tomatoes to cause all fruits to ripen at the same time for machine harvesting.

The identification of vegetable-growth inhibitors may yield improved storage methods for crops. Growth inhibitors for onions and cabbage have been identified, but further studies are necessary to determine their ultimate value. Other growth regulators of potential value include

Ethrel [2-Chloroethylphosphonic acid], which functions by releasing ethylene in plant tissues; it can increase appearance of fruit on pineapple.

Captan [*N*-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide], which is registered for use in increasing the fruit set of both oranges and tangelos.

Ripenthol, which contains endothall (7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid) and can delay sucrose breakdown in mature sugarcane, giving planters a longer harvest period; this has increased yields of sugar in sugarcane.

DESICCANTS AND DEFOLIANTS

Desiccants and defoliants become increasingly important as mechanical harvesting gains popularity. In the same way that removal of weeds by use of herbicides just before the combines are put into the fields to harvest wheat prevents clogging of the machines with weed debris, the removal of cotton leaves by chemical treatment aids mechanical harvesting of cotton and other leafy crops. Arsenic acid, pentachlorophenol, and more complex chemicals such as *S,S,S*-tributylphosphorotrithionate and *S,S,S*-tributylphosphorotrithioite and others are being used for this purpose. Requests for information concerning developments in this field should be addressed to the USDA, state experiment stations, or manufacturers of specific products. Questions on the legal status of pesticides should be sent to Director, Pesticides Regulation Div, Environmental Protection Agency (EPA), Washington, DC 20460.

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PART **8**

Pharmacy Practice

Nicholas G Popovich, PhD
Professor and Head
Department of Pharmacy Administration
University of Illinois at Chicago
College of Pharmacy
Chicago, IL

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PART **8A**

Fundamentals of Pharmacy Practice

Nicholas G Popovich, PhD
Professor and Head
Department of Pharmacy Administration
University of Illinois at Chicago
College of Pharmacy
Chicago, IL

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CHAPTER 94

Application of Ethical Principles to Practice Dilemmas

Amy Marie Haddad, PhD

The growing sophistication and complexity of contemporary health care practice presents many ethical challenges including: protecting privacy and confidentiality in an environment of easily accessible information and perplexing regulations, maternal-fetal conflicts, threats to the rights of human subjects in research, genetic engineering and screening, and delivery of treatment and services in a highly fragmented system to name only some of the more problematic issues. As pharmacy practice becomes more complex and increasingly patient-oriented, pharmacists have to deal with the aforementioned broader ethical issues shared by all health professionals and those unique to or more commonly encountered in pharmacy practice. New and difficult questions face pharmacists. Is it ever right to use controversial drugs such as cannabis or heroin in treating terminally ill patients? How does one reduce or eradicate the undertreatment of pain? Whose responsibility is it to manage an impaired colleague? What is the best system to lower the number of medication errors? When, if ever, should a pharmacist participate in assisted suicide? How will changing state and federal laws and new court decisions impact the delivery and quality of pharmaceutical care?

"Because ethical dilemmas are commonplace in pharmacy practice, pharmacists must develop a working knowledge of formal and systematic ethical analysis, as well as learn to distinguish ethical issues from social, psychological, political, and legal issues."[1] Moreover, the difficulty of the ethical issues mentioned thus far suggests that a collaborative approach to resolving them would be preferable to individuals struggling alone. Pharmacists must be able to work with others on the health care team to find a justifiable resolution. To collaborate with others and work effectively, there must be a systematic approach to working through an ethical dilemma. The purpose of this chapter is to define applied ethics and its application to pharmacy practice with emphasis on the use of normative models of ethical decision-making to resolve practice dilemmas. A process for ethical decision-making is explained and applied to clinical cases that refer to issues encountered on an individual, institutional, and societal level. Resources to help in the resolution of ethical dilemmas are also noted.

APPLIED ETHICS AND HEALTH CARE

The application of the ideas and concepts of ethics to issues in health care began in the late 1960s with questions about the allocation of the new technologies of hemodialysis, vital organ transplantation, and the treatment of human research subjects. Normative ethics is that branch of ethical inquiry that considers ethical questions whose answers have a relatively direct bearing on practice.[2] The results of such ethical inquiry have immediate application for actions or policies. Hence, the term "applied" ethics, in this case is applied to pharmacy practice. To arrive at a clearer understanding of ethics in general, it helps to have a baseline of key terms. Three terms underlie all the discussion in this chapter: (1) ethics, (2) values, and (3) dilemmas.

Ethics

Ethics is a careful, systematic inquiry into the nature of morality, guidelines, or standards that give meaning and direction to the human community. Simply put, ethics is the study of good and evil, of right and wrong. But, ethics is much more than that. Ethics is concerned with the duties and obligations one has to others and to him- or herself. Ethics is also concerned with the rights of individuals and how those rights are recognized and respected. The systematic nature of ethics helps illuminate what one ought to do, who one should be as a human being, and what and whom one should nurture and sustain in life.

Values

Values are an important part of ethics. One uses values to help explain how and why things are important to us. "Values are not to be confused with concrete goods. They are ideas, images, and notions. Values attract us. One aspires after the good they articulate. One expects to find our own good in relation to what they offer."[3] When one looks at the goodness or badness of an action, one must also look at the values attached to the action. Values are the internal motivators for our actions. Evidence of values is observed in human behavior. True values elicit deeply held positive or negative attachments. Basic values and a value system are developed in childhood and result from such influencing factors as family, teachers, friends, religious traditions, and culture. People of different religious faiths or of no faith ascribe to many values and principles one acts upon on a daily basis. Values also have their roots in professions. Some traditional values of the pharmacy profession are compassion, faithfulness, and fairness. With the introduction of pharmaceutical care as a standard for pharmacy practice, the values of patience, responsiveness, and kindness have been added to the list of traditional values.[4]

Usually, values remain unchanged after one reaches adulthood unless they are challenged by great spiritual or emotional distress. Of course, values can also change when it becomes apparent that an old value system doesn't work anymore. Whatever their origin or evolution, the resulting personal and professional values can profoundly affect the ethical decisions that pharmacists make.

Dilemmas

An individual has a dilemma when, wanting to make a good choice realizes that no matter what is done, a choice will result in loss or harm. Simply put, a dilemma is choosing among equally unappealing alternatives. "A difficult problem becomes a 'dilemma' when one is quite sure that one will be making a big mistake regardless of what path one choose. It is instructive to consider moral dilemmas in this context. The anxiety one experiences as one faces each unpalatable alternative informs us about the nature of moral dilemmas. It seems that any decision one makes will violate one or another value which one holds dear."[5] In particular, moral dilemmas in pharmacy can arise in several ways. They can arise when the right thing to do, such as telling the truth, conflicts with obligations like loyalty to a peer or protecting the patient from harm. They can also arise when what is best for the patient runs counter to patient self-determination or one's own well being–one's health, obligations to family or one's employer, and so on. To resolve a dilemma effectively, one must have a method for reviewing the facts, generating alternatives, and choosing the "best" alternative given the circumstances of the dilemma.

A PROCESS FOR APPROACHING AND RESOLVING ETHICAL DILEMMAS

A method to resolve ethical dilemmas should closely resemble the methods of work-up for drug-related or medical problems. In both cases, the pharmacist needs to know how to collect information, analyze it, and use the findings in ways compatible with standards of pharmacy practice. For example, when a patient asks the pharmacist for help in treating a rash that covers his arms and trunk, the pharmacist begins the assessment process with a careful history including questions about medications, dietary changes, allergies, what treatments have been tried, what has worked, and use of new products such as lotion or laundry detergents. Depending on the clinical setting, the pharmacist may conduct a physical inspection of the rash noting its appearance. When the collected data are analyzed, a clinical judgment designed to best help the patient is made. In resolving ethical dilemmas, a similar stepwise process is followed.

The following is a suggestion for such an approach that takes into account the impact of the decision on the patient, family, and health care team. There are five steps in this proposed model. The five steps are (1) gather clinical and situational information; (2) identify values of the people involved and legal implications; (3) identify the ethical problem or problems in terms of principles; (4) seek a justifiable resolution; (5) anticipate arguments to the proposed resolution and respond.[6] By following the stepwise process, one is able to recognize and remedy faulty thinking, avoid simplistic decisions or snap judgments, clarify conflicts between values and principles, explain *why* a choice is right or wrong, and guide us to the right choice in ambiguous or confusing situations.

Gather Clinical and Situational Information

Clinical facts include diagnosis, prognosis, what treatments, including drugs have been attempted, the success or failure of such treatments, and other pertinent data that would affect a decision. Once the clinical facts are clearly outlined, one can then look at the specific context of those facts.

Situational or contextual facts include information about the individuals involved in the case, their relationships, as well as their authority and stake in the outcome. The context of an ethical problem has direct bearing on how the problem is perceived and what resolutions are possible. For example, two patients may share the same diagnoses and prognoses but differ greatly in their cultural backgrounds, religious beliefs, or where they live any of which can impact ethical choices.

Identify Values

It is important to gather information about the values that the individuals involved in a case have. These include values toward quality of life, honesty and responsibility to others, among others. By identifying basic values, it is easier to determine the nature of the conflict in the case. Because patients' wishes generally take priority over other parties, their beliefs, wishes and values should be considered first. Also, it is important to ascertain the validity of the information on which a patient bases his or her values. If the patient doesn't have sound clinical information, that information should be provided in clear, understandable terms. Sometimes, merely by clarifying values and correcting misinformation, an ethical problem can be resolved or avoided entirely.

Identify the Ethical Problem

Most problematic situations in pharmacy practice contain more than one ethical problem. Often there is a conflict between two moral goods, such as the pharmacist's duty to do good for the patient by providing appropriate drug therapy and counseling and the patient's right to self-determination that can result in noncompliance. The four principles approach to biomedical ethics proposed by Beauchamp and Childress, provides a comprehensive framework for ethical analysis.[7] Besides the four basic principles of respect for autonomy (self-determination or freedom of choice), nonmaleficence (the duty not to harm), beneficence (the duty to do good), and justice, the derivative principles of truth telling, fidelity, and avoidance of killing are also addressed as they all play a central role in health care.

AUTONOMY, SELF-DETERMINATION AND FREEDOM OF CHOICE—Respect for persons and an individual's autonomy are foundational principles in most ethical traditions. The principle of respect for autonomy states that human beings have a moral dignity that should be respected. And, individuals should be able to exercise freedom in decisions that affect their lives with undue interference from others. To make sound decisions about one's life plans, one needs good information. So the doctrine of informed consent is derived from the basic principle of respect of autonomy. Pharmacists address the issue of autonomy when they contemplate whether to advise a patient that he or she needs additional medical attention for his or her condition in the case of an inappropriate prescription.

BENEFICENCE AND NONMALEFICENCE—Because pharmacists are in professional practice to care for others, it is almost automatic in the provision of care to assume the principle of beneficence, that is, to help or assist patients. A closely related principle is nonmaleficence, which requires the avoidance of harm in all cases. Specifically, the principle of beneficence applies to actions in pharmacy practice that prevent harm, remove harm, and the provision of benefit. In the delivery of pharmaceutical care, beneficence requires respect for the wishes and choices of patients and their families. Moreover, the principle of nonmaleficence requires that pharmacists deliver safe and quality care. For example, when a pharmacist is confronted with a prescription that will not be harmful but probably will not help the patient, he or she is dealing with weighing the benefits and harms of therapy.

JUSTICE—The principle of justice addresses the fair distribution of burdens and benefits. Allocating health care resources is an increasing problem in all areas of health care delivery. Pharmacy practice is no exception and perhaps one of the most problematic areas of health care because of the high cost of drug products. Pharmacists not only deal with the societal issue of fair drug costs, but with the more personal, direct meanings of justice, for example, whether to treat patients differently depending on their ability to pay.

Justice embodies the ethical ideal of fairness. Implicit in the idea of fairness is the conflict between interests to which the ethical principle provides resolution. Justice gives us the rules and standards by which to mediate these claims that

human beings make against each other on a daily basis. Justice requires that the pharmacist examine the fairness with which care is delivered in relationship to other competing demands. Consider this scenario, three patients arrive at a pharmacy at the same time, all equally sick and in need of the pharmacist's attention. When resources are limited, in this case the pharmacist's time, a decision must be made on some principle of justice to "break the tie" so to speak. The pharmacist could decide to spend his or her time where it would do the most good. Or, the pharmacist could decide to address the needs of the patient who holds the lengthiest relationship with the pharmacy, in a sense rewarding the patient's loyalty. This latter understanding of justice is referred to as "merit." In sum, determining the distribution of health care resources, whether it is a pharmacist's time or dollars, is one of the most complicated and painful areas of conflict in health care today.

TRUTHTELLING, HONESTY AND INTEGRITY—Regard for self-determination requires that health professionals be honest with their patients. Patients need accurate and understandable information to make good decisions. "Traditional ethics holds that it is simply wrong morally to lie to people, even if it is expedient to do so, even if greater good will come from the lie. According to this view, lying to people is morally wrong in that it shows lack of respect for them."[8] Pharmacists face the question of honesty when they are asked to withhold information from patients on the request of the physician or family member. Even if the reason for the request is to protect the patient from unnecessary harm, withholding the truth deprives the patient of his or her autonomy. Truth telling is one of the two cornerstones of trust between patient and pharmacist. Promise-keeping is the other.

PROMISE-KEEPING, COVENANT, OR FIDELITY—The principle of fidelity requires that promises, once made, should be kept. Our faithfulness in our relations with others ought to be respected and held in high esteem. When a pharmacist enters a relationship with a patient, there is an implicit agreement in the form of a promise or in the language of pharmaceutical care, a "covenant." It is important to explore the idea of covenant in pharmacy practice because it is a departure from the traditional relationship between patient and health professional that is based on a contractual model. Implicit in the covenantal relationship is the invitation for the patient to trust the pharmacist. Rather than a mere contract, which is external to a relationship, a covenant is internal to both parties. Covenants have a growing nature to them that extends rather than limits the relationship. This understanding of covenant requires that the pharmacist "be there" for the patient. So, when a pharmacist wonders whether to sell ineffective but heavily promoted nonprescription drug products or herbal remedies, the principle of fidelity asserts itself. What would this action do to the trust that patients place in the pharmacist?

AVOIDANCE OF KILLING—More and more, pharmacists will find themselves in positions where they will be parties to patient suicides or requests for active killing through lethal prescriptions. Although the principle of nonmaleficence counts strongly against taking the life of another human being, the seriousness and irreversible nature of killing requires a separate principle. Not all behavior that shortens an individual's life should be considered killing. For example, the use of opioids to manage pain in the terminally ill may hasten death, but the motive is not to kill the patient. Rather the intent in such situations is to manage pain even though an earlier death is a foreseen result. Many moral and religious traditions condemn active killing even for reasons of mercy. "If killing is always a wrong-making characteristic, then avoidance of killing can be thought of as another moral principle that must hold beneficence and nonmaleficence in check."[9]

Principles can be a means to determine if an ethical dilemma exists in a particular situation. By asking the following series of questions, one can quickly determine whether any of the principles previously mentioned are at work in a case. If the answer to any one of the questions is "yes," an ethical problem is present.

1. Is this unfair? To whom?
2. Does this break a promise?
3. Will this be harmful? To whom?
4. Will this threaten future or existing relationships?
5. Will I be compromising someone's rights (including my own)?
6. Will this benefit the patient from the patient's perspective?
7. Is this disrespectful? To whom?[10]

Seek a Justifiable Resolution

At this point, one can begin to explore possible courses of action. If the case is one of high urgency, there is little time to explore a variety of options. In those cases, it is best to comply with previously established policies or guidelines rather than responding rashly and emotionally. Principles can be action guides to moral behavior, in addition to helping one determine the source of the moral problem. Although it is likely that there will be conflicts between moral principles in a dilemma, it is a good place to begin to determine the morally correct thing to do. If there is time to reflect on various courses of action, it helps to consult with colleagues to determine the best course of action.

Anticipate Arguments and Respond

After determining the best course of action, it is prudent to critically look at one's choice by asking what others would think of the alternative. "Moral or practical reasoning entails defending judgments in a certain way. The goal in a moral justification is to be clear, to use all relevant information, and to give cogent reasons for one's views."[11]

APPLICATION TO COMPLEX CASES

Components of the five-step process of approaching ethical decisions is applied to three cases dealing with pharmacists involved in some aspect of clinical practice. The cases differ in that they explore three different levels of ethical importance. The first case explores personal, direct involvement with a patient and a colleague. The second case moves to an institutional level in which the pharmacist must attend not only to the needs of a particular patient but other patients with similar diagnoses, the values and concerns of co-workers, and the institution's reputation in the community. The third case explores societal implications of a decision at the institutional level as well as inequities in access to health care resources.

CASE ONE: PROTECTING THE REPUTATION OF A PEER AND PATIENT WELL-BEING—Jane Wagner, a 40-year-old freelance writer with a history of depression, left the community mental health center after her appointment and went straight to the nearest pharmacy to have her prescription filled before her long drive home. Ms. Wagner lived in the foothills of a mountain range. The closest town to her home was Maple River, 50 miles away, where Ms. Wagner did her shopping and visited the clinic. Ms. Wagner handed her prescription to Tara Sadler, PharmD, at the Maple River Pharmacy and told Dr. Sadler that she had some errands to run and would return for the prescription later. Dr. Sadler was the only pharmacist on duty with the help of one technician. Even though Maple River wasn't a large town, the pharmacy was exceptionally busy on this Friday afternoon. All Ms. Sadler had time for was to dispense prescriptions. Dr. Sadler barely had time to fill Ms. Wagner's prescription before she returned to the pharmacy to pick it up.

About 2 hours later, Ms. Wagner called the pharmacy and asked to speak to Dr. Sadler.

"I just opened my prescription and the pills are a different color than the ones I got the last time. These are blue and the last ones were pink. Are you sure these are right? I just drove 50 miles to get home and I sure don't want to turn around and drive another 100 miles round trip to get the right drug," Ms. Wagner stated.

Dr. Sadler quickly checked her records and noted that she must have dispensed 30-mg tablets rather than the 20-mg tablets prescribed BID. But, the written record showed that she dispensed the 20-mg tablets.

"Are you sure they're blue?" Dr. Sadler asked.

"Of course," Ms. Wagner responded. "I'm not color-blind!!"

Dr. Sadler responded, "Well, those pills will be okay. You're right, they are a different color from your last ones, but if you break them in half, they will be close enough to your old prescription. I think it will be just fine and it will save you a trip back into town. Just break them in half at the line down the middle."

Dr. Sadler hung up and returned to the rest of the prescriptions that were waiting for her. She reasoned that 15mg was close enough to 20mg Ms. Wagner was supposed to receive and wouldn't make that much difference.

One month later, Ms. Wagner visits Maple River Pharmacy for a refill on her prescription. John Winchester, PharmD, the manager of the pharmacy, notes that Ms. Wagner is right on time for her refill. Dr. Winchester asks Ms. Wagner how she is doing.

Ms. Wagner states, "I'm doing fine. By the way, I want you to fill this prescription with those blue tablets rather than the pink ones. I've been breaking the pills in half and taking a half in the morning and a half in the evening. I'm doing well on this dose."

Dr. Winchester was confused. "I don't understand. Who told you to break the pills in half?"

"The other pharmacist." Ms. Wagner replied.

After verifying that the prescription refill was for 20mg BID and that Dr. Sadler had filled the prescription a month ago, Dr. Winchester called Dr. Sadler at home to help resolve the situation. Dr. Sadler stated, "I won't admit to an error because I never saw the prescription after it left the pharmacy. The patient called and said the tablets were blue. I remember I checked the records and it said that I dispensed the 20-mg tablets. Since I didn't see the pills, its her word against mine."

Dr. Winchester is not happy with Dr. Sadler's attitude, but decides to refill the prescription as written until he can figure out where the true problem lies. When Ms. Wagner gets her prescription, she opens the bag, looks in the bottle and states, "These aren't blue. I told you I want the same prescription I got the last time. I'm not leaving until you fill this the right way." Dr. Winchester wonders what is the right thing to do.

Case One is fundamentally concerned with ethical issues on an individual level. "This realm also deals with weighing and balancing the values/goods/loyalties that stand in tension between two or more individuals."[12] For example, one must weigh Ms. Wagner's right to the most effective medication for her condition and Dr. Winchester's responsibility to dispense prescriptions as written.

Before the ethical problem or problems can be named in this case, it helps to gather information that is not in the case or that would help in understanding the different perspectives of those involved. The clinical or technical facts of the case are fairly clear. Ms. Wagner claims that she received blue (30-mg tablets) rather than the pink (20-mg) tablets she was supposed to receive. Dr. Sadler instructed Ms. Wagner to take half the blue tablet (15-mg) BID assuring her that it would be close enough to her prescribed dose. One month later when Ms. Wagner comes for a refill, Dr. Winchester discovers that Ms. Wagner claims she got 30mg tablets rather than the 20mg tablets ordered. Dr. Winchester checks with Dr. Sadler who denies making an error or instructing Ms. Wagner to take half a tablet twice a day. Ms. Wagner will not accept the correctly filled prescription and demands the "blue pills."

Other clinical or technical facts that are relevant in this case are: Ms. Wagner has a history of depression that requires medication; she lives in a rural, isolated area; she is functional enough to receive mental health services from a community mental health center; she pays attention to her prescriptions and the effect of the drug; she claims to be doing well on the 30-mg/day dose.

There are clinical facts that one does not know. For example, it would be important to know what drug is involved, its efficacy, dosing, and so on. It would also help to know Ms. Wagner's drug history, particularly, with antidepressants. What has worked for her before? Is one month long enough to know if this is the proper dose for Ms. Wagner? She seems to be compliant, but it would be important to know if this is a pattern or not.

The situational facts of the case include who is immediately involved in the case, their relationships, and perspectives. Situational information also includes attention to the context of a case such as time constraints or other environmental factors that could influence a decision. There is a sense of urgency in this case because Ms. Wagner is literally standing in the pharmacy waiting for an answer. Dr. Winchester has some time, but not a lot to come to a resolution. One knows that Dr. Winchester is the manager of the pharmacy so that places added responsibility on him. Dr. Sadler is not a manager, but a staff pharmacist so she is subordinate in the organization to Dr. Winchester. Because of the way the case is written in the third person voice, the reader of the case has more facts than Dr. Winchester. For example, one knows that Dr. Sadler did tell the patient to split the tablets in half even though she denies it. There is no information about any relationship between Ms. Wagner and the pharmacists at Maple River Pharmacy beyond that she is a customer. One does not know if she is a routine patient at the pharmacy or not. An important person in the case who remains unnamed is the prescriber who could be a physician's assistant, nurse practitioner, or physician. Regardless, the prescriber wrote a prescription for a drug at a specific dose. She or he presumes that the prescription was filled as written. There is no description of the relationship between the pharmacy and the mental health center nor the relationship between Dr. Winchester and the staff at the mental health center. We know Maple River is not a "large" town, but just how big a town is it? The size of the community can profoundly impact the relationships between health care institutions in the community and between individual health professionals. All these relationships play a part in formulating possible resolutions to the ethical problems posed by the case.

The relevant human values in the case can be discerned from the actions of the parties involved. Ms. Wagner appears to be an assertive patient with a history of mental illness that responds well to drug therapy if one is to accept her self-assessment about the medication's effects. In a way, Ms. Wagner is demanding respect from the pharmacists who care for her.

Dr. Sadler, at least when one first meets her in the case, is overworked. She tries to cover-up an error. She decides that she perhaps no real harm would come to the patient by "prescribing" a 30-mg/day dose. Later, she is unwilling to admit her mistake. Whether she denies wrongdoing because she is afraid of the repercussions or prideful, it is hard to say.

Dr. Winchester appears to want to do the right thing. He seems cautious. At first, he shows loyalty to his colleague and employee when he tries to sort out just what happened with Ms. Wagner's previous prescription. It seems that he values patient well-being. Although one does not have any information to gauge how he feels about the present situation, it is likely that he is feeling a sense of unfairness or anger at being placed in the center of a dilemma that he did not create. The case is a dilemma because whatever choice Dr. Winchester makes, there will be bad feelings and other harms.

The legal implications of the case include that Dr. Sadler prescribed 15-mg BID rather than the 20-mg BID that was ordered. One will assume that Dr. Sadler practices in a state that does not allow pharmacist prescribing. Even if Dr. Sadler could prescribe, one would expect that she would discuss a change in the medication with the original prescriber.

The ethical problem in the case can be posed as a question: How should Dr. Winchester fulfill his duty of beneficence to his patient, Ms. Wagner, and protect the reputation of his colleague, Dr. Sadler from unnecessary damage from the patient's and prescriber's perspectives? Moreover, Dr. Winchester has an obligation of honesty to the patient and prescriber that is in conflict with loyalty to a colleague.

Dr. Sadler did not fulfill her responsibility to the patient to dispense the medication as prescribed. Ms. Wagner has a right to properly dispensed medication. The judgment Dr. Sadler made about the safety and efficacy of the drug, that is, ". . . it will be close enough to your old prescription" could have resulted in harm to the patient. Dr. Sadler is not honest with the patient or her colleague, Dr. Winchester. Dr. Winchester is caught between his duty to do good and prevent harm to the patient. He also has a basic obligation to be loyal to his colleagues.

A duty also exists to the prescriber to dispense the medication as ordered. Ms. Wagner's autonomy is threatened because of lack of accurate information. Dr. Sadler's irresponsible behavior could reflect badly on Maple River Pharmacy and the pharmacy profession as a whole.

There are at least six actions that Dr. Winchester could take. First, he could fill the prescription as Ms. Wagner has requested. On one level this would be supported by beneficence because Ms. Wagner sees this as a good (ie, she claims that she is doing well on this dose). Second, Dr. Winchester could call the prescriber and explain that there was a prescription error, but the patient reports doing well on 15-mg BID. Dr. Winchester could do this without telling Ms. Wagner about the error. This action is supported by beneficence regarding the dose that Ms. Wagner wants, but suppresses the truth and limits patient autonomy because Ms. Wagner doesn't have all the information. Also, the prescriber may tell Ms. Wagner about the error during a later visit that could affect her trust in the pharmacy. Truth telling to the prescriber is supported by the principle of veracity. But, Dr. Winchester's honesty could be met by anger or mistrust by the prescriber.

Third, Dr. Winchester could follow the same actions as in alternative #2 but this time tell the patient about Dr. Sadler's error. This action would fulfill all the principles mentioned in alternative #2, but also includes veracity to the patient. Like the prescriber, Ms. Wagner could be angry or mistrustful because of learning about Dr. Sadler's error and the way she chose to remedy it.

Fourth, Dr. Winchester could stall. He could tell Ms. Wagner that he needs to speak to the prescriber to straighten out some confusion with the prescription. This is dishonest to a degree because he is not telling Ms. Wagner the truth. This alternative, at a minimum, would inconvenience the patient by making her wait or return at a later time for her prescription. One knows that she lives 50 miles from the pharmacy and the extra driving is time consuming.

Fifth, Dr. Winchester could call Dr. Sadler and demand that she come into the pharmacy and resolve the problem because she created it in the first place. This alternative is not supported by any of the ethical principles mentioned thus far. Dr. Winchester cannot shift responsibility this easily. He knows about the mix-up, and he has attempted to refill Ms. Wagner's prescription as written. Dr. Sadler could resolve the problem by dispensing the wrong dose again. Then, it might be clearer to Dr. Winchester what to do with his colleague.

Sixth, Dr. Winchester could bring all the parties involved together and resolve the problem through a discussion. This action is supported by autonomy and veracity. Practically speaking, this may not be possible. Also, this action could result in bad feelings and disrespect among parties, for example, the prescriber may not trust the pharmacy in the future or the patient could be angry and accusatory.

The best option, based on available facts and the values of the parties involved, is the third one of informing the prescriber and Ms. Wagner about the error. Also, Dr. Winchester should bring in Dr. Sadler to discuss her moral standards about personal responsibility, patient welfare, and obligations to peers. This alternative, although fraught with unpleasantness, places the welfare of the patient first (care-orientation), honors patient autonomy and veracity, and honors veracity with the prescriber. Dr. Winchester's willingness to be honest with the prescriber could result in getting the best therapy for the patient. Even if therapy weren't changed in the way Ms. Wagner would like, future medication adjustments would be made on facts rather than fallacies. Dr. Winchester would need the virtue of courage because revealing Dr. Sadler's actions does expose the profession to criticism for incompetence and deception. But, by being honest, it also shows a willingness to correct errors and assume responsibility.

An objection to this action could be that Dr. Winchester is somehow being disloyal to a colleague and is, perhaps, harming the reputation of the profession unnecessarily. A response to this objection would be based on the primacy of patient welfare and the trust relationships between all parties involved in patient care.

In brief, the first case deals with questions about individual good and relationships between a specific patient and two pharmacists. The second case moves the ethical analysis to the level of the organization or institution in which pharmacists work, in this case a hospital. Just as individuals have relationships, commitments, and claims, so do organizations. Hospitals not only have responsibilities to patients and families, they also have responsibilities to employees and the community at large.

CASE TWO: INCOMPETENT PATIENTS AND LIFE-SUSTAINING TREATMENT—Julian Russell is a 25-year-old man with a history of severe mental retardation (microcephaly) secondary to prematurity. He has been a resident of a custodial care center for most of his life. Besides profound mental incapacity, he has spasticity, severe scoliosis, and multiple contractures. He also has significant ocular myopathy, is nonverbal, and does not respond to verbal or tactile stimuli. He does respond to painful stimulation with grimacing and physical withdrawal.

Mr. Russell was admitted with a principle diagnosis of anemia secondary to Grade III-IV esophagitis. Diagnostic tests led to a thoracotomy and surgical repair. Following surgery, Mr. Russell was placed in the intensive care unit (ICU). Twenty-four hours postoperatively, he experienced severe respiratory distress. Chest x-rays showed a right upper lobe infiltrate, so he was intubated and placed on a ventilator for 3 weeks. To prevent him from extubating himself, which he repeatedly attempted, he was placed in full restraints. Tube feedings began during this period by a Dobhoff tube. When he was finally transferred to a general floor 1 month after surgery, the main concern was to encourage him to take food by mouth with supplementation from the tube feeding for 12 hours at night. Although Mr. Russell ate well before his hospitalization, he now refused most oral feedings. He continued to require restraints because he attempted to remove the feeding tube at every opportunity. The attending physician is contemplating ordering the placement of a percutaneous endoscopic gastrostomy (PEG).

Mr. Russell's father is his legal guardian and only living family member. The senior Mr. Russell has been consulted by telephone for every surgical permit. At no time during the hospitalization did the senior Mr. Russell visit his son. The father told the physician at the outset of Julian's hospitalization, "I agree to whatever you think is best for my son."

Before the attending physician decides about further surgery, he requests a consultation from the institution's ethics committee (IEC). Christine Gibbs, PharmD is a member of the ethics committee and works on the critical care units at the hospital. She is familiar with Mr. Russell's case. The nursing staff expressed much concern about the continued use of restraints and were equally worried about sedating Mr. Russell. Dr. Gibbs was personally concerned about the treatment of patients like Mr. Russell who were never competent.

This case is fundamentally concerned with ethical issues on an institutional basis although Mr. Russell's case is the genesis for these institutional concerns. When Dr. Gibbs worries about "the treatment of patients like Mr. Russell," she moves the focus to the institution as a whole considering the good of "never competent" patients overall. The concerns expressed by the nursing staff can also be viewed on an institutional level by considering the affect of working in such an environment (ie, one that restrains helpless patients or forces unwanted treatment on patients over time).

Gathering clinical facts in Mr. Russell's case about his medical condition is the most important first step in determining what is the right thing to do in his case, and by extension, cases like his. Understanding his medical status is key to resolving the ethical questions his case raises. For decisions involving withholding or withdrawing of treatment, the following questions are relevant:

- What is the patient's present medical status? Are there other contributing medical conditions?
- What is the diagnosis? Prognosis?
- How reliable are these?
- Are there other medical tests that could help clarify the situation?
- What is the life expectancy and general condition if treatment(s) is (are) given?
- Is treatment overall expected to benefit the patient?
- What are the goals of treatment?

The diagnosis, prognosis, and goals of treatment may point to the most appropriate alternative for treatment and eliminate some alternatives as well. For example, in Mr. Russell's case, an underlying condition such as impaired respiratory function due to pulmonary edema, pneumonia, or ineffective breathing, may keep him dependent on the ventilator. Such clinical information is essential to answering questions about further treatment.

All treatment options need to be considered in light of the goals of treatment and future quality of life of the patient. Medical goals differ depending on the clinical facts of the case. For example, if the main treatment goal is to make Mr. Russell comfortable and decrease his agitation, then inserting the PEG tube will be seen in a different light. Even if a treatment can achieve a limited goal such as maintenance of nutrition and hydration in a less uncomfortable manner, this should be examined in light of long-range goals for the patient.

Sometimes clinical facts point to a clear course of action. Only one right thing can be done if a patient presents with severe chest pain in the emergency department because he can't find his nitroglycerin prescription. The ethically correct course of action dictates the treatment of a reversible, acute condition. In a complex, chronic case, like Mr. Russell's, patient benefit is decidedly less clear. Would it benefit Mr. Russell in the long run to continue to provide artificially administered nutrition and hydration? What about continuing ventilator support? These types of questions regarding withholding or withdrawing life-sustaining treatment are always difficult, but if a patient's preferences are known it helps diminish doubts about the right course of action. Mr. Russell's case is complicated by the situational facts, particularly involving his incapacity to participate in decisions about his treatment.

As a rule, most ethicists agree that competent patients have the right to make decisions about their own care, including the right to refuse life-sustaining treatment such as a ventilator, artificial food and fluids, or medications. In this case, Mr. Russell is not presently competent nor has he ever been so. That fact cuts out the possibility of previously expressed medical preferences in the form of a living will or durable power of attorney for health care decisions. In the case of never competent patients, the pharmacist and other members of the health care team must do their best to determine what is best for the patient by consulting with others who have prior knowledge of the patient and his life. In short, the health care team and the IEC in such circumstances are seeking to base decisions on withholding or continuing treatment on the judgment of persons who know the patient best. The patient's father probably never heard his son express any medical preferences, but he would most likely be a sympathetic surrogate decision-maker for him. Also, it is likely that the senior Mr. Russell would be serving his son's best interest. But, this would only be true if he fully understood his son's present condition, the goals of treatment, and probability of reaching agreed upon goals.

It is not clear that Mr. Russell fulfills the previously stated criteria for being a morally valid surrogate. From the little one can gather about the senior Mr. Russell's acceptance of the role of decision maker, he has delegated his autonomy to the physician. In other words, the physician has Mr. Russell's permission to act in his son's best interest. But, the physician still has doubts and has decided to consult the IEC.

Situational facts of the case also include the views of other caregivers. When an ethics committee is asked to consider a case, it is good to invite the primary caregivers to be present for the discussion. Because the primary physician instigated the meeting with the IEC, the other caregivers who might be asked to attend are the nurses, the social worker, therapists from occupational, physical or respiratory therapy, and perhaps the chaplain. It is important to use this forum for discussion of the views of these "others" involved in Mr. Russell's care so that their feelings can be expressed and areas of disagreement or conflicts of values, such as comfort *versus* sustaining biological life, can be resolved.

One can determine the ethical problem(s) in the case by using the series of questions previously listed, for example, "Is this unfair? To whom?" In a complex case such as this, it is possible that more than one question could be answered in the affirmative, thus showing that more than one ethical principle is involved. First, could the treatment to date and future treatment decisions such as the placement of the PEG be considered fair? The concept of fairness is integral to an understanding of justice. Justice requires that patients should be treated as equals unless there is a compelling reason to treat individuals differently. Mr. Russell seems to have received the same treatment anyone with his medical condition would receive. The decision-making process surrounding withholding or withdrawing treatment is fair in that this is the standard applied to all "never competent" patients. Health professionals use the "best interest" standard, the generally agreed upon standard in law and ethics, to determine what is best for a patient who never expressed any views on end-of-life treatment. Furthermore, Mr. Russell's case has been brought to an IEC to assure that the patient's care receives impartial, thoughtful consideration.

As for the next question regarding promise keeping, an implicit promise of providing quality care is made to all patients who receive care in a hospital. It does not appear that this promise has been broken or compromised in any way. If the treatment team decides to withhold the PEG or withdraw the ventilator, it needs to be certain to keep the basic promise of caring for Mr. Russell and not abandon him. Specifically, the pharmacist should attend to measures to keep Mr. Russell comfortable and calm.

The third question, "Will this be harmful? To whom?" is pivotal. All treatments and procedures, particularly those that are invasive and painful will be construed as harmful and frightening from Mr. Russell's perspective because he is incapable of assigning meaning to the experiences. The very act of restraining an agitated, confused patient can cause physical and emotional harms. The harms of surgery, continual restraints, and dependence on a ventilator must be weighed against the potential benefits to be gained for Mr. Russell. Because he cannot make sense of the experience and cannot speak, the health care team must rely on the nonverbal messages his struggle sends as well as a judgment about objective best interest. Because the answer to the question regarding harm is "yes," it is clear that the case does contain ethical issues. The principles of nonmaleficence and beneficence are in conflict. Perspectives about what benefit means in light of Mr. Russell's present state can vary between members of the health care team. And, there are harms to other individuals besides Mr. Russell that should be considered. The nursing staff could be psychologically harmed if it believes it is causing harm to Mr. Russell out of proportion to benefit. Therapists who work with Mr. Russell may see their work as futile at a minimum or harmful to the patient because it causes discomfort to the patient and little to no benefit. Once the key ethical issues are identified, one can move to determining alternative courses of action.

Some possible alternatives that the IEC could explore are (1) continue all reasonable measures of life-sustaining treatment including drugs, surgery, ventilator support, among others, even if it requires physical or chemical restraints; (2) continue with ventilator support and comfort measures to decrease pain and anxiety, but do not place the PEG, offer fluids or ice chips by mouth, and the like; (3) discontinue all life-sustaining measures and offer comfort measures only perhaps including terminal sedation when the ventilator is withdrawn. Terminal or total sedation is pharmacologically induced reduction of patient awareness to obviate symptoms of intractable pain or, in this case, overwhelming distress that often accompanies disconnection from a ventilator.[13]

All health care treatments are morally required or not based on considerations of their benefits and burdens. "If the benefits exceed the burdens, then the treatment is acceptable; if they do not, then it makes no sense to require it. This notion of the rel-

ative amount of benefits and burdens is now generally referred to as the criterion of proportionality."[14] The ethics committee should review these alternatives and others to determine if the burdens equal or exceed the benefits for each alternative. The IEC can then advise the attending physician which alternative brings about the most benefit.

Before leaving this case, it is important to explore the institutional implications, that is, the individual (patients, staff members) good within the institution and the common good of the society within which the institution exists. "For health care institutions not only provide health services, they are also a powerful cultural force and agent. By their presence, their promotional efforts, their budgets and their services health care institutions have a significant influence on what the general population thinks, hopes and demands in terms of health care. Hospitals not only respond to but also create demand in the general public about what to expect of a hospital by way of service, convenience, and opulence."[15]

Thus, the IEC needs to focus on individual patients and their needs, and the overall well-being of the whole and its public position on complex issues such as end-of-life care. The IEC must consider the impact of policies and guidelines on the internal workings of the hospital while also promoting the common good of society in such areas as respect for persons, support of the dying, and avoidance of futile treatment, to name a few. The final case deals with the societal realm of ethics as well as institutional ethical concerns.

CASE THREE: RESTRICTIONS ON OUTPATIENT PRESCRIPTIONS—The Good Shepherd Hospital, a private, not-for-profit, religiously based institution, adopted a policy based on its mission statement that any person "in the community" who experiences a medical emergency or is in labor can and will be treated in the emergency department (ED) regardless of ability to pay. This policy was extended to the hospital's inpatient pharmacy as well. The inpatient pharmacy dispensed the prescriptions of the "outpatients" in the ED because technically ED patients are "inpatients" of the hospital while they are being treated. Also, it seemed more practical to have prescriptions dispensed at the inpatient pharmacy because most pharmacies in the area were closed in the middle of the night and some prescriptions needed to be dispensed immediately.

ED patients who came to the inpatient pharmacy and presented their prescriptions had their insurance billed if they belong to a drug card plan. For patients without insurance, their bills were marked "self-pay." This practice went on for a while until the Director of Pharmacy Services, Natalie Norita, PharmD began to review accounts left unpaid by patients. What she found were patient accounts from the community who had unpaid balances in the thousands of dollars. For example, one patient had an outstanding debt of $8,000. Many patients with unpaid accounts were repeat patients in the ED who continued to use the inpatient pharmacy to get their prescriptions. Second, Dr. Norita was concerned that Good Shepherd might be attracting patients to their ED because of the "self-pay" policy. She suspected that word had gotten out that Good Shepherd would dispense prescriptions for free if a patient was treated in the ED. Third, there were several cases in which patients returned to the inpatient pharmacy shortly after receiving a prescription for a narcotic analgesic claiming that they had "dropped" their medication on the sidewalk and needed more.

Dr. Norita decided that drastic measures were in order because pressure was being placed on all units of the hospital to be more efficient and stop loss. The pharmacy could not continue losing money in this way. Dr. Norita posted the new policy in the inpatient pharmacy—no prescriptions for outpatients would be dispensed. There would be no exceptions even if the patient had insurance or the ability to pay. The policy was in place for less than a week when Dr. Norita heard from the ED physicians who complained, "How can we provide adequate care to patients when they can't get the prescriptions that we write filled at the hospital?" The nursing staff joined those who were unhappy with the new policy. The head of nursing stated, "The Code of Ethics for nurses states that we are to serve all patients regardless of economic status. I think the policy puts the nursing staff in conflict with the Code. Also, I don't think it is a good idea to inconvenience everyone merely because of the bad actions of a few." Dr. Norita wasn't really certain that her "no prescriptions" policy was the answer to the problems with bad debt in the ED, but it was a start. It appeared that the policy needed more work and perhaps input from others who would be affected by it.

The situation at Good Shepherd Hospital in the pharmacy department is a complicated one as Dr. Norita is discovering. There is a lot of information that is missing and would help in developing an ethical policy. Whatever policy is developed will have implications for the community that Good Shepherd serves. Questions at the societal level of ethics take on a broader perspective than those encountered at the institutional and individual levels. Clinical questions now look at groups of patients and their collective well-being. First, how does the pharmacy director define "emergency?" What is meant by "treatment?" Is sufficient treatment a few doses of a drug to get the patient through a couple of days or is it, for example, a full course of antibiotic drug therapy?

Situational data concerns relationships between groups and organizations within the community. For example, is Good Shepherd the only hospital in the community who is willing to care for indigent patients? Are unpaid accounts or bad debt basically different from those involving patients who request refills on lost or "dropped" medications? How many patients does this really involve? Is it possible to determine which patients have the ability to pay, which patients might be eligible for welfare and which patients' care will need to written off as unrecoverable debt? What is the overall institutional position on care for indigent patients?

Dr. Norita has a responsibility as Director of Pharmacy to the hospital as a whole, to the staff pharmacists who work for her, to other health professionals who work there, and last, but assuredly not least, patients. In an attempt to reduce loss and perhaps to be absolutely fair, Dr. Norita decided no prescriptions for outpatients would be dispensed. Although Dr. Norita is treating everyone equally, it may not be in everyone's best interest for her to do so. Under this absolute policy, children who are diagnosed with otitis media would not receive appropriate medications from the inpatient pharmacy. Perhaps Dr. Norita believed that the policy would stop patients from "abusing" the inpatient pharmacy and didn't anticipate the impact it would have on "deserving" patients with true medical emergencies.

The basic ethical problem in the case can be posed in the form of a question: How can Good Shepherd Hospital fulfill its mission to serve "all patients" and stay fiscally sound? What would be a reasonable balance between these competing goods?

Because the problem includes institutional and societal concerns, it makes sense that the deliberations about the policy would be best conducted with an interdisciplinary committee that would represent the different constituencies affected by the policy. At whatever level the deliberations take place, Dr. Norita should be involved to present the pharmacy perspective.

An IEC might be the place to start such a discussion, but it is not the only committee or group that can discuss such an issue. In fact, most ethics committees have dealt narrowly with patient care issues "at the bedside" and not institutional or organizational ethical issues. "Organizational ethics may be defined as the study of the ethical issues associated with the systems, structures and processes that shape the encounter between health care providers and patients."[16] The senior administrative team of Good Shepherd, rather than the ethics committee, is the proper group to address the larger questions that Dr. Norita's policy raises because they are the ones who make staffing and budget determinations. A reasonable argument could be made that senior management teams act as ethics committees when they are making value-based decisions that impact the organization as a whole and the community the organization serves. If Good Shepherd wants to survive as an institution, it must balance the need to increase contribution to margin (revenue minus variable costs) to better cover fixed costs, provide indigent care, and meet other community service responsibilities.[17] Decisions made at this level of an organization have far-reaching implications and affect a broader constituency. The basic ethical principles that are action guides for moral decisions on an individual level can be used to resolve societal level problems, but must be reconstructed and, perhaps, prioritized differently. For example, the good of one patient is conceptually and practically different from the good of many

patients, as in the third case where one considers all patients who cannot pay for their medications. In reaching a resolution to Dr. Norita's problem in pharmacy, one must remember that Dr. Norita's problem doesn't exist in isolation. The optimum resolution will take into account the connection between balancing the pharmacy's budget, the institution's mission, and implications for the individuals the hospital serves.

CONTRIBUTION OF ETHICS TO CLINICAL PRACTICE

Sometimes, even when the normative model for decision-making is followed to the letter, it is not possible to arrive at a resolution. At this point, one might believe that a resolution could be reached if only there were more information or if there were a better model for making such decisions. However, even with the best models and information, it may not be possible to resolve a problem because of the limits of human knowledge and understanding. Further, it is the nature of ethical dilemmas to involve tragedy and loss. A morally correct way of dealing with dilemmas is to share them *as* dilemmas with those involved. Face the fact that serious matters are at issue. Do not allow secondary inference that there is no right answer to detract from the seriousness of the situation and the benefits of systematically working toward a solution.[18]

Besides decision-making models, there are other sources for moral guidance such as family and peers, laws and regulations (although the law sometimes diverges from ethics), professional codes of ethics, and religious beliefs. Further, there are resources within organizations such as policies and guidelines that have been thoughtfully written with ethical norms in mind. Colleagues in specialty areas of pharmacy practice could work together to establish mutually held values about complex ethical issues that are encountered in daily practice.

As noted in case two, IECs are becoming more common in hospitals and long-term care facilities. Pharmacists should not only seek out the advice and guidance of an IEC when problems seem beyond resolution; they should also offer to serve on such committees and bring their expertise regarding drugs and proper use of medications to the overall treatment plan. Unfortunately, the perspective and assistance of pharmacists is often missing from the committee's membership. Although IECs do not make the decision for the individuals involved in the ethical problem, they do offer a safe environment in which to discuss contentious issues and guidelines that affirm the values of the institution so that sound decisions can be reached.

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CHAPTER 95

Technology and Automation

Bill G Felkey, MS
Kenneth N Barker, PhD

The American Heritage Dictionary defines a system as, "A group of interacting, interrelated, or interdependent elements forming a complex whole; a condition of harmonious, orderly interaction."[1] Providing contemporary pharmacy services involves a sufficiently complex process that it most certainly necessitates a systems approach. Pharmacy is, of course, a subsystem of a larger, comprehensive health-care system. In this chapter, the authors will attempt to focus on a systems approach in utilizing technology to support a practice of pharmacy and describe the complex interactions that occur in a pharmacy practice between people and technologies. These interactions focus primarily on the welfare of patients and are performed by pharmacists and their associates who share a common vision because they are involved in the pursuit of rendering appropriate pharmaceutical care.[2]

It is impossible to imagine any scenario for the future of pharmacy that does not involve the use of many forms of technology and automation. This assumption holds true regardless of the practice setting selected. Consider that technology has two primary purposes. Both of the purposes of technology involve the work of humans. One purpose for technology is to replace completely the work done by humans. Technology usually excels at replacing work that is repetitive and work that is often found to be tedious by humans. Ideally, technology should be considered for selection and implementation when it can free a human being to be redeployed into a work process that requires the abstract, judgmental, and higher-level cognitive processes at which humans excel.[3]

The second role of technology involves the enhancement of human work. With over 6000 articles being published every week in the biomedical literature, it is impossible for any human to "keep up" with the dynamic field health care represents. Evidence-based medicine experts estimate that in even the narrowest specialty approximately 14 articles per day would need to be read from the literature to maintain one's professional competency at the highest level. Information technology can present the highest quality, empirically derived, evidence-based information that reduces a pharmacist's uncertainty while making decisions. Information technology helps to overcome the limits of human memory and helps reduce the use of conjecture (opinion-based) decision-making.[4]

Another example of a performance enhancing technology can be found in the use of bar codes. In community pharmacies, hospitals, and nursing homes, bar codes can be scanned in the dispensing process and at the point-of-administration to assure that the right drug is being given to the right patient in the right form by the right route in the right strength at the right time. Use of bar codes in health-care are proving to significantly reduce accidents and errors.[5]

Generally, one can assert that, over time, technology continues to weigh less while it does more. The ubiquitous nature of the Internet, microcomputers, and personal digital assistants (PDAs) makes technology touch everyone to an increasing amount in our everyday work and existence. Do you know anyone who receives more voicemail than e-mail? Are you aware that the new definition of the Internet involves every computer, cell phone, PDA, and pager in the world now potentially being able to communicate with one another? Where will it end? It is difficult to imagine all of the permutations and possibilities.

Health care as a discipline tends to lag behind other areas and industries with regard to its adoption and diffusion of technological innovation. In fact, health care had been described as one of the few remaining predigital industries. The authors believe the banking and financial industry is the best example to follow when determining how health care will continue to evolve. Granted there are differences, but trust is needed in both systems and technologies. If people are willing to trust their money to banking technologies, it might follow that they will become more comfortable trusting the management of their health-care information to technology. Most pharmacists state that they are less than 10% paperless in their practices. The authors can imagine no scenario where the digitization of transactions will not increase over time.[6]

Compare the adoption of "cash cards," a.k.a. ATM cards and imagine that a similar card for health care would serve as the means for caregivers to gain access to patients' medical records. There are several technologies that provide this kind of access. Everything from biometric fingerprint or retina scanning to smart cards is being examined. No true standard has emerged as of yet. In fact, some people say (tongue in cheek), that the nice thing about information technology standards is that there are so many to pick from. The authors do not believe the smart card is the future unless it can totally reduce the thickness of one's wallet by serving all identity functions for all health, business, travel, entertainment, and other related transactions of daily living.[7] Getting all of the businesses represented to agree on a single standard would certainly be a prodigious task.

Understanding Computers

Computers constitute a core technology in support of the practice of pharmacy. When anyone thinks about technology or automation, it is likely that computers are involved in almost every circumstance. Our watches, automobiles, entertainment systems, and even kitchen appliances are getting "smarter" through the incorporation of computers into their design. Computers are data processors. Simply stated, computers receive input, they process that input, and they produce outputs. The hardware components of the computer are controlled by software systems. Software that constitutes a set of instructions used to tell computer hardware how to operate can be further

divided into two categories. These categories are operating systems and applications. Operating systems such as Microsoft Windows are needed to govern the basic operation of the hardware. After the hardware is functioning, software applications are used to support the practice of pharmacy and user desired tasks.

Computers can be fairly confusing to the uninitiated. Basically, computers can be understood very readily by looking at the five components that comprise a computer system. By understanding these five components one should be able to see how the computers have evolved historically and examine current and future workstations for their performance and functionality.

Computer inputs are the first component encountered in any computer system. Of course, the most common computer input is the keyboard. A pointing device such as a mouse or trackball is also considered an input. Microphones can be input devices for computers to either record sounds, or, when used with speech recognition software, they can transcribe continuous speech at over 160 words per minute with 99% accuracy. Public kiosks often use touch screens as computer inputs. Quadriplegics can even use their eyes to gaze at an apparatus to allow them to type with this special computer input device and thereby interact with a computer.

Computer outputs fall into the second component category. The most common output device is a monitor or display. Speakers are also classified as output devices. Printers and plotters also fall into the category of outputs. There are other kinds of devices that alternately can be involved in both inputs and outputs. Modems (ie, a truncated term for modulator demodulator) alternate as input devices on a system and then as an output devices for that same system. Modems translate digital signals into sounds that are carried over telecommunication media and then reconverted into digital signals at remote locations.

Network cards found on microcomputers and faxes that are internal to workstations also serve as input and output devices. Personal computers used to be thought of as "islands" or standalone workstations when they were first invented. At first, computers were replacing typewriters and most people did not consider them as tools to connect personnel and work processes within organizations. It is now commonplace for computers to be connected globally.

The third computer category of components is called memory. Memory is also classified as RAM, an acronym for "random access memory" and provides the computer with a temporary workspace to do work or tasks. Think about the memory of the computer being roughly equivalent to the size of one's desk. The bigger the desk, the more possible it is to have multiple tasks being worked on concurrently. The drawback of memory is its temporary nature. If a power failure occurs and a document has not been moved from memory to the next computer component, storage, the most profound writing created by the user will be lost.

The fourth component of a computer, storage, is a more permanent place for work to be stored. Storage can be thought of as the filing cabinets of the computer. Any media that is capable of storing documents such as hard drives, floppy drives, removable data cartridges, and read-write CD-ROM drives can be classified as storage devices. There are now even storage devices one carries on his/her keychains. These devices use the USB port of a computer and create miniature hard drives with up to two gigabyte capacity for portable storage and transfer of material between systems.

The fifth and final component of a computer system is the processor of the computer. Think of this component as being the brain of the workstation. Computer inputs go through the processor, are manipulated in the memory of the computer, stored on the storage media of the workstation and are outputted in a variety of different ways. All of these activities require the processor, which is made up of millions of transistors in a single large electronic component called a processor chip.

Computer processors are classified in two ways. They usually belonged to a family of processors (eg, Pentium, Pentium II, Pentium III, Pentium IV), and each chip is assigned a clock speed that determines how quickly it processes information on the computer. It is not uncommon to see computers operating at Pentium IV, two gigahertz speeds in today's performance systems.

Understanding how computers function should potentially demystify these important devices for users who increasingly depend on them to practice their profession.

Pharmacy Informatics

"Medical informatics is the rapidly developing scientific field that deals with the storage, retrieval, and optimal use of biomedical information, data, and knowledge for problem-solving and decision-making."[8] Health-care informatics is the umbrella term for all health-related disciplines and pharmacy's related discipline is commonly called either pharmacy informatics or pharmacoinformatics.[9] Is impossible to consider that any individual can keep up with the flood of information that is being created concerning the safe and appropriate use of medications in humans. Information technology is, therefore, required to manage these data efficiently and effectively.

One might ask the question, "While I am providing pharmaceutical care, what is my computer supposed to be doing?" At the core of nearly every pharmacy software program is a database application. In a pharmacy management, database application program there are multiple databases being managed. Database tables can include: patients, prescribers, drugs, payers, drug interactions, and many others. Historically, pharmacists assisted by their technology, have always been challenged to deliver the right information, to the right people, at the right time and place, in the right format.

Years ago, the only format for the delivery of decision support information was a tertiary reference book that was, hopefully, from an authoritative source. Some of these trusted references were only updated every few years. As computer systems began to be commonplace, "nuggets" of information from the literature were incorporated into prospective drug utilization review (DUR) databases and pharmacists would be "flagged" when patients were about to be exposed to duplicate therapy, significant drug interactions, or the entry of a new prescription to which a patient was potentially allergic. As these DUR products matured, monographs discussing the management of the problem were included on the systems.

Initially, respected tertiary books were transformed to on-screen versions of the books upon which they were based and were typically distributed every three months by CD-ROM. As the Internet developed, drug information became increasingly available from providers who offered their products online. While a pharmacist's printed books might be available for new editions annually or have inserts mailed out on a quarterly basis, online drug information could be updated on a daily basis. It was also found that many busy practitioners needed information packaged in phrases rather than sentences and paragraphs. Many products now reflect a "just the facts" approach to information.

The latest trends place these resources into the hands of practitioners in a variety of different media. One will still see books being published. One will also see CD-ROM and Internet versions of the same products. The majority of these reference tools are also available in formats that allow them to be displayed on personal digital assistants. This allows the most mobile of practitioners to use high-quality evidence in decision-making wherever they require it. These tools are also updated on a daily basis and, in some cases, wireless access makes it possible for real-time updates to arrive where they are needed when they are needed. An ideal informatics support system allows the integration, management, delivery, and display of data in support of a pharmaceutical care practice.

Table 95-1. Using Evidence-Based Approaches with Individual Patients

TOOL	EXPLANATION
1. Start with the old.	Do your normal clinical workup of appraisal and interpretation of data before formulating the primary question to be pursued. Go through the other tools below and then decide your intervention, evaluation methods, and followup/monitoring scheduling.
2. Search and Match.	Find guidelines, protocols, and other literature that match the current patient and setting in which you are practicing.
3. Estimate Outcomes.	Use clinical judgment or decision analysis methods to determine how your patient may respond relative to randomized, controlled patients who were enrolled into a trial.
4. Verify Resources.	Are your local factors that you actually can use, such as expertise and available resources, feasible for use?
5. Patient-Oriented	Listening to your patients and their family for emotional, spiritual, and other non-biological aspects of illness and being willing to share and ask, "What else?" until solutions match patients' values.[15]

The Point of Care

One of the most critical focus areas in information technology is the place where pharmacists and their patients and colleagues attempt to address the identification, resolution, and prevention of drug-related problems. This place is termed "the point of care." Sometimes the point of care in a pharmacy practice is a stationary position. When stationary, a desktop computer can be utilized to bring necessary content and communication capability to bear for the purpose of problem-solving. There are over 5 billion pages of the World Wide Web available and over 1 billion of these pages concern health-care content. While there is a quality issue with this content, there is no doubt that tens of thousands of websites offer valid and reliable information to patients and practitioners alike.[10]

Mobile practitioners can utilize more portable technology that could include personal digital assistants (PDAs), notebook or tablet computers, or even wirelessly connected COWs (ie, computers on wheels). The ideal point of care device would be a large (17–21-inch display) that would offer long life, battery power, and high-speed wireless connectivity to the data and information required to practice pharmaceutical care. The information synopsis easily viewed on the large screen display would again, ideally, be ported onto a PDA screen in a device that would fit easily into a shirt pocket, lab coat pocket, or purse. In many instances a combination of complementary information technology devices should be utilized to maximize the "power" that the information availability can yield in an evidence-based practice.

Evidence-Based Pharmacy

Again, point of care technology that offers high quality clinical information can help overcome the limits of human memory and reduce the use of conjecture or opinion-based decision processes. There can be clinical decisions being made that are arbitrary and highly variable. While these decisions may not be entirely wrong, they might not represent the best possible patient care management. The complexity of pharmacotherapy demands that high-quality evidence be applied at the point of care to the decisions made by pharmacists. "Clinical decision-making used to be based on physicians' (and pharmacists') experience and authority. Now this is no longer considered to be enough. The dissemination of the practice of evidence-based medicine (EBM) has closely appended science to art."[11] The potential benefits of EBM are numerous and well-described.[12,13]

Sackett and his colleagues define evidence-based practice as, "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[14] When carefully selected, disease and drug information can be presented from reference compendia that are updated daily and contain decision support information that was empirically derived using proper scientific methodologies. Individual practitioners can also select practice guidelines and helpful review articles from the primary literature and incorporate them into point of care technologies to support their pharmacotherapy decision-making. Care should be taken to adapt population-derived data when doing therapy with individual patients (Table 95-1).

Computerized Physician Order Entry (CPOE)

The computerized physician order entry (CPOE) eliminates illegible handwriting, reduces medical errors, and improves patient care.[16] Electronic order entry of prescriptions and other medical interventions is gaining momentum as a response primarily to patient safety concerns. Unfortunately, it can be argued that order entry technology belongs in normal sequence behind the adoption and diffusion of an electronic medical record. Because electronic medical records are more difficult to implement, the profession will see order entry systems preceding them. In some help institutions, however, it has been so frustrating an experience that deinstallation of the order entry system has been started. Data holes, incomplete information, poor implementation and planning practices, resistance by physicians, and other problems are being encountered.

A very large behavior change is required in an organization adopting an electronic order entry system. Successful implementations may require two years of preparation for the clinical decision support used in the system. Customer advisory panels should be convened to assist in the process acceptance by those affected by the change. Success from a physician standpoint has always centered around the speed which the order entry system operates when compared with previous systems. Unfortunately, physician time has increased in many health system implementations. Time savings have been encountered by people who typically were charged with untangling order entry problems. Shifting the problem resolution back onto the physician, as one would expect, has been poorly received by physicians.[17] Table 95-2 describes the desired attributes and functions of a CPOE system.

Integration of the Internet

Patients are increasingly using the Internet to obtain medical information. A recent Harris poll estimated that 98 million Americans have retrieved health-related information online, an increase of 44 million since 1998.[19] The quality of information on the Internet is, however, highly suspect. In 2002, Eysebach et al. found that empirical content research done on Internet health information found significant problems, criticizing lack of completeness, difficulty in finding high-quality sites, and lack of accuracy.[20]

Internet connectivity is nearly ubiquitous in US pharmacies. High-speed or broadband access is more easily justified now that electronic adjudication of prescription claims has been placed in the mainstream. Significant claims processing transaction fee decreases are helping pharmacists achieve an easy return on investment (ROI) for broadband connectivity to the Internet.[21]

Table 95-2. CPOE Attributes and Functions

CPOE must be selected and implemented with the following in mind:

- Access to the system is simple where the application sign-on and sign-off is achieved through a combination of password, biometrics, or proximity devices.
- Access to needed decision support information is available from any patient care setting, pharmacy, physician's office, or home.
- Mobility is maintained through a combination of mobile and stationary devices that are readily available and located at various point of care locations based on the workflow of the specific patient care area.
- Navigation is from a main screen with direct links to screens designed for patient data review, ordering, and information compendia. Moving forward and back to the main screen is clear and easy.
- Patient data to support the ordering process is readily available electronically. Prerequisites for most forms of decision support are allergies, height, weight, current medications, laboratory values, radiology results, and medical problem list.
- The maximum amount of relevant information is available on each screen. (Content beats aesthetic design every time.)
- System response is fast, and there is virtually no down time.[18]

The possession of Internet connectivity in pharmacies is high, but the use of Internet connectivity at the point of care is lagging behind the front and back office operations of pharmacy. A major movement toward application service providers (ASP) that essentially offer subscription based access via the Internet to remote servers externally is likely to be the information technology architecture utilized by most physicians and pharmacists in the future. While currently there are many concerns about mission critical information being stored and secured externally, adoption of this architecture is increasing.

Grover et al. looked at how patients desired better access to health services and not surprisingly found that they wanted more than was there. "Patients were especially interested in getting e-mail reminders. They wanted online booking of appointments in real time and wished to receive updates about new advances in treatment. Patients were also interested in virtual visits for simple and chronic medical problems and for following chronic conditions through virtual means. We concluded that computer-using patients desire Internet services to augment their medical care."[22]

Telepharmacy

Telehealth is the use of communication and information technology to deliver health, health-care services, and information over large and small distances.[23] While most people think of telehealth in relation to surgeries performed between countries using remote robotic control, telehealth can be delivered in the same room in which a practitioner is standing. Consider that a diabetes educator can delegate the initial education of the newly diagnosed patient with diabetes to a technology that is a multimedia program. This program can deliver age-specific, gender-specific, race-specific, and diagnosis-specific education in an interactive format that allows the patient to comprehend and retain the educational material as effectively as a one-to-one interaction with a human educator.

As long as the content provided by the technology is maintained to be accurate, complete, reliable, and relevant one can allow technology to totally replace the repetitive work of educating a newly diagnosed patient with diabetes. What is left for the practitioner is the more complex customization and troubleshooting that is needed by these patients. By delegating to the technology, the practitioner is able to be in two places at the same time in a literal sense.

Telepharmacy involves bringing care to patients when it is not feasible to have patients brought to the care setting. Many clinics, upon diagnosis, would like to dispense prescriptions and other medical supplies to patients, but the clinic volume of prescribing activity may not be significantly high enough to justify the placement of a pharmacist in the clinic. Some clinics are connecting, using telecommunication technology dispensing devices, to a remotely located pharmacist who is able to control the verification and dispensing process without physically being in the clinic.

Using video conferencing, pharmacists are able to provide real-time patient counseling and manage a medication use system via remote control. Telepharmacy operations are proving to be a cost-effective method to render high-quality pharmacy services in underserved regions and can be a much-preferred alternative to physician/nurse/clerk dispensing options. Organizations such as the Veterans Administration are reporting early successes for many of their telehealth initiatives. Outside of closed system uses of this technology, reimbursement is a barrier to the implementation of the technology. Currently, real-time, live consultation over telecommunication technologies is the only practice interventions/consultation being reimbursed by the payers who recognize the value of these services. "Despite the slow growth of interactive and noninteractive telemedicine, technological development continues, and many new applications are under study. Remote patient monitoring programs, especially those based on store-and-forward technologies, are appealing because they are relatively inexpensive, increasingly convenient for patients and providers, and have the potential to cut the costs of care while improving outcomes. Medicare and other insurer reluctance to cover telemedicine has slowed its dissemination, but recent years have seen progressive, though limited, steps to extend reimbursement."[24]

Outcomes Measurement

"Outcome measures are used to monitor the effects of interventions in clinical practice or in formal clinical trials. They may also be used to assess changes within populations either spontaneously or as a result of public-health measures. They are used to monitor the course of illness as part of a management plan or, for larger groups, to identify changes brought about, for instance, by migration or immunization."[25]

Currently, outcomes are divided into four categories. The first category, therapeutic outcomes, requires the measurement of objective clinical results following the appraisal and intervention steps in the work-up of patients in a clinical setting. For example, patients are diagnosed with hypertension and will receive a prescription to treat this condition. The desired therapeutic outcome in the case of a normal adult would be a 120 systolic over a diastolic of 80 mm Hg. Technology is readily available to assist in the measurement of therapeutic outcomes. These technologies can enter measurements directly into a medical record or even a patient's specific web page.

The second outcome category, financial outcomes, measures the cost to achieve a therapeutic outcome. In the example of a patient with hypertension, the most cost-effective financial outcome could come from a lifestyle change on the part of the patient. Many patients' blood pressure will respond to positive changes in their diet and exercise. If a medication is required, a simple potassium sparing diuretic that achieves the therapeutic objective would have a favorable financial outcome when compared with a prescribed combination of calcium channel blocker and ACE inhibitor interventions. The selection of interventions that are effective and contain health-care costs can be assisted by care management algorithms' practice guidelines, and decision support software that prompts practitioners through the intervention selection process.

The third outcome category, quality of life (QOL), measures how health-care impacts patients' activities for daily living and physical and emotional performance in their work, home life, or recreation. It may be possible to achieve a therapeutic outcome at a cost that would meet the objectives for financial outcomes in the treatment of hypertension, but do this at the expense of patients' quality of life. For example, a male can be well-controlled with regard to his blood pressure when he is in his 30s through the use of a beta blocker. Upon entering his 40s, however, the same medication could cause him to experience fatigue and even impotence. Thus, a therapeutic and financial objective would be met but results in a negative quality of life impact. Some health-care systems administer QOL scales to patients to assess this outcome.

The fourth outcome category, satisfaction with the health-care system, has been measured in increasing numbers as managed care organizations seek to measure quality in the provision of health services. A "report card" called the Health Employer Data and Information Set (HEDIS) is given to patients to provide feedback to health systems and the employers who are paying for health services. Satisfaction can be determined by patients through factors such as how long it takes to get an appointment with a primary care physician and how they are treated during their appointments.

Technology can be employed to support the measurement of therapeutic outcomes. Technology can direct the achievement of a desired financial outcome. QOL can be assessed by technology and the results can be fed back into the healthcare system. Patient satisfaction can be measured and addressed using technological means. What is required is a systems approach throughout the delivery of care to assure maximum efficacy and the avoidance of negative outcomes.

Technology and HIPAA

"Medical records contain intimate information about a person's physical and mental health, behaviors, and relationships. Intrusions into privacy can result in loss of trust, with an unwillingness to confide in health care professionals. Unauthorized disclosures of intimate information can cause embarrassment, stigma, and discrimination."[26] Many pharmacists are greatly concerned that the legislation called Health Insurance Portability and Accountability Act (HIPAA) will make technological innovation more difficult. The new laws require that identifiable or protected patient information be held confidentially and the regulations impose severe penalties for security breaches. The authors know of at least 14 different methods to secure electronically held information. In many ways, it is more secure than paper records.

The regulations of HIPAA also provide that patients should have better access to their own medical records. In most US states, patients own the information contained in their medical records. Unfortunately, they do not feel as if they all miss information. Some US companies are creating a collaborative medical record that allows patients, through the World Wide Web, to become partners or coproducers in their own healthcare by allowing access to their medical records. The patient can also elect to allow access to their medical record by trusted relatives and other agents. In this way, an adult child can "look in" on his parents or grandparents health status.

Other technologies such as prescriber order entry are actually complementing HIPAA regulations and provide additional incentives for moving toward electronic medical record implementation. The portability aspect of the regulations can also be made possible through technology support. An Internet standard called extensible markup language (XML) allows the use of health information that is stored on the World Wide Web to be able to "move" between systems because the information on the web page is field tagged so that it can be portable between systems. Technology standards will again facilitate many processes and are necessary for rapid improvement.

Documentation of Interventions

There is a saying in health care, "If it wasn't documented, you didn't do it!" The authors believe that the documentation component of health care has been one of the reasons that pharmacy has struggled with obtaining provider status in Medicare regulations and other private sector circumstances. The ideal documentation system would allow documentation to take place as a natural byproduct of the rendering of patient care.

"Coding systems are important tools for the documentation of drug-related problems and following interventions. They should be suitable for scientific studies and for the broader implementation of Pharmaceutical Care in the pharmacy. A suitable coding system must be easy to use in a daily routine. To facilitate later computer aided use, it should be preferably structured like a decision tree and consist of three parts: the classification of drug-related problems; the intervention taken to solve the problem; and the degree to which the problem was solved."[27] Table 95-3 describes other documentation attributes and principles.

For example, if a drug reference is accessed at the point of care to determine what alternative dosing strategy should be

Table 95-3. Essential Documentation Principles

The following list contains the principles and summarizes what the systems, policies and practices should provide to accomplish them.

- Unique patient identification. Provide unique identification of each patient when recording or accessing information; provide—within and across organizations.
- Accuracy. Promote accuracy throughout information capture and report generation and during transfer among systems.
- Completeness. Identify minimum set of information required to completely describe incident, observation or intent; provide means to ensure that recorded information meets legal, regulatory, institutional policy or other requirements for specific reports.
- Timeliness. Require and facilitate healthcare documentation during or immediately after event so memory is accurate and information is immediately available for subsequent care.
- Interoperability across documentation systems. Provide highest realistically achievable level of interoperability; enable authorized practitioners to capture, share, and report information from any system, whether paper or electronic.
- Retrievability. Support achievement of worldwide consensus on information structuring—requiring use of standardized titles, formats, templates, macros, terminology, abbreviations and coding; enable authorized data searches, indexing and mining.
- Authentication and accountability. Uniquely identify persons, devices, systems that create or generate information and that take responsibility for its accuracy, timeliness; require that all information be attributable to its source (person or device); require that unsigned documents be readily recognizable as such; require review of documents before authentication.
- Auditability. Allow users to examine basic information elements, such as data fields; audit access and disclosure of protected health information; alert users of errors, inappropriate changes, potential security breaches; promote use of performance metrics as part of audit capacity.
- Confidentiality and security. Demonstrate adherence to related legislation, regulations, guidelines, and policies throughout the documentation process; alert users to potential confidentially and security breaches.[28]

used for a medication, an intervention communication and documentation application would automatically grab the medication name (and any patient information that was active) and populate those fields in the intervention and documentation program.

Some pharmaceutical care software packages manage the entire process and integrate clinical "to do's" into a pharmacist's calendar. For example, if a pharmacist is doing an appraisal with a pediatric patient diagnosed with asthma, the software will prompt the appropriate questions to ask. If a drug-related problem is identified, the software will prompt the appropriate options for intervention. If an intervention is initiated, the software will require that an evaluation of the intervention be performed at an appropriate interval. Once the evaluation is performed the software will schedule the patient for monitoring and follow-up intervals. All of these functions are integrated into the time management features of the software so that a pharmacist must respond or be "nagged" until the clinically appropriate action is taken.

The Role of Automation

Automation in general means that the machines that are used to perform work are controlled by a computer. The scope here is limited to machines used in pharmacy practice sites for work that includes the storage, packaging, compounding, dispensing, and distribution of medications. It includes collecting, controlling, and maintaining transaction information during such work, but excludes drug delivery systems such as infusion pumps.

The potential benefits of automated pharmacy are substantial. Automated systems can outperform humans in tasks that require tedious repetition, tiresome movement, intense concentration, immense memory retention, and meticulous record keeping. This describes many (though not all) of the tasks in the distribution process. Automated pharmacy systems are replacing many labor-intensive tasks already, thereby saving pharmacist, technician, and nursing time.

Of particular importance to the profession is the potential value of automation as an enabler for the re-engineering of pharmacy practice and for freeing pharmacists for the practice of pharmaceutical care. Automated pharmacy systems can reduce medication errors, improve documentation, increase authorized access to both medications and information, and enhance security. Turnover of personnel and on-the-job stress may be reduced when pharmacists are freed from "count and pour" dispensing. These potential benefits can be summarized in terms of increased productivity, accuracy, drug use control, and improved patient care.

Automated work systems are desirable because they are capable of achieving efficiency and accuracy far superior to that achievable in any other way, in appropriate applications. Identifying those applications where automation can and should be applied in pharmacy is still underway at this time. It is clear that factors such as proper training and the redesign of the physical environment to accommodate such automation are important. Automation to reduce medication errors may actually increase costs. Efforts are underway to show that error reduction actually reduces costs related to corrective actions and liability, which in turn offsets the cost of the automation.

Automated pharmacy systems (ie, pharmacy work systems incorporating one or more automated processes) are in widespread use throughout pharmacy practice. Their primary use today is for the functions of counting, packaging, and labeling dosage forms for pharmacists to dispense and/or administer to patients while electronically documenting the process.

Automated pharmacy systems may be centralized, pharmacy-based devices, or decentralized devices on nursing units, in long-term care facilities, and in other health care facilities. Currently, there are two types of pharmacy-based automated pharmacy systems: systems that repackage medications from bulk, and robotic systems that utilize "overwrapping" of unit-dose medications.

Decentralized automated pharmacy systems store and dispense drugs and supplies in locations outside the pharmacy, and may be interfaced to a central pharmacy computer to maintain centralized control over the drug storage and distribution processes. Some devices are used to dispense multiple-dose packages, while others dispense unit-doses. Some systems package the doses, while others dispense only prepackaged medications.

Community pharmacies have used technology to improve the efficiency of the drug distribution process since the 1970s; the first such system simply counted tablets. Today, automated pharmacy systems are available that automate the entire dispensing process. There are automated medication dispensing devices that serve different segments of the community pharmacy market based on prescription volume.

Prescription processing begins when an order is inputted into the pharmacy computer system and sent to the automated pharmacy system computer, which then initiates printing of bar-coded labels and receipts, selecting the prescription bottle, labeling of the container, filling, and capping. A video image of the drug inside the bottle is obtained before capping. After the bottle-specific bar code is scanned by the pharmacist, the video image for that medication is displayed to allow for a final check by the pharmacist. The technology allows for pricing of the prescription, adjusting the inventory, and documenting the transaction.

Mail service pharmacies use "assembly line," automated, drug distribution systems to dispense prescriptions. These are checked by a pharmacist and mailed with patient information directly to the patient. Mail service pharmacy has taken advantage of the economies of scale offered by automation, and is attractive for serving some patients with chronic diseases who are taking maintenance medication and need to have the prescription delivered to their homes.

Large, fully automated mail service pharmacies integrate the patient medication database with "assembly line," automated drug distribution systems to dispense thousands of prescriptions per day. In the Veterans Affairs (VA) system, consolidated mail outpatient pharmacies (CMOPs) located across the country use automation to fill 8,000 to 10,000 prescriptions in a 10-hour day. This has freed pharmacists to spend more time on direct patient care.[29]

Medication orders are entered into patient databases at the local VA medical center and are electronically transmitted to the CMOP where they are automatically processed. All items to be dispensed to one patient are placed in a bar-coded tote bin. A technician scans the tote's bar code and a computer screen indicates which items are needed. The tote is placed on a conveyor belt, where prepackaged items, loaded into racks mounted over the conveyor belt, are automatically dispensed onto an area of the belt that the computer has designated for the individual order. The items are then transported to a chute and deposited into the appropriate tote. The tote travels to the final dispensing area, where machines automatically dispense oral solids into plastic vials. The automated bottle filler scans the tote to determine what medication is to be dispensed. A label containing the patient and medication information is printed and applied to the vial, and the vial is filled and capped. Before releasing the vial, the computer verifies the tablet count, cap integrity, and label placement. When the order is complete, a pharmacist checks the items and sends the tote to technicians who prepare the medications for mailing.[29]

Hospitals and institutional long-term care pharmacies employ various centralized automated pharmacy systems, which are integrated with the pharmacy information system, for repackaging and labeling of solid oral medications. These automated pharmacy systems count, package, and label medication in patient-, date-, and time-specific single unit-dose, multidose, or patient "med pak" packaging (all medications for a particular administration time are packaged together.

Bulk medications are identified by humans and manually loaded into an individual, medication-specific canister that is calibrated, according to the size and shape of the specific drug product, and that will only fit into its assigned location. Some systems incorporate bar-code labeling on the canister, which can be scanned against the bulk medication supply to ensure accuracy. With information downloaded from the pharmacy information system, the automated pharmacy system packages medication in unit-dose packets, labels the packet with the required information, and dispenses the medications in the order in which they appear on the fill list. Integrated robotic systems that read bar-coded over-wrapped unit-dose packages are used to prepare patient medication cassettes and have the ability to return unused medications to stock. These systems are not limited solely to oral solid mediations; injectables, suppositories, and liquid unit-dose containers can all be handled.

A comprehensive and electronically sophisticated automated pharmacy system counts, packages, and labels patient-specific medications in unit-of-use envelopes at the time of mediation administration, and also sorts the envelopes by patient in the order in which the medications are to be administered. It can be used centrally in the pharmacy or in decentralized patient care areas. Nursing unit-based, decentralized systems feature "ATM-like" dispensing cabinets, which offer secure, computer-controlled access to medications and related supplies. When linked with the pharmacy computer system, as soon as a pharmacy-verified order is activated, the nurse may request a dose from the automated pharmacy system. Mobile systems offer the ability to move the dispensing cabinets from bedside to bedside, and enter and review orders from a terminal mounted on the cabinet. An important optional feature permits bar-code checking and the reading of the dose being administered at the patient's bedside.

Today, integrated drug distribution systems are being planned to meet the needs of an entire community by providing seamless distribution to primary care clinics, hospitals, long-term care facilities, and private homes. Automated pharmacy systems are making it possible for large health care systems to provide just-in-time deliveries of doses to refill drug distribution machines in an area-wide system of health care delivery sites.

The central fill concept allows a group of pharmacies to operate a central, high-volume dispensing facility. Once filled, the prescriptions are delivered to the patient's local pharmacy.[30] Telepharmacy is the provision of medications and pharmaceutical care by remote control from a distance. The Veterans Health Care System and others have demonstrated that such systems can provide pharmacy services to sites where the demand is too small to justify employment of a pharmacist in that location.[31]

In community pharmacy, the use of some form of automated dispensing automation differs widely. Among chain pharmacies, the percentage utilizing automated counting devices is high; among independent pharmacies, it is only about one in five.[32] In hospital pharmacies, automation is used to support centralized unit dose dispensing in 9.4% of hospitals, decentralized drug storage and distribution in 49.2%, IV production and manufacturing in 27.5%, and for transportation systems in 29.4%. Use of automation is more common in larger hospitals and systems, and those affiliated with a medical school.[33]

In pharmacy, the application of bar-code systems has received considerable attention for a long time, because of the recognition that pharmacy practice must store, process, and distribute a type of product (eg, dosage forms) which have numerous and a challenging variety of forms, storage, labeling, security, and patient safety requirements. The need for product identification by machines at the manufacturing, wholesaling, and ambulatory pharmacy level is similar to that for the processing of many other types of products (eg, canned foods) and the National Drug Code system maintained by the FDA has served well for this purpose.

In community pharmacy practice, the benefits of bar coding appear so evident and achievable that three major organizations, the American Pharmaceutical Association, the National Association of Chair Drug Stores, and the National Community Pharmacists Associations joined in recommending the use of bar-code verification in all pharmacy practices within 3–5 years.[34]

In hospital pharmacy practice, though the benefits of the bar coding of drug products at the unit dose level are very attractive in theory, as a practical matter the complexity involved has thwarted years of attempts to achieve this goal. The problems have included such practical matters as the small size of unit dose packaging, the unwillingness of the pharmaceutical industry to offer larger packages, the difficulty in achievement a standardized approach, and the unwillingness of hospitals to pay the extra premium at which such packaging has been offered or can be achieved by in-house packaging operation.

The technology of product recognition by machines has advanced such that alternatives to bar-code systems are becoming available. Though the barriers to achievement are being narrowed to cost alone, that may not be inconsiderable. For example, the added cost of nursing time required for involvement in the bar-code reading process has been projected to have a negative effect on nursing productivity nationally.[35] In a report on pharmacy manpower in 2002, Knapp estimated that by the year 2020, the need for pharmacists would exceed the supply by 157,000. Though today automated systems prepare only 125,000 of the 3 billion prescriptions dispensed annually, Knapp assumed that by 2020 the use of automation and information technology plus supportive personnel will achieve an improvement in productivity by a factor of *five*. One of the assumptions was that a properly designed automated system would *not* require a personal final check by a pharmacist of every filled order, currently a requirement in many states.[36] Nevertheless, the projected shortfall accompanied by rising salaries makes further automation of the dispensing function appear essential.

Automation and Patient Safety

Patients are threatened by adverse drug events, and there is evidence that many can be prevented by pharmacy automation. The death rate associated with medication errors in hospitals was estimated in 1999 to be about 7,000 per year.[37] The relative frequency of medication errors was studied in 2002 in 36 hospitals and skilled nursing facilities in Georgia and Colorado, using three different methods to detect and confirm each error: direct observation of the nurses as they administered the doses, chart review, and incident report review. Medication errors were common: almost one of every five doses were in error in the typical facility. The percentage rated potentially harmful was 7%, or more than 40 per day in a typical 300 patient facility.[38]

The death rate from ambulatory patient errors has been difficult to estimate. Although the patients are not as ill, there are many more of them. The relative frequency of medication errors in ambulatory pharmacies was estimated in 2003 in a study involving the observation of pharmacists filling prescriptions in 50 pharmacies in six major cities. Prescriptions containing one or more errors occurred at a rate of l.7%, or about four per day in a pharmacy dispensing 250 prescriptions daily. The percentage rated potentially harmful was 7%. Based on these findings, among the approximately 3 billion prescriptions filled annually are an estimated 51.5 million prescriptions that contain one or more errors, of which 3.3 million are potentially dangerous.[39] The need for the improvement in the quality of the drug dispensing and administration processes, in institutional and community pharmacies, is clear and compelling.

In hospitals, the first measure of the impact of automation on medication errors was reported in 1969. A patient-profile linked dispensing envelope system delivered each unit dose to the patients' bedside at the time for administration, in an envelope labeled with the complete physicians order. In a prospective, controlled clinical trial, data were collected by direct observation of the nurses and pharmacists at work, involving 192 8-hour

work shifts observed for the old system and 64 work shifts for the new (automated) system. The error rate declined from 13% to 1.9%.[40]

In 1975, a similar system achieved an error rate reduction from 7.35% to l.6l% (omission errors were not counted).[41] Barker et al. reported a prospective controlled clinical trial in 1984 in which a bedside unit-dose dispensing machine system controlled by a pharmacy computer reduced the error rate from 15.9% to 10.6% on a medical-surgical nursing unit. The design involved a crossover design during the 2-week study period.[40]

In 1995, two studies focused on a nursing unit-based automated device. When used for narcotics and selected first-dose medications and not integrated with the patient's medication profile, the error rate for all doses retrieved from the Pyxis device as detected by observation was 16.3%, compared to 5.4% for doses retrieved from a medication drawer.[43]

The same year, Borel and Rascati compared medication error rates before and 2 months after implementation of Pyxis integrated with the patient profiles and found that the error rate declined from 16.9% down to l0.4%.[44] In community pharmacy, in 1993 Maliekal evaluated an automated dispensing system in an ambulatory pharmacy, by pulling 270 prescriptions off the line, and comparing the count delivered with that called for by the label. Thirty-eight discrepancies were discovered; 22 overfills, l4 underfills, and two could not be classified.[45]

Current studies underway at Auburn University have demonstrated that in a prospective controlled clinical trial an automated prescription filling system (ie, ScriptPro) reduced the rate of dispensing errors among the prescriptions to which it was applied from 2.8% down to 2.1% in a community pharmacy, and from 0.3% down to zero in a chain pharmacy. Each pharmacy was observed for 2 weeks before and after the implementation of the automated system.[46]

Automation may contribute to human errors when it engenders complacency. In a hospital study, the observers reported that typically nurses administered drugs from an automated device without checking them, whereas those taken from the patient's medication drawer were typically checked.[43] It must be recognized that automation is only one component of a human-machine system, and the education and training required for the human part must not be neglected.

Features shown desirable for reducing errors in automated pharmacy systems, as supported by research to date, are outlined below:

1. Controls are comprehensive—Controls extend all the way from the point of order-entry to the point of dispensing or administration, and are integrated with the pharmacy or facility information system.
2. *Electronic identification (eg, bar coding)*—All components including the drug, patient, and person dispensing are identified.
3. *Access to medications is limited and controlled*—Medications are accessible only when needed, and only by authorized personnel.
4. *Dispensing/administration is captured*—Documentation is automatic and complete.
5. *Drug use information is provided*—Access must be immediate.
6. *Labeling machine prints and affixes a label*
7. Controls are not easily compromised—System overrides are signaled visibly and/or audibly at the time of the event, and electronically documented.[47]

Although there are no *national* standards for automated pharmacy systems, most State Boards of Pharmacy have, or are in the process of writing, regulations for the use of automated systems. Model regulations for automated pharmacy systems have been adopted for incorporation into the National Association of Boards of Pharmacy Model State Pharmacy Act and Model Rules.[48]

The American Society of Health-Systems Pharmacists has published Guidelines on the Safe Use of Automated Storage and Distribution Devices.[49] The Joint Commission of the Accreditation of Healthcare Organizations has published standards for automated medication distribution systems.[50]

Pharmacists contribute to positive medication outcomes by assuring that each patient receives safe, appropriate, and effective drug therapy through the provision of pharmaceutical care, which is the responsible provision of drug therapy for the purpose of achieving defined therapeutic outcomes that improve a patient's quality of life while minimizing patient risk.[49] The provision of pharmaceutical care extends the pharmacist's responsibility beyond the delivery of the drug product to include the outcomes of drug therapy. Within the broad concept of pharmaceutical care, the public must be assured that pharmacists will retain their crucial role in the medication use process—specifically the pharmacist's review and evaluation of all prescriptions or medication orders before dispensing or administration, and control of the distribution of every dose dispensed or administered to every individual patient—even as the dispensing process becomes increasingly automated.

Although control of medication distribution will be increasingly exercised through automated systems, the ultimate responsibility for these systems must remain with the pharmacist, the drug use expert who best understands the purpose of these systems and their limitations. The exercise of control over an automated pharmacy system will require that the pharmacist implement standards developed by the profession for the performance of the system, and provide a mechanism for identifying deviations from those standards and a responsive system for taking action to correct any deviations when they occur. Thus, in each of the automated pharmacy systems evolving, the focus of the pharmacist should be on the control system—its performance standards and contribution to the achievement of pharmaceutical care outcomes. Pharmacists must obtain the needed education and training to implement and monitor these control systems effectively.

As the use of automation increases, the complexity of drug distribution systems will be such that the pharmacist will no longer be able to comprehend all aspects of these systems, nor should the pharmacist be expected to do so. The crucial new skills for the pharmacist will encompass: (1) how to operate automated pharmacy systems to produce the outcomes desired, (2) how to recognize when a system failure occurs or is imminent, (3) how to compensate to protect patient safety when failures occur, and (4) how to get failures corrected expeditiously.

A *White Paper on Automation in Pharmacy* describes automation including quality, safety, manpower and professional issues, and model regulations for State Boards of Pharmacy.[48]

The Systems Approach

The authors began this chapter by defining the word *system*. They continued throughout the chapter looking at subsystems and focal points for the use of technology in pharmacy practice. The authors propose that all of the pieces of the technology puzzle are truly in place and are readily available for implementation into all pharmacy practice settings.

Taking any technology topic to a search engine such as www.google.com will yield hundreds and potentially thousands of "hits" for consideration. Technology vendors are fully aware of the marketing potential for their products and services via the World Wide Web. The authors believe pharmacists will increase their efficiency and effectiveness through the appropriate selection of technology.

To maximize operational effectiveness in pharmacy practice, it is necessary to approach any pharmacy operation with a goal of integration of work systems in mind. It is usually possible to build an interface between any two devices such as a pharmacy management system and an automated dispensing robot. A simple interface between two devices is called a "point-to-point" interface. Multiple interfaces can exist in any pharmacy operation. The authors promote a systems approach that seeks to integrate the entire operation through the interconnection of all work systems.

For example, consider a retail pharmacy operation. The operation can be divided into the following functional areas: intake; processing and exceptions; fulfillment; quality assurance; front store; counseling; delivery; knowledge management; and external connectivity. Specific technologies exist within each functional area. For example, integration within the intake area might involve electronic prescribing, interactive voice response systems, a fax server, predictive fulfillment applications, and customer relations management software.

The authors recommend that a careful examination of opportunities for integration takes place for the entire operation. One goal should be to take work out of the system that would normally be performed by costly personnel. Error reduction is another primary goal. Providing value added services and features and benefits from association with the pharmacy operation is another desired goal. While it is possible to achieve some benefits from piecemeal enhancements to a pharmacy operation, the authors are confident that a combination of technology, training, and facilities designed will maximize results.

Emerging Technologies

"The imperatives of improving documentation, reducing error, and empowering patients will continue to motivate use of information technology in health care."[51] There are so many exciting and emerging technologies to investigate that we usually find it more interesting to look at the technological "low hanging fruit" than we do future implications of genomics and nanotechnologies. There are a number of futurists who predict that disruptive technologies must be anticipated because they will heavily impact organizations on both strategic and tactical levels. One nonprofit organization that looks 2–5 years into the future is the HealthTech Center (www.healthtech.org). This organization envisions a bulging pipeline of new clinical technologies that excites consumers and drives and integrates change in health-care systems.

HealthTech predicts that less invasive surgeries and therapies will take place as care increasingly moves to ambulatory and home care settings. It reports that patients and caregivers will see more real-time access to health data. Further, it also predicts that work for shortages will be softened by technology deployment.

Another corporation HEALTHvision (www.healthvision.com) predicts the future containing technology offered through subscription services via the Internet to caregivers. This corporation anticipates the complete electronic prescription pad to be a near future reality. It also anticipates that patient access to a shared medical record will occur in increasing numbers. Finally, HEALTHvision sees a proliferation of health device monitoring at home and the realization of health demographic and clinical information availability on the Internet.

At Auburn University, the authors investigate technologies such as continuous speech recognition. While many believe that this technology is not ready for prime time, these authors use it on a daily basis. They are tracking literally thousands of innovations that include clinician-tailored software, PDA programming for patient health-care uses, the use of digital pens in health-care, and all modes of wireless communication.

Surveys performed in 2003 are still demonstrating that the establishment of wireless networks in health-care systems remains a top priority for implementation. A combination of cellular, WiFi (802.11b), Bluetooth, 3G, and infrared technologies are rapidly proliferating to assure real-time access to needed information.[52] A Danish implementation of a wireless healthcare network successfully used existing capability with wireless phones to move clinical information to the point of care. "The Wireless Application Protocol (WAP) technology implemented in newer mobile phones has built-in facilities for handling much of the information processing needed in clinical work."[53]

Currently, the authors are tracking over 160 technologies to impact patient compliance to drug therapies. This is believed to be a natural outreach activity for the pharmacist wishing to move beyond a product focused, traditional practice.

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CHAPTER 96

The Patient: Behavioral Determinants

Bonnie L Svarstad, PhD
Dara Bultman Sitter, PhD, RPh

Health professionals often assume that the process of health care simply involves a patient to seek care for his/her symptoms, a physician to prescribe appropriately, a pharmacist to dispense appropriately, and a patient to follow directions and take the medication properly. Similarly, it is tempting to believe that patients, upon following physician and pharmacist suggestions, readily experience symptom improvement and better health. The reality is that many individuals needing health care do not receive it, receive it late, or do not follow through with directions. For example, a National Health Survey shows that at least 30% of those considering help for emotional problems do not actually seek care.[1] In other cases, there may be a considerable delay in seeking care. While most breast cancer symptoms are discovered by women, at least one third of breast cancer patients will be aware of their symptoms for 3 months or more before seeking an initial provider evaluation.[2] In addition, 30% to 60% of all individuals who obtain medical care do not follow through with prescribed treatment[3] and almost half of those taking medications do not ask any questions when visiting the physician.[4]

Why do some people seek medical advice while others with similar symptoms do not? Why do some individuals who obtain medical care follow recommendations and take an active role in their care, while others with similar diagnoses and treatments not follow through with recommendations and not ask any questions about their treatment. To answer these questions, we need to understand the determinants of patient behavior. This chapter begins with a section on theories related to patient behavior in health. Four sections describe how patient behavior is influenced by characteristics of the patient, drug regimen, environmental factors, and interaction with providers. Finally, a health collaboration model is presented as a tool to help pharmacists understand how they can positively affect patient behavior and health outcomes.

TYPES OF PATIENT BEHAVIOR IN HEALTH

The three main areas in the study of patient behavior are: (1) preventing illness or detecting it in an asymptomatic stage, (2) obtaining a diagnosis and discovering suitable treatment, and (3) undertaking or maintaining treatment aimed at restoring health or halting disease progression. Kasl and Cobb[5] defined these health-related behaviors and labeled them health behavior, illness behavior, and sick-role behavior, respectively. The definitions are still useful today, although some terminology has changed to reflect contemporary theory and research on health behavior.

Health behavior that is preventive in nature generally is referred to as *preventive health behavior*. Expanding on the original definition, preventive health behavior is defined as actions taken to prevent illness and maintain physical, emotional, intellectual, spiritual, and social well-being. Examples of preventive health behaviors include participation in health screening programs, following healthy diet recommendations, participation in relaxation and cardiovascular exercises, and creating and maintaining close personal relationships.

Illness behavior is any activity undertaken by individuals who perceive themselves to be ill that defines the state of their health and aids in discovering a suitable remedy.[6] Illness behavior is the way persons respond to bodily indications that they experience as abnormal; thus it involves the manner in which persons monitor their bodies, define and interpret their symptoms, and seek health care.[7] Individuals attempt to ascribe cause and meaning to their illness symptoms and may self-diagnose and treat. Alternatively, individuals may visit a doctor or another prescriber and a pharmacist in order to obtain a prescription drug.

Actions taken to restore health or halt disease progression traditionally have been referred to as sick-role behaviors and now are referred to as *treatment behaviors*. Originally, the conceptualization of sick-role behavior[8] offered a systematic approach for analyzing the behavior of sick individuals in the US and other modern Western societies. This functionalist perspective regarded illness as dysfunctional to society and considered sick-role behavior as seeing the physician, passively following his or her prescription, and regaining health. This traditional view of the patient as a passive individual has been criticized extensively in recent years.[9]

Patients today are considered to be thinking, able decision makers who can play an important role in the treatment process.[10] Because patients are now recognized as active individuals, more attention is being paid to ways of restoring health or slowing illness progression through improved provider-patient communication and patients' involvement in their own treatment. Emphasis therefore is placed on a range of patient treatment behaviors including sharing beliefs and expectations, asking questions, adhering to regimens, using home monitoring devices, keeping appointments, identifying and reporting side effects and drug-taking problems, and other valuable forms of communication that are necessary in contemporary health care.

MODELS OF PREVENTIVE BEHAVIOR AND HEALTH UTILIZATION

People experience illness and treatment at many levels. Physiological, intellectual, social, and emotional processes are all a part of an individual's illness experience. A patient's understanding of illness or symptoms, the information provided by health-care providers, how the illness and treatment affect usual daily activities as well as the individual's previous experiences and beliefs with illness all influence behavior. Behavioral scientists have attempted to understand human responses

to illness by using a number of different theoretical perspectives and models of health behavior.[11–16] The two models commonly referred to in the study of patient behavior are the Health Belief Model developed by Rosenstock[14] and Andersen's Model of Health Service Utilization.[11]

The Health Belief Model was developed when studying preventive health behaviors. The model suggests that individuals seek preventive care if they possess some relevant health motivation and view themselves as vulnerable, if they view the condition as threatening, and if they believe action will be beneficial. In other words, these individuals believe themselves to be susceptible, the condition to be serious, and the benefits of action to outweigh the potential barriers. In addition, some cue to action must occur, either as a symptom or as an outside motivational message, thus inspiring the individual to take action. This model focuses on individuals, placing decision-making in their hands, and suggests that individuals determine how to balance the intricacies of their own lives.

The study of illness behavior often is examined using Andersen's Model of Health Services Utilization. Andersen suggested that three main factors affect an individual's use of health services:

1. Predisposing factors
2. Enabling factors
3. Need factors

Predisposing factors are those factors that vary an individual's inclination to use services. Andersen suggested that prior to illness, individuals have a measure of propensity toward use of medical services. These predisposing factors include demographic variables such as age and gender; social structure variables such as education, occupation, and ethnicity; and health beliefs about medical care, physicians, disease, and medication use. Enabling factors are those factors influencing the individual's ability to use services, thus they reflect the fact that an individual's ability to use services depends on individual family and community resources. Finally, need factors are those factors related to the individual's belief in the seriousness of illness symptoms and the necessity of intervention. Need factors are separated into two categories, perceived need and evaluated need.

Both the Rosenstock and Andersen models of health utilization include the patient perspective, patient demographics, patient resources, and provider variables. As previously stated, these models are very useful when focusing on preventive health behavior and initial use of health services. In cases of chronic illness requiring ongoing treatment, the models could be improved. At the very least, additional influencing factors such as drug characteristics and the treatment environment must be incorporated into a model of health behavior. Ongoing treatment also requires continual interaction between the patient and the provider, and that aspect must be incorporated into a health behavior model, as discussed later. Because patient behavior and outcomes are influenced by the patients themselves, provider characteristics, drug factors, and the treatment environment, the discussion begins here.

PATIENT FACTORS INFLUENCING BEHAVIOR

Many patient factors have been examined in relation to behavior and health. Although study findings vary, the two demographic factors continually observed are patient age and sex. The relationship between age, sex, and health is in part physiological and in part a social construct. Age and gender influence health experiences through life. Survey information related to age, sex, illness, and drug use gives evidence to this point.

Older people tend to use health services more than younger people. While the elderly represent 12% of the population, they account for 34% of total pharmaceutical expenditures.[17] The relationship between age and drug use is in part related to more chronic illnesses in old age. Approximately 36% of the elderly have three or more chronic conditions, while about one third of the nonelderly have at least one chronic condition.[17] Biological age is not the only reason for increased use of health services among the elderly. Gerontologists argue that age often brings loss of customary resources and thus changes the way individuals are attended to and the way they cope with stress.[18]

Women tend to use health services more than men. In a survey of 1360 elderly rural individuals, women reported taking twice as much medication as men.[19] The self-reported use of OTC medications in the rural older population also shows that women take more OTC medications than men.[20] A longitudinal study of 488 healthy, community-dwelling, elderly volunteers show that female subjects, those older than 80 years or those who reported themselves to be in fair or poor health on initial health self-report have a significantly increased use of prescription medications. Moreover, increased medication use did not predict mortality over the next 10 years in this population.[21]

Sex also makes a difference in psychotropic medication use. In the case of children, the gender effect on psychotropic drug use varies across child age.[22] At younger ages, male children are more likely to use psychotropic drugs. However, at older ages, female children were more likely to use psychotropic drugs. Use of psychotropic drugs varies by gender in adults.[23] After controlling for statistically significant factors such as demographic and health services, presenting complaints, and psychiatric diagnoses, women were still 37% more likely than men to receive a prescription for an anxiolytic and 82% more likely than men to receive an antidepressant prescription. Conversely, Sleath et al[24] found that men were more likely to receive psychotropic medications than women, in a poorer, older, and more nonwhite sample of patients.

Age and gender make a difference in the number of visits made to the doctor's office per year. Across age groups males visit the doctor less often than females do.[9] The greatest difference occurs in the reproductive years, when women make about twice the number of office visits of men (3.1 versus 1.7). Men and women 65 years or older make the most office visits, followed by middle-aged persons and children under 15 years.[9]

Age and gender make a difference in experiences at the community pharmacy. Schommer and Wiederholt[25] report that male patients and older patients are more likely to be solicited for feedback and have drug use monitored by pharmacists. A separate survey from 2135 randomly selected respondents also suggests that men receive more consultation from pharmacists; however, individuals younger than 40 years reported receiving more consultation from pharmacists than older respondents.[26] In another study, younger patients were more likely than older patients to know how their prescribed antidepressant worked, when it started working, common side effects, how to manage side effects, and how long their physician wanted them to take the medication.[27]

The influence of social factors may explain the consistent finding that males report fewer physical symptoms than females and typically have a lower level of drug use. Physical differences only partially explain gender differences in symptom reporting and medication use.[28] Studies of children's illness behavior suggest that boys and girls acquire different beliefs and ways of coping with pain through the process of socialization into traditional male and female roles: girls are encouraged to express their pain, whereas boys are encouraged to deny their pain and avoid feminine or sissy-like behaviors.[29] Consequently, men may be less likely to complain about, and seek relief from, pain unless they are encouraged to do so by their caregivers.

Other important patient factors examined in relation to behavior and health include socioeconomic level, race, and ethnicity. Socioeconomic level is a measure used to reflect income, education, and occupation; it describes social class within a community. Differences between socioeconomic groups in accessibility, use, and quality of care are contributing factors

to the widening gap in rates of morbidity and mortality. Recent evidence of the inequality that persists comes from the National Longitudinal Mortality Study; higher levels of both income and education are associated with lower rates of mortality.[30] Race and ethnicity are associated with differences in health-related problems, including access to health-care services. Socioeconomic resources also influence children's health behavior, with uninsured children being more likely than insured children to have gone without needed medical, dental, and other health care (22% versus 6%).[31] Health-care providers may find it useful to be aware of and explore potential differences in health beliefs, diet, and other health behaviors.

In a classic sociological study, Zborowski[32] demonstrated that patients from different ethnic backgrounds had very different reactions to pain, even though they were suffering from similar physical problems (ie, herniated disks and spinal lesions). For example, Jewish and Italian patients tended to have a more emotional response to pain; they felt freer to discuss their pain, complain about it, groan and cry, and ask for relief. In contrast, patients from other backgrounds tried to deny their pain and appear more stoic. Based on observational and interview data, Zborowski concluded that the patients had learned different ways of reacting to pain and that they simply were behaving in a manner that was expected, accepted, and approved by their families and others in their community.

The primary chronic health problem among Mexican Americans in the US is non-insulin-dependent diabetes mellitus. In fact, diabetes is the fifth leading cause of death among Latino women and seventh among men.[33] The US Hispanic populations experience diabetes complications such as nephropathy leading to end-stage renal disease, retinopathy and blindness, neuropathy, and nontraumatic lower extremity amputations.[34] While access to medical care or extent of medical care may not be the reason for the differences in complications in Hispanics and African Americans, the researchers suggest that the quality of medical care is a likely determinant of morbidity.

Health-care providers interviewed about perceived barriers to treating Latino patients have mentioned a number of problems, including communication barriers, financial problems, and cultural barriers.[35] Specifically, Latino patients are often very polite to doctors, so polite that rather than discuss their diabetes care, the patients nod their heads and agree with the doctor. Patients often do not believe that the medication supplies are free and therefore do not take the necessary diabetic supplies as often as needed. Other patients believe that receiving government assistance in medical supplies will decrease chances of US citizenship. For the families that do pay for medical supplies, a different problem arises. Expenses for a woman's needs often are considered secondary to the good of her family, and therefore expenditures for diabetes medications and supplies are considered less important than other family necessities. Finally, traditional folk remedies, such as aloe, cactus, and garlic, compete with the use of prescribed diet and medications, because patients (and possibly providers) are not aware that treatments can be combined.

Understanding patient behavior requires an attention to possible and common emotional experiences. Emotional factors of concern to patients include uncertainty of what to expect with this new illness or symptom; dependency on providers to give the best treatment and on family to help with daily life; fear of change and death; pain and discomfort; lack of privacy in physical examinations; loss of identity as a healthy person; isolation from usual support systems such as coworkers, teammates, and friends; and a search for meaning on how to put all of these experiences into perspective. Emotional factors are of particular concern when the patient has been diagnosed with a terminal illness, an illness with a social stigma, or an illness that requires change in daily behavior.

A look at some empirical work emphasizes the importance of health beliefs, perceptions, and expectations. In a study focused on medication adherence, using patient interview and record reviews, researchers found that the best predictor of treatment adherence was previous patient experience with the medication.[36] In addition, patients were more likely to adhere to the medication treatment when they had been told more about taking the medication, were asked about prior experience with antidepressants, and discussed other things they could do to make their life more pleasant. It is not understood if these messages influenced patient beliefs or if these messages allowed enough communication between the patient and provider to influence patient beliefs. In another study of patients receiving treatment for depression, positive patient beliefs at the beginning of treatment were the best predictor of continued antidepressant use and a positive evaluation of the medication at followup.[27]

The meaning of insulin treatments differs for patients and providers. For example, surveys suggest that most Hispanic patients recognize positive aspects of insulin treatment, but virtually all report negative effects, and nearly one third believe that receiving a prescription for insulin indicates that the disease has advanced into a very serious stage.[37] Forty-three percent of patients were concerned that insulin causes serious health problems. In fact, 25% of Hispanic patients report fear that insulin causes blindness. Patients need information that may not appear obvious to providers.

Patient expectations of pharmacist care affects patient behavior.[38] Pharmacy clients may not ask pharmacists questions because of client embarrassment or because they are not aware that it is appropriate to seek information from pharmacists. Clients may not realize that pharmacists check for drug interaction and that patient consultation is required by law in some states, while an offer to counsel is required in others.

In general, patient age, sex, ethnicity, socioeconomic level, and health beliefs affect patient behavior in health. Older individuals and women tend to use more health resources. Ethnicity affects health beliefs, diagnosis, and treatment. Socioeconomic level affects health service use, morbidity, and mortality. Social distance may exist between patients and providers with different ages, gender, ethnicity, and socioeconomic level and is a potential barrier to effective treatment. Barriers to more appropriate patient health behaviors can be reduced by providers.

DRUG FACTORS INFLUENCING PATIENT BEHAVIOR

Drug regimens can be complex. The complexity of a drug regimen often is measured in the total number of medications taken daily, number of daily doses, duration of treatment, the extent to which the regimen is tailored to daily routines, and the side-effect profile. Medications may require special behaviors, for example having to take a dose 1 hr before or 2 hr after a meal, avoiding foods that are common in the diet, taking doses three or more times in a day, refrigerator storage, or skill in administration. In addition, just learning the name of the drug prescribed, purpose of the drug, proper dose, when to begin taking it, frequency of dosing, and when to stop treatment is complex.

The complexity of a therapeutic regimen may prevent patients from adhering completely. Complex regimens may produce information overload. Alternatively, medications requiring behaviors that are difficult to fit into regular daily activities are less likely to be taken as prescribed by a patient. A drug adherence study using an electronic monitoring device to measure dose compliance shows that patients adhere better to once-daily dosing than twice-daily dosing.[39]

Medication treatment often is accompanied by adverse drug effects. Antidepressant and antipsychotic medication nonadherence has been related to adverse drug experiences.[40,41] Blackwell[42] suggests that it is mainly unexpected or alarming side effects of treatment that patients offer as the reason for stopping treatment and that a discussion of side effects along with an explanation of the therapeutic benefits of the medication would be helpful to patients. Myers and Calvert[43] found that patients given information on antidepressant benefits and

adverse effects were less likely to report side effects than patients given only adverse effect information or almost no information. In another study of treatment with antidepressants, 27% the patients were bothered by the medication and their dissatisfaction with the medication significantly increased the number of medication omissions.[27]

ENVIRONMENTAL FACTORS INFLUENCING PATIENT BEHAVIOR

CHOICE AND CONTROL—Patients given more autonomy and opportunities for self-determination tend to show greater health and morale improvements. Rodin and Janis[44] suggest that asking patients for their opinions during the medical encounter increases their feelings of involvement and self-efficacy. The researchers believe that internalization of treatment plans and feelings of greater control result in better adherence to recommendations and improved health status. Social and environmental restrictions in choice and control over daily activities can have negative effects on physical health and well-being of nursing-home residents.[45]

Allowing patients a choice in their medication regimen also can affect patient adherence positively.[46] Patients were randomly allocated to one of three treatment groups: group A received one dose of medication (75 mg) at night; group B received three doses of medication (25 mg each) during the day; group C were allowed to choose either A or B above. Researchers report the greatest rate of adherence occurred in the group who chose to take 1 tablet three times a day.

PHARMACY ENVIRONMENT—The structural layout of many community pharmacies does not include an area for private consultation and dialog between the patient and the pharmacist. In addition to this lack of privacy, pharmacists often experience other environmental barriers to meaningful interaction with their patients, including insufficient supportive personnel, a heavy workload and backlog, people waiting to present prescriptions or receive pharmacist assistance, incoming phone calls and requests for information or help from coworkers, interns, and other staff, and inadequate computer technology, software, and preparation for new consultation roles. The impact of these environmental factors are not well studied, but they are believed to be major barriers to pharmacist and patient interaction.[47] For example, a recent observational study in 306 pharmacies found that pharmacists working in busy versus non-busy environments are less likely to talk with patients, to give oral information to patients, and to ask questions assessing patients' understanding.[48] Patients also have reported that pharmacy site barriers (including pharmacist time limitations and lack of privacy) are among the most common reasons why they do not ask the pharmacist their questions.[38] Research examining the effects of these environmental factors on patient behavior is rich in potential for improving patient care.

EFFECTS OF PROVIDER-PATIENT INTERACTION ON PATIENT BEHAVIOR

The relationship between patient and health-care provider has been studied much more extensively between patient and doctor than between patient and pharmacist. Research using observation, audio-transcriptions, and interventions suggests that both physician-patient interactions and pharmacist-patient interactions are related to patient behaviors and outcomes.[49,50] Patients use three main sources of information when making decisions about their illness and treatment: their personal experience with the illness and various treatments; information obtained from family, friends, and the larger culture; and their interaction with health professionals.[12] In recent years, there have been increased efforts to understand and improve the ways in which providers and patients interact with each other, because of changing societal views about the patient's role in health care and growing evidence that provider-patient interaction plays a central role in the safe and effective use of medications and health behavior change.[51–53] For example, many consumer and professional groups have criticized the lack of drug information provided by physicians and pharmacists and advocated a new *health culture* in which patients take a more active collaborative role in their health care.[52] Scientific studies also have found that the quality of provider-patient communication about drugs varies greatly and that efforts to improve communication can affect the patient's health behavior and quality of life in multiple ways, suggesting new goals and models of communication.[10,16,52]

In the sections below, scientific research is briefly reviewed, examining the different ways in which provider-patient interaction can affect the patient's health behavior. A new model of interaction called the Health Collaboration Model (HCM) then is presented. This new model incorporates current research and philosophies of care and can be used to guide pharmacists' efforts to understand and improve collaboration processes and outcomes in their practice. In contrast to traditional models of medical care, the HCM emphasizes the importance of patient feedback and participation in treatment decisions. It also clarifies the different ways in which providers can enhance patient comprehension and recall of regimens, patient motivation and satisfaction with care, patient feedback, and collaborative problem-solving and resolution of conflicts.

EFFECTS OF PROVIDER INSTRUCTION ON PATIENT COMPREHENSION AND RECALL—Physicians and pharmacists continue to be the main sources of drug information and advice given to patients. However, observational studies of provider-patient interaction point to a number of problems. Patients often receive information about the drug name and recommended dose and dosage frequency, but the majority of patients still receive no specific oral counseling about the purpose of therapy, how long to take their medication, side effects, other precautions, and when the medication will begin to work.[26,48] Studies also have demonstrated a direct link between the *provision of explicit or specific instructions* and patient comprehension of the regimen and its components; patients whose providers do give them more explicit or specific instructions clearly have a better understanding of how they are supposed to take their medication.[16,27] In fact, the quality of medication instruction by a provider is a better predictor of patient comprehension and recall than the patient's age and education.[27]

Research in psychology suggests that people are more likely to comprehend and recall those items that are considered important or relevant to them. Studies of health communication support this notion; patients whose providers communicate the *purpose or importance* of drug therapy are more likely to have an accurate interpretation and recall of the regimen than patients whose providers do not discuss these points.[49] Emphasizing the importance of certain recommendations also enhances patient recall of these particular recommendations, according to experimental studies conducted by Ley.[54] Another proven method of improving patient recall of advice is *repetition* of those items that are likely to be misinterpreted or forgotten. While repetition does not always have the predicted effect, it generally produces a 20% to 30% improvement in patient recall of advice.[55]

Research also has shown that there are substantial gains in patient comprehension and recall when providers use *written reinforcement* and *visual aids,* including printed leaflets or information sheets, expanded prescription labels and stickers, calibrated liquid measuring devices, and special containers or calendars that indicate exactly when each dose is to be taken.[56]

Several qualifications must be noted, however. First, none of these techniques is effective by itself. In fact, provision of written information without oral review and discussion by a pharmacist or physician usually fails to achieve desired outcomes.[56] Written information and memory aids cannot eliminate side effects and other problems that undermine patients' motivation

to follow certain regimens. Thus, it is not surprising that written information generally leads to improved adherence with short-term regimens but is not sufficient for maintaining long-term adherence.[49]

The difficulty and length of informational materials can interfere with the patient's ability to comprehend and recall advice. This may explain why written information occasionally fails to achieve desired results. In general, patients have fewer difficulties if providers *simplify instructions* by avoiding medical jargon and using shorter words and sentences.[57] Ley et al[58] tested this hypothesis by developing easy, moderate, and difficult-to-read leaflets for patients who were prescribed an antidepressant or tranquilizer. As predicted, the easier leaflets were more effective in reducing nonadherence. In fact, the patients who received the difficult leaflet made nearly the same number of medication errors as those who received no information.

EFFECTS OF PROVIDER SUPPORT ON PATIENT MOTIVATION AND EVALUATION OF CARE—Being ill and undergoing treatment can involve a variety of stresses, practical problems, and other concerns that adversely affect patients' evaluations of treatment and their motivation to perform difficult tasks such as changing an unhealthy life-style, taking multiple medications, tolerating adverse events, and maintaining a positive self-image and outlook.[59] A number of studies therefore have examined the ways in which providers attempt to motivate or support their patients during the treatment process. In general, the findings are consistent with social psychological research on social interaction and influence; patients react more positively if their providers give information and reinforcement about the benefits or value of a prescribed treatment (informational support), if providers express positive affect and concern for the patient (social support), and if providers adopt a participatory, as opposed to autocratic, style of decision-making (decisional support).[16,50,60,61]

Providing information about the potential benefits or value of a preventive or therapeutic regimen is important, because our behavior is determined, in part, by how highly we value a particular outcome and by our expectation that a particular action will produce that outcome. Support for this hypothesis is found in numerous studies examining the relationship between information giving and patient satisfaction with care. Hall and her colleagues[50] reviewed 41 separate studies conducted over a 20-year period and found that giving information was significantly predictive of patient satisfaction across studies.

Patients also develop more positive attitudes and achieve better treatment outcomes when their caregivers make a systematic effort to *reinforce* the value of therapy. This reinforcement can take multiple forms, such as giving feedback to patients about their conditions during follow-up medical and pharmacy visits, encouraging patients to monitor their own conditions with special devices, or making home visits to increase family support and reinforcement. For example, experimental studies in hypertension management have documented substantial gains in patient adherence and clinical outcomes if patients receive regular blood pressure monitoring and feedback about their condition from a pharmacist or nurse,[62] if patients are encouraged to monitor their condition using a blood pressure cuff,[63,64] and if a care team member visits the patient's home to increase family support and reinforcement.[65] Similar findings have been reported in studies of other chronic medical and psychiatric disorders.[66,67] While these findings are encouraging, it is important to note that the effects of information and reinforcement generally are lost when these special programs are discontinued.[62] Home monitoring devices also fail to achieve desired results if the provider does not follow up with patients who are using such devices.[68] This suggests that regular communication with a health-care provider is a key factor in maintaining the patient's motivation or satisfaction with care.

Conveying social support also is important, because people are more likely to trust or respond positively to another person if they have an emotionally satisfying relationship with that person. The rate of communication between two persons also tends to increase as their attitudes toward each other become more favorable. Results from observational studies of provider-patient interaction are consistent with these hypotheses. For example, provider expressions of empathy, warmth, and positive feelings toward the patient generally are associated with higher levels of patient satisfaction and adherence, whereas provider expressions of anger, hostility, and other negative talk are associated with lower levels of patient satisfaction, adherence, and treatment continuation.[49,50]

Providers also can influence their patients' motivation and evaluations of care by the ways in which they use (or misuse) their professional authority or power to make decisions affecting the patient. These different decision-making styles have been labeled the *autocratic* (provider-centered) approach versus the *participatory* (patient-centered) approach to care.[16,60] Providers who adopt an autocratic approach assume a dominant or controlling role, speaking with an authoritarian tone and giving directions without seeking patient input. In contrast, providers who adopt a participatory approach collaborate with the patient to develop a mutually acceptable treatment plan, *providing decisional support* or guidance without ignoring patient views and demanding compliance with a certain therapeutic plan.

Not surprisingly, patient satisfaction is greater when providers adopt more participatory or patient-centered approaches, when providers respond positively to patient requests and expectations, and when patients and providers are able to reach agreement about the treatment plan.[50] Allowing patients to participate in treatment decisions also is likely to increase their feelings of control and acceptance of recommendations, as noted earlier.[44] On the other hand, adopting an overly permissive approach in which patients are allowed to take a domineering or controlling role can have a negative effect on patient adherence and treatment outcomes.[50] In this case, providers *give in* to patient requests or stop pursuing more effective therapies to please the patient or save time.

EFFECTS OF PROVIDER MONITORING ON PATIENT FEEDBACK AND SATISFACTION—Surveys suggest that patients experience a wide variety of subjective and objective problems and concerns that contribute to nonadherence, dissatisfaction with care, and treatment dropout. These *barriers* to treatment adherence include doubts about the physician's diagnosis or need for treatment, misunderstandings about the regimen, difficulties remembering each dose, doubts about the effectiveness of the prescribed drug for their condition, concerns about side effects and other bothersome features of a drug, and fears about the long-term effects of treatment or social stigma associated with certain conditions or treatments.[52,69]

While these patient concerns can have detrimental effects on the patient's behavior, many patients are reluctant to complain or ask their providers about their medications.[4,38,70] At the same time, physicians and pharmacists do not always ask patients about their medication concerns, beliefs, understandings, and behaviors. Studies have found that some physicians use fairly intensive and effective methods of adherence monitoring (eg, ask open-ended versus closed-ended questions, multiple versus single questions, and specific versus general questions), while other physicians either ask no questions or global questions that yield limited patient feedback about patients' medication-taking concerns and behavior.[4,27,49] Recent work on adherence monitoring in community pharmacies[71] also reveals considerable variation in the extent to which pharmacists "monitor" or ask patients about their medication concerns, beliefs, understandings, and adherence. While most patients with prescribed antidepressants were asked by their pharmacist if they had any questions or concerns, only 53% of the patients felt the pharmacist encouraged them to express their concerns.

According to theories of communication, providers who ask carefully designed, open-ended questions about patient concerns and adherence will be more likely to receive accurate

patient feedback than those who wait for their patients to volunteer this information.[16,72] To test this hypothesis, Rickles randomly assigned pharmacy patients to two study groups, a control group that received usual pharmacist care and an experimental group that received brief telephone monitoring from a pharmacist using a specially designed monitoring tool for assessing patient beliefs, concerns, and adherence. As predicted, patients in the experimental group were more likely to tell the pharmacist about side effects, changes in symptoms, nonadherence, and other issues. Experimental programs designed to increase patients' involvement in medical care also have found that patients are more willing to share their opinions when physicians encourage them to do so and that higher levels of patient involvement during interaction are significantly correlated with better postintervention outcomes.[73,74]

STYLES OF CONFLICT RESOLUTION AND PROBLEM SOLVING—Because providers and patients are likely to have different viewpoints and agendas, some interpersonal conflict or disagreement is inevitable during their interaction.[75] This conflict is especially likely after patients have gained more experience with their illness and recommended treatments. For example, providers may want patients to comply as fully and rapidly as possible with their *ideal* treatment plan, whereas patients may prefer a slower or less aggressive approach or even request alternative therapies that providers would consider ineffective, inappropriate, or unnecessary. Providers also may consider certain side effects or drug-taking problems to be clinically insignificant or trivial, while patients consider the same side effects or problems to be intolerable. As a result, providers often are confronted with both explicit and subtle forms of *negative feedback* from their patients (eg, complaints about the drug or dosage schedule, admissions of nonadherence, reported difficulties administering or paying for medication, expressions of fear and uncertainty about drug efficacy or safety).

Information about how pharmacists actually manage these types of problems in their daily practice is lacking; however, insights can be gained from observational studies of physicians and from experimental studies in which pharmacists and physicians have attempted new ways of identifying and managing adverse drug reactions and other patient concerns. For example, observational research suggests that medical practitioners use at least two different styles of conflict resolution and problem-solving: the *authoritarian* or noncollaborative approach and the *participatory* or collaborative approach.[16] Practitioners who rely on an authoritarian approach often assume that patients' perceived side effects, fears, concerns, and doubts are clinically insignificant or trivial and that patients should either comply with medical advice or find another practitioner. It is not uncommon for these practitioners to ignore or dismiss patient complaints in a derogatory manner and become angry or hostile when their patients admit nonadherence. Not surprisingly, these tactics often result in a serious breakdown of communication, patient reluctance to admit nonadherence, errors in clinical judgment, and higher patient dropout rates.[16]

In contrast, the participatory/collaborative approach involves acknowledging the legitimacy of patient concerns, assessing patient concerns in a more thorough and respectful manner, *tailoring* or adjusting drug regimens to *fit* patient routines and preferences, and negotiating mutually acceptable solutions. Experimental studies suggest that these collaborative strategies are more effective than authoritarian or noncollaborative approaches. For example, patient adherence is significantly improved if the dosage schedule has been *tailored* to the patient's daily routine,[63] if the patient is allowed to change the regimen within a preapproved protocol,[64] and if the patient identifies the areas in which he or she would like assistance.[76] Experimental studies also have shown that pharmacists who implement participatory/collaborative methods of managing adverse drug reactions and other patient complaints about their medication can significantly reduce the incidence of side effects, the average recommended dosage, number of physician visits, rehospitalization rates, and treatment failure.[62,66]

THE HEALTH COLLABORATION MODEL: A TOOL FOR ANALYZING AND IMPROVING PATIENT CARE—In this chapter we have discussed many factors that can affect patient behavior in health. Figure 96-1 summarizes current knowledge about these factors, how they are interrelated, and the specific ways in which pharmacists and other health providers can influence patient treatment behaviors and outcomes. The model extends previous work on the Health Communication Model[16,27] and is referred to as the Health Collaboration Model to highlight the central role of patient feedback and collaborative problem solving in health care. The diagram is best understood by beginning at the left side of the diagram and following each arrow in numerical order. Each box represents a different set of provider behaviors or background factors affecting the collaboration process; whereas, each circle represents a different set of patient cognitions, beliefs, behaviors, or clinical outcomes affected by collaboration and background factors.

The top part of the model (arrows 1–5) emphasizes the various factors that can impact the patient's *initial* reactions after receiving a new prescription or other new regimen; whereas, the bottom part of the model (arrows 6–13) emphasizes the various factors that can impact the patient's behavior after he/she has experienced the drug and barriers to adherence. First, we see that patient, provider, drug, and environmental factors (arrow 1) can impact both provider and patient behavior during the initial stages of collaboration and treatment, including the quality of provider instruction and support, patient comprehension/recall and motivation, and initial patient adherence and barriers to adherence. During the initial stages of collaboration, the provider plays a critical role in facilitating and verifying patient comprehension/recall of the regimen (arrow 2). The provider also plays a critical role in facilitating and verifying the patient's initial motivation and satisfaction with the regimen (arrow 3). It is not enough to give drug information. Rather, the provider must assess the individual's initial understandings and beliefs and make adjustments as necessary. In some cases, he/she will need to provide additional instruction or reinforcement to make sure the patient will understand and remember the dosage schedule. In other cases, he/she will need to provide additional informational, social, or technical support to address the individual's initial doubts or concerns about the drug and its short-term or long-term effects. If effective collaboration occurs at this stage, then the patient will have greater comprehension/recall and greater motivation which, in turn, lead to greater initial adherence and fewer barriers to adherence (arrows 4–5).

The bottom part of the model draws attention to the fact that patients actively monitor their reactions to drug therapy and experience a variety of barriers to adherence after initiating therapy. They may find it difficult to remember each dose or simply question whether the drug is still needed or working for them. They also may experience unwanted effects or have concerns about high drug costs, possible dependence, or unknown long-term effects. Since these patient-perceived barriers seriously undermine the patient's willingness and ability to continue therapy as prescribed, patient feedback plays a central role in follow-up visits with the provider (as shown in Fig 96-1). Soliciting accurate patient feedback is a complex process that depends on: the patient's personal experience with the drug (arrow 6); background characteristics and expectations of the patient and provider, characteristics of the drug and environment, and past patient-provider interactions (arrow 7); and quality of provider monitoring. Providers who regularly ask carefully designed, open-ended questions in a supportive, nonaccusatory manner can be very successful in soliciting negative patient feedback even among patients who initially appear reluctant or hesitant to share their personal doubts, difficulties,

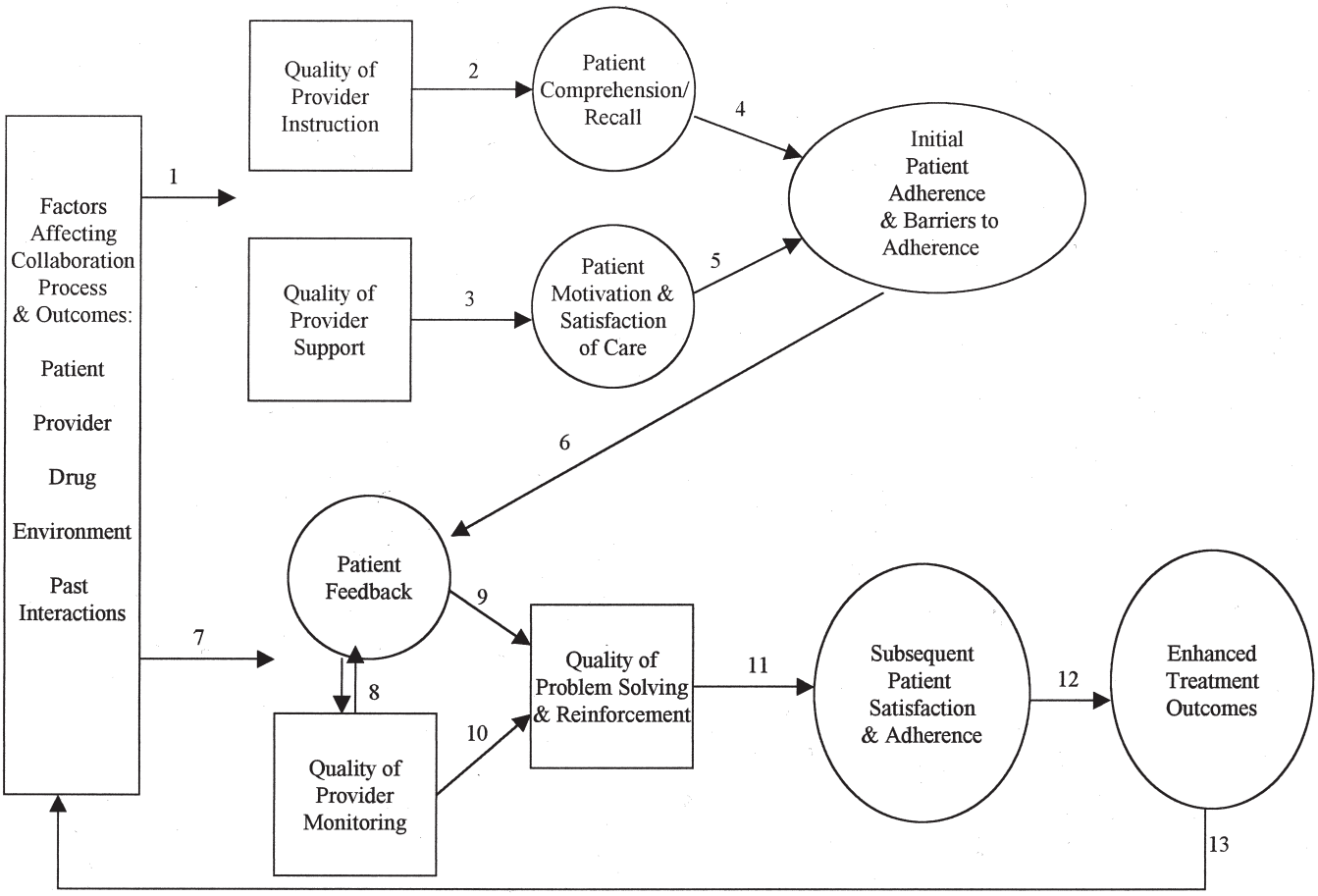

Figure 96-1. Health collaboration model.

and concerns. The provider who is able to solicit accurate patient feedback is then able to resolve patient-specific problems and provide appropriate reinforcement as necessary (arrows 9–10). This type of two-way communication and collaborative problem-solving leads to greater patient satisfaction and adherence (arrow 11) and enhanced treatment outcomes (arrow 12). The final arrow (14) illustrates the importance of past interactions and treatment experiences in establishing and maintaining a trusting relationship that is the cornerstone of effective health and pharmaceutical care.

Like other conceptual tools, the Health Collaboration Model can play an important role in pharmacy practice and research. First, it enables pharmacy practitioners and researchers to organize large amounts of information that would otherwise be confusing or difficult to interpret and use. Second, it enables pharmacists to identify potential connections and implications that are not obvious when examining results from a single study or set of observations. Finally, it can be used as a stimulus and guide for further discussion, evaluation, and practice development. It helps us see that the patient's behavior depends more upon the patient's beliefs, feelings, and interactions than on the patient's medical diagnosis or severity of illness. It also helps us see pharmacists who have a good understanding of patient behavior can have a positive impact on treatment outcomes by providing quality instruction, support, monitoring, and collaborative problem-solving and reinforcement.

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CHAPTER 97

Patient Communication

Peggy Piascik, PhD
Heidi M Anderson, PhD

A constructive pharmacist-patient relationship is essential to sound health care practice and the optimal well-being of the patient. These pharmacist-patient relationships begin and develop with effective communication, both verbal and nonverbal. Mutual trust and respect are basic characteristics of this relationship. Ineffective communication may reduce the accuracy of the medical diagnosis.

Mock asserts that "the concept of effective clinician-patient communication is a necessity, not an option. Because communication is both a science and an art that can be learned and mastered, there are many resulting benefits for those who work diligently to improve their technique, not the least of which is increased clinician satisfaction."[1] Therefore, health care professions education, and specifically pharmacy education, should include specific training in patient communication skills and an understanding of the psychological reactions to illness and treatment.

To provide quality patient care, pharmacists must have the desire and ability to communicate effectively with patients, other health care professionals, and the public. This chapter will describe the factors a pharmacist must consider and techniques that are useful in effective patient communication.

THE COMMUNICATION PROCESS

Communication is the sharing of information, ideas, thoughts, and feelings. It involves not just the spoken word, but also what is conveyed through inflection, vocal quality, facial expression, body posture, and other behavioral responses. As a first step toward communicating more effectively, pharmacists must understand the communication process.

The goal of all communication is understanding. For one person to understand a message composed by another, the receiver must do more than recognize the words used in the message by the sender. Effective communication occurs only when the meaning of a message is held in common by the participants. Human nature makes it difficult to attain this point of understanding between two or more people because each person's view of reality is influenced by past life experiences, the current situation, and perceptions of each other. This individualistic perception influences both the way in which a message is sent and the way in which it is received.

When a person wishes to share information with another, the sender must choose how to transmit that message. The medium of the message can be written, oral, nonverbal, or electronic. If the sender decides to transmit the message through words, the sender must encode the message by choosing words that best convey the intended meaning to the receiver.

Once the information is encoded, the sender loses control of the message because its meaning comes from the receiver's decoding of it. If the receiver responds to the message, that response acts as feedback to the sender. This gives the sender an opportunity to clarify and correct any misunderstanding. This sequence of encoding, transmitting, and decoding messages continues so long as sender and receiver continue to communicate.

Communication usually takes place through multiple nonverbal channels as well. For example, as the words of a message are transmitted, facial expressions, gestures, vocal quality, and other nonverbal cues also are sent. These nonverbal signs may modify the intended meaning of a message. A mixed message may result when the intended verbal and nonverbal messages are not understood as meaning similar things.

INFORMATION GATHERING AND PATIENT EMPOWERMENT

The interactions of a pharmacist and a patient usually can be categorized as either an information-gathering or information-giving session.[2] Information gathering usually is done during a medication-history interview, which is a conversation with a multifaceted purpose. Pharmacists initiate the interaction to investigate and acquire data about a patient's medication-taking experiences, assess a patient's understanding of past and current medication-taking experiences, assess a patient's motivation for complying with the medication regimen, and possibly suggest to the prescriber a change in regimen if the information gathered warrants such an action. The direct patient-pharmacist interaction during a medication-history interview frequently provides the pharmacist with an opportunity to begin a professional relationship with the patient.

Research has revealed that a patient who is involved in deciding on his or her treatment is more likely to comply with the treatment.[3,4] Patient empowerment is a concept that refers to patients having the right to make their own choices about their health care.[5] Feste argues that "the empowerment model has evolved out of the realization that patients cannot be forced to follow a lifestyle dictated by health-care professionals."[5] The patient empowerment model is based on the assumption that to be healthy, people must be able to bring about changes not only in their personal behavior but also in their social situations and the institutions that influence their lives.

Effective communication should involve patient empowerment in the health care-patient relationship. Patient empowerment posits that since patients are the ones who experience the consequences of both having and treating their illness, they have the right to be the primary decision makers regarding their medical condition. This philosophy further asserts that although the health care provider should be involved in the decision, the final determination of what is best for the pa-

Table 97-1. Outline of a Patient Empowerment Program

1. Health care professional assess current status (physical, emotional, cognitive, etc.)
   - Review patient's actual self-care practices
   - Reviews patient's recommended self-care practices
2. Health care professional provides relevant medical information
   - Describes various treatment options
   - Reviews costs and benefits for each option
3. Health care professional acknowledges patient's responsibility for self-care
   - Helps patient clarify personal values specific to their illness
   - Helps patient assess level of personal responsibility for their care
   - Helps patient select treatment goals
4. Patient identifies barriers and strengths related to achieving self-care
   - Assesses medical barriers and sources of support
   - Assesses life/social barriers and sources of support
5. Patient assumes problem-solving responsibility
   - Develops skills to optimize support (eg, communication and assertiveness skills to enhance support from family and friends; increases support networks)
   - Identifies potential barriers
   - Learns strategies/skills to overcome barriers (eg, negotiation, self-care agreements and plans, conflict resolution)
6. Patient establishes plan with assistance from provider
7. Patient carriers out plan
8. Patient and provider evaluate and review plan using problem-solving model

Adapted from Funnell MM, et al. *The Diabetes Educator* 1991; 17(1):37.

tient is both the right and responsibility of the individual patient.[5]

Feste further states that "the empowerment model speaks of self-awareness, personal responsibility, informed choices and quality of life. Therefore, in the empowerment view, the primary purpose of the health care professional is to prepare patients to make informed decisions about their own [medical] care."[5]

Funnell and associates also explain the process and outcome of patient empowerment.[6] They suggest that "people are empowered when they have sufficient knowledge to make rational decisions, sufficient control and resources to implement their decisions, and sufficient experience to evaluate the effectiveness of their decisions. Empowerment is more than an intervention or strategy to help people make behavior changes to adhere to a treatment plan. Fundamentally, patient empowerment is an outcome. Patients are empowered when they have knowledge, skills, attitudes, and self-awareness necessary to influence their own behavior and that of others in order to improve the quality of their lives."[6] Table 97-1 provides an outline of patient empowerment as adapted from Funnell's model.

WHY PHARMACISTS COUNSEL PATIENTS

Communicating with patients about their medications provides significant benefits to both the patient and the pharmacist. The patient will have a better understanding of the purpose for the prescribed therapy and the appropriate use of the medication. This leads to several potential benefits:

- Improved therapeutic outcomes and decreased adverse effects
- Improved patient adherence to the treatment plan
- Decreased medication errors and misuse
- Enhanced patient self-management by involving the patient in designing the therapeutic plan
- Potential for decreased health care costs due to appropriate use of medications and prevention of adverse events

The pharmacist also benefits in this process. Potential benefits to the pharmacist in this process include:

- Enhanced professional status in the view of patients and other health care providers
- Establishment of an essential component of patient care that cannot be replaced by technicians or automation
- Enhanced job satisfaction through improving patient outcomes
- A value-added service to offer patients
- Revenue generation through payment for counseling services–limited at present but growing
- Fulfillment of legal responsibility to counsel patients according to the OBRA 90 guidelines

The Ad Hoc Panel on Medication Counseling Behavior Guidelines of the USP has identified six desired outcomes of patient counseling.[7] It is expected that, as a result of a properly conducted counseling interaction, the patient will:

- Recognize why a prescribed medication is helpful for maintaining or promoting well-being
- Accept the support from the health care professional in establishing a working relationship and foundation for continual interaction and consultation
- Develop the ability to make more appropriate medication-related decisions concerning compliance or adherence
- Improve coping strategies to deal with medication side effects and drug interactions
- Become a more informed, efficient, active participant in disease treatment and self-care management
- Show motivation toward taking medications to improve his or her health status

OPTIMIZING THE ENVIRONMENT FOR PATIENT COMMUNICATION

The optimal setting for communicating with patients is a private consultation room adjacent to the dispensing area. A private setting has been shown to enhance patient retention of the counseling information, increase patient adherence to the drug regimen, and increase patient satisfaction with the counseling experience[8]; however, many pharmacy settings lack sufficient space to create this type of environment. The pharmacist must be aware of the physical barriers that exist in the pharmacy and work to minimize them.

The physical layout of the pharmacy may include a prescription counter that separates the pharmacist from the patient, a partition made of glass or other materials, a raised floor that puts the pharmacist on a higher level than the patient, floor or counter displays that add to congestion and separate the patient from the pharmacist, or inadequate lighting. Use of the following techniques may overcome these physical barriers:

- Come out from behind the counter to greet the patient
- Face the patient and maintain eye contact
- Position yourself a comfortable distance from the patient, usually 1 1/2 to 4 feet from the patient

The noise and distractions in a busy pharmacy can be handled using the following techniques:

- Move away from the pharmacy counter when possible to a more private area of the pharmacy
- Ask other employees in the pharmacy not to interrupt during a patient session
- Face the patient and speak clearly and distinctly in a tone loud enough to be heard but not so loud as to be heard by others in the pharmacy

PHARMACIST BARRIERS TO COMMUNICATION

Pharmacists who are uncomfortable interacting with patients or who have had little training in patient interaction may engage in inappropriate nonverbal behaviors that interfere with

good pharmacist-patient communication. Examples of such behaviors include nervous movements or "fidgeting," crossed arms or legs, turning or leaning away from the patient, failure to maintain eye contact, and obvious distractedness. Techniques that improve patient interaction have been described by Muldary[9] using the acronym CLOSER. The suggested techniques include:

- Control distractions, such as nervous habits
- Lean toward patient
- Open body posture, uncross arms and legs
- Squarely face patient
- Eye contact 50–75% of the time
- Relax

Other barriers to effective communication cited by pharmacists include lack of time, economic considerations, poor communication skills or lack of confidence in those skills, lack of knowledge about current drugs or patient history, and the patient's failure to value the counseling session or pharmacist expertise.[10,11] Lack of time and economic considerations in patient counseling can be overcome by increasing the use of technical personnel to relieve pharmacists from dispensing functions and allowing the pharmacist to spend time with patients. Poor communication skills or lack of expertise about recent drug advances can be overcome by appropriate choice of continuing professional education opportunities to improve knowledge and skills in areas of identified weakness. The patient's failure to appreciate the value of consultation with the pharmacist can be overcome by advertising the service provided and personally offering the consultation to each patient with a brief description of the importance of this process in improving patient medication therapy outcomes. Another barrier to effective communication is taking into account the patient's cultural perspective.

CULTURE AS A BARRIER TO COMMUNICATION

Galanti states that a problem that is beginning to receive attention in the United States is the cultural gap between the medical system and the huge number of ethnic minorities served by the health care system.[12] Galanti asserts that "the goal of the medical system is to provide optimal care for all patients."[12] In a multiethnic society, this can be accomplished only if the health care providers understand cultural differences " . . . that create conflicts and misunderstandings and that may result in inferior medical care".[12]

All health care professionals are finding themselves faced with an increased number of patients from various cultures. Cultural diversity challenges health care providers to facilitate bridging cross-cultural gaps with patients. The patient-health care provider relationship may be seriously disrupted by misunderstandings due to different beliefs, values, or language. It is through providing culturally relevant care that health care professionals truly serve the needs of all patients in our diverse society.

Health care providers must find effective ways to communicate with patients from diverse backgrounds. In an effective patient communication session, the pharmacist gathers not only objective information about the patient's health condition, but also an understanding of the patient's own perspective regarding his or her health. This perspective may include the patient's viewpoint from his or her own cultural perspective. Discovering the patient's perspective can help diagnosis and make for a more effective and efficient health care process.

Galanti identifies several cultural areas in which communication may be misunderstood.[12] A few of these areas are identified in Table 97-2 and briefly discussed below. The reader is encouraged to read Galanti's book to learn more about other cultural aspects and practices that may affect a patient's health care.

Table 97-2. Cultural Factors that May Affect Health Care

- Verbal and Nonverbal Communication
  - Idioms
  - Same Word, Different Meaning
  - Format for Names
  - Eye Contact
  - Touching
- Time Orientation
  - Patients may operate with a present orientation, past orientation, or future orientation
- Religion & Spirituality
  - Blood Beliefs
    - Transfusions
    - Drawing Blood
  - Prayer
  - Holy Days
  - Sacred Symbols
  - Lucky and Unlucky numbers
- Dietary practices
  - Specific diets
  - Special holiday preparations
  - Taboos for certain foods
  - Nutritional deficiencies
- Folk Medicine
  - Fevers
  - Coin Rubbing
  - Medications

Verbal and Nonverbal Communication

Verbal and nonverbal communication may lead to misunderstandings. Miscommunication may occur when individuals use idioms (eg, patient has 'cold feet'). Avoid using idioms. Different words have different meanings in the same language (eg, 'horita' means right now in Mexico; it means an hour in Puerto Rico). Using a first name of anyone other than a friend is considered inappropriate or discourteous in most cultures. Still other cultures consider it disrespectful to look someone directly in the eye especially if that person is in a superior position, and some cultures may not be comfortable with casual touching and hugging that many Americans do without even thinking.

Time Orientation

Time orientation varies among cultures. When scheduling an appointment with a patient who has a different time orientation, be sure to specify clock time instead of scheduling in relation to an activity. For example, for some patients, lunchtime means between 1:00 and 2:00 PM rather than 12:00, and some European countries eat dinner at 10:00 in the evening. Be aware that not every culture eats meals at the same time.

Religion and Spirituality

Religion and spirituality are common sources of miscommunication. Some religions do not accept blood transfusions; others may refuse to have blood drawn because of beliefs about getting bad fortune or death if blood is drawn. Some cultures have certain times of day that prayer is mandated and holy days may dictate that certain behaviors are restricted, such as driving on the Sabbath. Various cultures have symbols that are sacred. These may be worn (eg, rosary) or be placed in the patient's room. If the patient is hospitalized, health care professionals need to respect the item and explain the reason the item may need to be removed from the individual. Finally, certain cultures believe that there are lucky and unlucky numbers (eg, Chinese regard 8 and 9 as lucky; the number 4 is seen as unlucky by some Japanese). Therefore, health professionals need to respect patients' religious beliefs and try to accommodate their practices as much as possible.

Dietary Practices

Dietary practices may include such activities as Ramadan by Muslim patients. Some ethnic groups cannot tolerate certain foods or are forbidden to eat certain foods (eg, Hindu are forbidden to eat beef). Health care providers need to be aware of the patient's diet, both in terms of content and preparation.

Folk Medicine

Many cultures have developed local methods for treating illnesses and diseases. Galanti reminds us that "some techniques, such as coin rubbing may produce marks that appear to be signs of child abuse or are unrelated to symptoms. It is important to recognize these before jumping to unwarranted conclusions."[12]

In summary, health professionals must consider the patient's cultural perspective to provide effective communication and thus effective health care. Some final suggestions are:

- Be aware of the customs and beliefs of religious, ethnic, and recent immigrant groups in your area
- Try to work within the health belief system of the patient and family
- Respect patients' viewpoints; listen to them
- Learn about the customs of the patient, alternate health care methods and medications
- Explain risks of not taking medication

A MODEL PATIENT COUNSELING SESSION FOR A NEW PRESCRIPTION

A correct diagnosis and appropriately prescribed drug therapy will be ineffective unless the patient understands the reasons for the therapy, how it is to be used, and the outcomes of the therapy. In addition, it is critical that the patient is motivated to adhere to the prescribed regimen so that he or she will experience optimal effectiveness of the drug therapy.

The pharmacist should view the patient counseling interaction as a two way sharing of knowledge. The pharmacist is the expert in drug therapy. The patient is the expert with regard to the personal medical history, past medication use, life-style issues, and patient attitudes toward medication use. The pharmacist must first assess the patient's knowledge and attitudes about the prescribed medication and adjust the counseling session to assist the patient in achieving the best possible outcome.

Each pharmacist should develop a personal patient counseling routine to ensure that all important issues are discussed with each patient. It is useful to work from a checklist, at least until the process becomes second nature to the pharmacist. The essential elements described below should be considered for each counseling session. The pharmacist must then tailor the steps to the particular patient and the situation. For example, a patient interaction with a new patient who is receiving a medication for the first time will be significantly different than a session with a well-known patient who has been taking the same medications for a period of time.

PREPARING FOR THE SESSION

Pharmacists should spend a few moments mentally preparing for the interchange about to occur. Preparation greatly enhances the experience for both parties and, ultimately, the quality of the interaction. The pharmacist should know as much as possible about the patient before approaching the patient or caregiver. This is easier in a hospital setting where the patient's medical record and other health care providers can provide valuable background information about the patient. In the community setting, the pharmacist can review the prescription as well as the patient's medication record if the patient has been to the pharmacy before. It rarely is possible to know much about a patient before a first pharmacy visit, but the patient can be asked to fill out a medication history form if there is not time to complete a medication history interview at the time the prescription is dispensed. Review of the prescription tells the pharmacist the patient name, when the prescriber was seen, whether it is a new medication or a refill, and the name of the medication. This may provide clues to the patient's medical condition if that information is not available from the patient's profile information.

Another important issue to consider before a session actually begins is the physical state of the patient. Observation of the patient prior to the counseling session can reveal many clues about the patient's physical and mental state.

STEPS TO A SUCCESSFUL PATIENT COUNSELING SESSION

The following steps represent a logical outline for counseling a patient on a new prescription (Fig 97-1).

1. **Introduce yourself and identify the patient.** Greet the patient. Smile and offer your hand in greeting if appropriate. Provide your name as well as your position in the pharmacy and identify the person with whom you are speaking. If the person is not the patient, determine the relationship between the patient and person picking up the prescription. A counseling session may

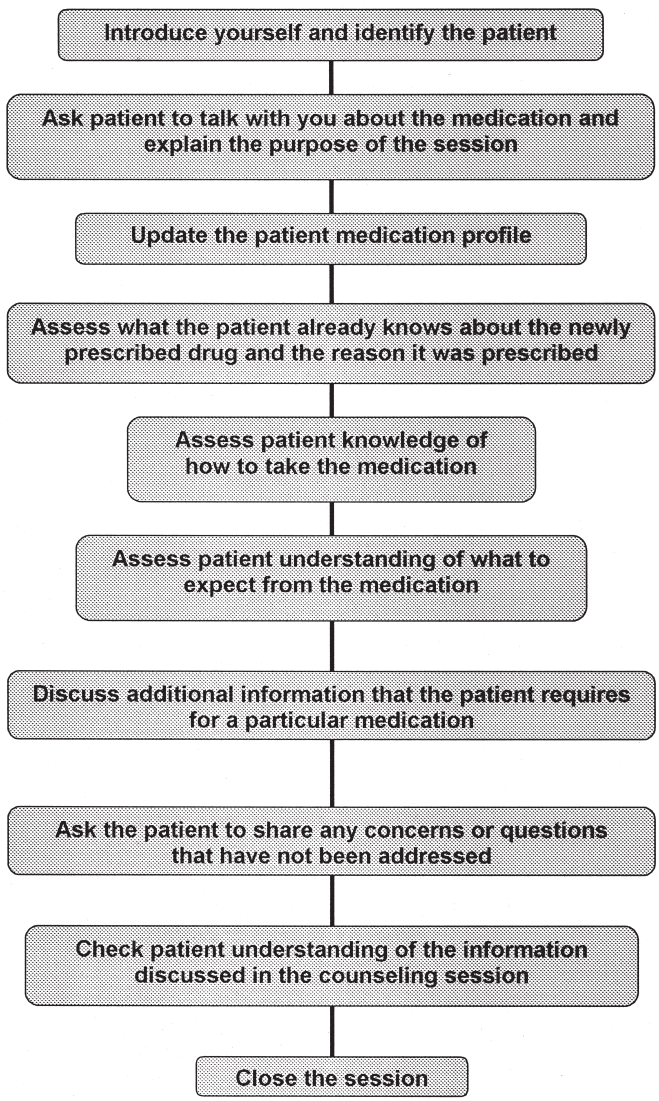

Figure 97-1. Steps in a patient counseling session.

not be appropriate if the person picking up the prescription is merely a friend or neighbor rather than a caregiver. In this case, arrangements should be made for phone consultation or provision of written counseling materials.

2. **Ask patient to talk with you about the medication. Explain the purpose and the importance of the counseling session.** Determine that the patient has sufficient time for a conversation. A distracted patient will not listen to any information provided in the session. Explaining the purpose and importance of the counseling session in terms of the benefits to the patient will increase the effectiveness of the session. Many patients do not receive patient counseling regularly and are not aware of the benefits to be gained. It is helpful to ask the patient if he or she has any concerns about the new medication before you start through the counseling process. This allows you to deal with any issues that are bothering the patient first so that the patient is not distracted by other concerns while you are providing drug information to her. For example, the patient may be wondering if the drug will be covered by her health plan or whether she will have to pay the full cost of the medicine. Answering that question first will relieve the patient's mind and allow her to concentrate on what you are saying to her.
3. **Update the patient medication profile.** Review with the patient any profile information relevant to the new prescription. This ensures that the pharmacist knows about any recent changes that would affect the patient's current therapy. This may include the following:
   - Allergy and disease state status
   - New or discontinued prescription drugs that may not be included in the patient record
   - New or discontinued non-prescription drugs including dietary supplements and herbal products that may not be included in the patient record
   - Changes to social/lifestyle history
4. **Assess what the patient already knows about the newly prescribed drug and the reason it was prescribed.** Ask the patient why he or she saw the prescriber today and what the patient has already been told about the new medication. This not only tells the pharmacist whether the patient was given information about the new prescription, but it also reveals what information the patient actually understood and remembered from the medical visit. Confirm any correct information provided by the patient, correct any misconceptions and fill in any missing information. Be sure that the patient knows the name, strength and purpose of the medication. This is an appropriate time to show the medication to the patient so that he will make the connection between the appearance of the drug and its proper use. This is particularly important for patients who take multiple medications and may occasionally confuse their uses. This is also an appropriate time to review how the new medication will benefit the patient.
5. **Assess whether the patient knows how to take the medication.** Ask the patient how she will take the new medication. It is often necessary to follow up with a few specific questions to ensure that the patient will adhere to the prescribed dosing regimen. Examples of appropriate follow-up questions include:
   - What times of day do you plan to take the medication?
   - How can you schedule the medication around your daily activities to help you remember to take the medication regularly?
   - How will you plan for doses that need to be taken during the day while you are at work?
   - How can you store your medication while you are traveling?

   Confirm any correct information provided by the patient, correct any misconceptions and fill in any missing information. Be sure that the dosing regimen the patient agrees to use works well with the patient's work schedule and life-style. Discuss ways to help patient adhere to the dosing regimen.
6. **Assess the patient's understanding of what to expect from the medication including the expected outcomes of the therapy as well as its potential adverse effects.** The patient's response tells the pharmacist what outcomes the patient expects from the medication as well as any potential adverse effects the patient anticipates from the medication. Confirm any correct information provided by the patient, correct any misconceptions and fill in any missing information. Be sure to discuss the therapeutic benefits to be gained by taking the medication appropriately. The patient should have a realistic expectation of any potential common or potentially serious adverse effects that the regimen may produce. Patients are more likely to adhere to a drug regimen when they are aware of potential problems and know what to do if those problems occur. The patient should know if the adverse effect will resolve by itself and how long that may take, whether there are any steps a patient should take to relieve or resolve adverse effects, or if an adverse effect should be reported to the prescriber or pharmacist. Offering solutions to resolve drug-related problems relieves patient anxiety and empowers the patient to deal with the problem directly. Patients who are not prepared to deal with adverse effects often quit taking medication and do not report it to a health care provider.
7. **Discuss any additional information that the patient requires for a particular medication.** Examples of additional information that the pharmacist may provide to the patient includes:
   - Potential interactions with other drugs, foods or diseases
   - Missed doses
   - Monitoring information–how will the patient know the medication is working, any testing that should be done to assess the therapy, follow-up appointments with health care providers
   - Refill information
   - Storage information
   - Life-style changes to implement–changes in diet, exercise, avoid sun, etc.

   The pharmacist must use professional judgment in determining what information is essential to provide to a particular patient in a given situation and when to stop talking so that "information overload" does not become a problem.
8. **Ask the patient if he or she has any concerns or questions that have not been addressed in the previous discussion.** Patients usually do not bring up these concerns unless they are asked directly by the pharmacist. The patient may be distracted by these concerns while the pharmacist is providing information. It is best to address concerns as soon as they are identified. A follow-up question about unresolved issues and problems ensures that the patient has had an opportunity to voice any concerns that may be a barrier to medication use.
9. **Check patient understanding of the information discussed in the counseling session.** Perhaps the most critical step in the process is to check patient understanding of the newly prescribed medication and its use. This can be accomplished by putting the question in the context of checking the pharmacist's success in communicating the information clearly to the patient. This avoids putting the patient "on the spot" or making him feel that he is being quizzed. An example question might be the following:

   "Mrs. Jones, we've discussed a lot of information about your new prescription today. To be sure that I did a good job explaining everything, would you recap for me what you learned today about your new medication?"

   As the patient recaps her understanding of the information, the pharmacist can assess the patient's knowledge and retention of the information. This provides the opportunity to reinforce any critical information, correct any misinformation, and fill in any information that the pharmacist may have omitted during the counseling session. This also gives the pharmacist the opportunity to praise and encourage the patient.
10. **Closing the session.** To close the counseling session:
    - Provide written counseling information you have used during the session.
    - Tell the patient how to reach you if other questions or concerns arise.
    - Confirm when you expect the patient to return for a refill or follow-up with health care provider.
    - Reinforce the value to the patient of appropriate medication use and the positive outcomes possible for the patient.
    - Thank the patient for spending the time to discuss the new medication with you.

COUNSELING PATIENTS ON THE USE OF REFILL PRESCRIPTIONS

The basic principles of a patient counseling session do not change whether the patient is starting a new medication or refilling an ongoing prescription. However, the focus of the discussion is somewhat different during a counseling session for a refill. A refill counseling session should concentrate on the following three areas:

- Confirm that the patient has been taking the correct medication and knows the indication for its use. Show the medication to the patient to determine that there is no confusion with a different prescription.
- Ask how the patient has been taking the medication. This tells the pharmacist whether the patient has adhered to the regimen. Ad-

ditional evidence of the patient's compliance comes from the medication profile information. Has the patient returned at the appropriate time for a refill? When the patient describes how he or she has been taking the medication, does he appear sure of the information? Praise appropriate medication use and assist the patient in resolving any issues that have interfered with adherence to the regimen.

- Ask how the medication is working for the patient. What benefits has the patient gained from taking the medication? What problems have arisen while taking the medication? How has the patient handled these problems? Provide potential solutions to any unresolved problems. Encourage the patient by reiterating the benefits of continued medication use. Confirm the appropriate follow-up steps for monitoring the patient.

For sample dialogues between pharmacists and patients that illustrate the process described above, the reader is referred to the Bibliography at the end of the chapter.

APPROPRIATE TECHNIQUES TO USE DURING A COUNSELING SESSION

Throughout the patient counseling session, the following techniques for good communication should be utilized.

1. **Nonverbal cues.** Pharmacists and patients alike communicate emotions and other information in nonverbal ways. Blank stares, inattentiveness, nervous speech patterns, and interruptions are distracting and detrimental to effective communication. The verbal and nonverbal aspects of an interaction cannot be separated if one wishes to appreciate fully the nature of the interaction.
   Eye Contact—Facial features, as well as facial expressions, are assumed to reveal personality traits. A great deal of information is communicated through head and facial movements, but perhaps the movement of another person's eyes provides more clues than any other facial structure. Therefore, a gaze is a major nonverbal signal to others.
   Patients vary in the amount of eye contact that makes them comfortable, so interviewers should take cues from them. The best a pharmacist can offer is frequent and attentive eye contact, avoiding blank stares. Eye contact helps assess the meaning that is behind the patient's words and conveys the message "I'm listening." Thus, eye contact represents an important building block toward establishing patient trust and rapport.
   Mannerisms—The study of nonverbal facilitation has led to the marketing of provocative bestsellers that promise readers "You'll be able to read people like a book." Gestures, vocal qualities, body movement, clothing, and hygiene can provide information about interviewers and patients, but ferreting out clues to hidden meanings can be more damaging than helpful to professional relationships.
   The pharmacist needs to make the patient feel comfortable by enhancing physical and psychological privacy. The pharmacist communicates a posture of involvement by facing the patient directly and leaning forward at a slight angle, which is a sign of attentiveness to the patient's needs. If the patient is seated or lying down, the interviewer should sit, if possible. Some other examples of nonverbal facilitation are an inclined head, a head nod, and hand gestures that suggest understanding or the desire for more information.
   Taking notes is appropriate so long as it is not the major focus of attention for either the pharmacist or patient. Excessive writing of notes has disadvantages. It is distracting to patients, impairs interpersonal dynamics, and provides a convenient and absorbing escape for pharmacists. Novice interviewers should take whatever notes are needed to achieve accuracy, but they should strive to improve their listening skills by recording only selected information at the moment and then completing the notes immediately after the interview.
   Vocal Qualities—Pitch, range, tone, clarity, and tempo are vocal qualities. Pitch refers to the frequency level of the voice. Pitch level influences patient attitudes toward pharmacists and the content of the message. While a monotone is generally disliked by most individuals, exaggerated pitch changes are disliked even more. Speakers with naturally spontaneous voices using neither a wide nor narrow range of pitch tend to be perceived more favorably.
   Voice clarity is an important attribute for effective communication. To ensure that the patient can hear and comprehend, the pharmacist should assess the patient's language and hearing abilities and then change speech patterns, if necessary.
   Tempo is the speed of vocal production. Inappropriate delays may irritate patients, while interruptions may rush patients and interfere with the smooth flow of conversation. Fast tempo and frequent pauses often are associated with emotions such as fear or anger. Slow tempo also often is associated with anger, as well as sadness and depression. A slow tempo with frequent pauses and utterances such as "uh," "er," and "um" can indicate uncertainty; perhaps the pharmacist is stalling while waiting for the patient's response or while formulating the next question to ask.
   People often express their emotions by talking too fast. Pharmacists should keep their rate of speech conversational.
   Touch—Touch can enhance verbal communications and facilitate social interactions with patients. For example, a greeting handshake by a pharmacist may be part of the introduction to the patient session. Touch can also be used to attend to the patient's comfort, and the appropriate touch can display sympathy, empathy, concern, and even be used to get a patient's attention.
   The patient's cultural background should be used as a guide to help any health care professional know when to use touch. It is important to keep in mind that not everyone is comfortable being touched. Some cultures consider it inappropriate for men and women to touch, even in a professional setting. Patients from these cultures would not even shake the hand of someone from the opposite sex. In the patient-pharmacist relationship, observe the patient's behavior, and if possible the behavior of the family, to see what they are comfortable with.
2. **Listening.** Listening appropriately to the patient is hard work, but it is extremely important to effective communication. The pharmacist must allow the patient to speak without interruption and concentrate on the words and meaning of the patient's message. The pharmacist should rid himself or herself of distractions, ask clarifying questions where appropriate, and avoid jumping to conclusions or judging the patient's words.
3. **Open-ended questions**. Ask the patient open-ended questions when gathering information. An open-ended question is one that cannot be answered with a yes or no. It requires that the patient provide information to you rather than merely telling you they know the answer to the question. A yes or no answer tells you whether the patient thinks she knows the information but does not allow you to assess the accuracy of the information. Open-ended questions start with who, what, where, when, why, or how. Avoid leading or restrictive questions. Leading or restrictive questions cue the patient to respond with answers predetermined by the questioner rather than allowing the patient to determine the answer to the question. A leading question usually supplies a hint to the patient about the answer the pharmacist is expecting. Like closed-ended questions, leading or restrictive questions do not provide complete information about what the patient knows or thinks. To illustrate the difference between these types of questions, look at the following example:
   Mrs. Woods comes into the pharmacy with a new prescription for metoprolol. The pharmacist wishes to determine Mrs. Woods' understanding of the use of this drug. She asks the question in one of the following ways:
   Closed question: Did Dr. Hart tell you what this medication is to be used for?
   Leading question: Did you see Dr. Hart for your high blood pressure today?
   Open question: Why did you see Dr. Hart today?
   The answer to the closed question will tell whether the prescriber talked to Mrs. Woods about the purpose of the new medication. But it will not reveal anything about her understanding and recollection of the information. The leading question tells Mrs. Woods that the expected answer is to say that she saw the doctor about her high blood pressure and she is likely to answer yes regardless of her true reason for seeing the doctor. The open question allows the patient the freedom to tell, in her own words, exactly why she visited the doctor today.
4. **Use paraphrasing to clarify what the patient says.** Paraphrasing is a technique in which the pharmacist reframes what the patient has said in his own words. This tells the patient that the pharmacist has listened to the information provided and is confirming that the message was received accurately. Use of paraphrasing is sometimes also called active listening. An example of paraphrasing is provided below.
   Patient comment: "I have so many medicines. It is hard to keep them all straight. Sometimes I get confused and I might take them wrong."

Pharmacist paraphrasing: "It sounds like you have a hard time managing all of your medications and that you worry you sometimes might confuse them and take them incorrectly."
Use of paraphrasing allows the patient to check the pharmacist's understanding of the information provided and correct any misinformation.

5. **Avoid technical jargon.** Jargon is the language of specialized terms used by a group or profession. The unnecessary use of technical terms may increase patient anxiety. If use of technical terms is necessary, they should be explained after assessing the patient's understanding of the terms.
   The language of pharmacy is filled with medical terminology, drug names, and abbreviations. Words with Latin or Greek prefixes that are commonly used in health communication are particularly confusing. Examples might include prenatal, postprandial, antimicrobial, and dysmenorrhea. The partnership for Clear Health Communication has published a fact sheet called *Words to Watch*.[13] This fact sheet identifies four kinds of words that cause the majority of misunderstanding in health literacy. The types of words that have been identified as easily misunderstood are:
   - Medical words–frequently used by health care professionals and in health care instructions
   - Concept words–used to describe an idea, metaphor, or notion
   - Category words–describe a group or subset, and may be unfamiliar
   - Value judgment words–may need an example or visual to convey their meaning with clarity

   Table 97-3 provides examples of words in each category that are easily misunderstood by patients and suggests alternative wording to increase patient comprehension.
6. **Organize the session in a logical manner.** The session should be organized so that the information flows logically from one issue to the next. Information should be structured to begin with simple concepts and progress to more complex issues. The most important information should be presented first and then reiterated at the end of the session. Patients will retain information longer when it is presented this way.
   Using a standard format to the session helps the pharmacist develop techniques to address each essential element in the process. A disorganized approach increases the likelihood that important questions or information are omitted. In addition, the patient is more likely to become confused if the pharmacist jumps around from one topic to another.
7. **Maintain control of the session.** Time is usually a critical factor in a counseling session. The pharmacist must be sure to permit sufficient time to gather all necessary information and discuss pertinent drug-related issues. The pharmacist must direct the session efficiently and assertively to bring the conversation back to the topic when the patient strays too far from the purpose of the session or dwells on particular concerns too long.
8. **Use written information to supplement verbal counseling.** Research shows that using multiple methods of communication is most effective in delivering the message and having that message understood and retained by the patient. The pharmacist can use the prescription vial as a source of written communication. After showing the medication to the patient, the pharmacist can refer to the directions on the label as well as any ancillary information contained in auxiliary labels. Plain language written counseling materials can be used during the discussion to highlight important information. The pharmacist may use a highlighter to accent the most critical pieces of information and provide the highlighted copy to the patient for later reference. The materials should also contain contact information for the patient to call the pharmacist with any questions that arise later.

TECHNIQUES FOR COUNSELING PATIENTS WHO PRESENT BARRIERS

Patient counseling is a difficult process when performed in ideal circumstances. The process becomes even more challenging when the patient presents barriers that must be overcome to achieve effective communication. Patient barriers generally fall into two categories—functional or emotional.[14]

Functional barriers occur because the patient has difficulty receiving and understanding the communication provided by the pharmacist. Examples of this type of barrier include low illiteracy, hearing or visual impairment, and non-English speaking patients.

Emotional barriers occur when the patient is experiencing strong emotions that may interfere with the patient's thought processes and prevent her from listening to communications or responding appropriately. Examples of emotional barriers would be anger, frustration, sadness, worry, or embarrassment.

The pharmacist must be able to recognize the presence of these barriers and should be prepared to use appropriate strategies to overcome the barrier presented by the patient. Observation of the patient prior to beginning the counseling session, review of the patient medication profile for notes about the patient, and the patient's behavior during the counseling session will usually reveal the presence of a barrier to a watchful pharmacist. Each type of barrier will be addressed individually to provide clues to identifying the patient barrier that may exist and provide potential strategies to assisting the patient to overcome the barrier.

Table 97-3. Words Easily Misunderstood by Patients

	PROBLEM WORD	REPLACE WITH:
Medical Word Examples	Benign	Won't cause harm; is not cancer
	Condition	How you feel; health problem
	Lesion	Wound; sore
	Oral	By mouth
Concept Word Examples	Avoid	Stay away from; do not use or eat
	Intake	What you eat or drink; what goes into your body
	Option	Choice
	Referral	Ask you to see another doctor; get a second opinion
Category Word Examples	Adverse (reaction)	Bad
	Hazardous	Not safe; dangerous
	Generic	Product sold without a brand name, like ibuprofen (Advil is brand name)
	Noncancerous	Not cancer
Value Judgment Word Examples	Adequate	Enough *Example (adequate water): 6–8 glasses a day*
	Excessive	Too much *Example (bleeding): if blood soaks through the bandage*
	Increase gradually	Add to *Example (exercise): add 5 minutes a week*
	Moderately	Not too much *Example (exercise): so you don't get out of breath*

Adapted from *Words to Watch Fact Sheet.* Partnership for Clear Health Communication, available at http://www.askme3.org, accessed 6/10/03.

Functional Barriers

Functional barriers can be grouped into four subcategories:[14]

1. Sensory abnormalities–visual and hearing impairment
2. Language differences–low literacy, non-English speaking
3. Comprehension difficulties–psychiatric conditions, mental retardation, dementia.
4. Alternative health beliefs were discussed earlier in the chapter under *Culture as a Barrier to Communication*.

The pharmacist must remember to treat patients who have functional impairments with respect and avoid patronizing, talking down to the patient, or directing comments to a third party as if the patient is not present. The pharmacist must exercise patience in identifying and solving the patient barrier to communication.

1. **Sensory abnormalities**
   The Visually-Impaired Patient. Clues to visual impairment such as a seeing-eye dog, dark glasses, or a cane may be obvious if the patient is blind. Other patients may have unusually thick glasses or may hold written materials very close to their eyes. For patients who cannot use written materials, verbal communication with a follow-up to recap the session is critical.
   Suggested techniques to improve counseling include:
   - Large type labels and written materials, use of bold print and pastel-colored background on paper to improve contrast
   - Braille label or instructions
   - Well-lighted counseling area
   - Shape, size, and smell of medication and container to distinguish medicines from each other; mark containers with something to set them apart
   - Devices such as a magnifier for a syringe
   - The local Society for the Prevention of Blindness for more tips or suggestions

   The Hearing-Impaired Patient. Clues to hearing impairment may be age, presence of a hearing aid, use of sign language, loud speech, asking for frequent repetition, ignoring questions, or failing to respond to sounds in the pharmacy.
   Suggested techniques to improve counseling include:
   - Face the patient and speak slowly and distinctly; use low pitch, higher volume voice, but do not yell
   - Quiet area for counseling; this is especially helpful for patients with hearing aids
   - Sign language (flash cards for basic words are available) or gestures to explain
   - Facial expressions to communicate
   - Notes to patient or written counseling materials
   - Pictograms or auxiliary labels to convey ideas
   - TDD technology to communicate by phone when appropriate
2. **Language barriers**
   The Low Literacy Patient. Patients who have difficulty reading or writing are often embarrassed and attempt to hide the problem. Pharmacists may not be able to detect this problem quickly or easily. Some clues that may indicate poor literacy in a patient include making excuses for not reading or writing due to a headache or having forgotten reading glasses. The patient may ask the pharmacist to fill out a check or write down information to take with him. The patient usually appears eager to follow the verbal instructions given and asks few questions. He or she may also ignore written information during the counseling session.
   If the pharmacist suspects that a patient has low literacy skills, he or she might say to the patient, "A lot of people have trouble reading and remembering these instructions. Does this ever happen to you?" Another strategy is to ask the patient, "Does anyone help you at home to take your medicine correctly?" That person usually reads for the patient also. In that case, the surrogate reader, who is usually another family member, should be present at the counseling session to understand the instructions so that he or she can reinforce the counseling information for the patient at home. Finally, the pharmacist may suggest peer-group literacy or health education classes where the patient can interact with other patients who have the same literacy issues.
   Suggested techniques to improve counseling include:
   - Careful verbal instructions; slow down if necessary; ask for recap of information
   - Pictograms or auxiliary labels that provide pictorial reminders to patient
   - Rewritten materials prepared for the appropriate reading level
   - Video instructions
   - Use of numbers, colors and shapes to distinguish meds
   - Pill containers to keep medicines organized by day and time of dose
   - Phone number for follow-up if patient forgets any verbal information provided

   Preparing written materials for the low literacy patient. Most patients need help understanding the written counseling information that pharmacies provide from their computer systems or through other sources. Research has shown that health care materials are written at or above the 10th grade level.[15] However, the average American reads at the 8th or 9th grade level, and one in five patients read at or below the 5th grade level. According to the Center for Health Care Strategies, minorities, immigrants, and the elderly have a greater problem with literacy than the general population. More than 66% of Americans over the age of 60 have either marginal or inadequate literacy skills.[15]
   Patients with low literacy skills have health care costs four times higher than patients with adequate literacy skills.[16] This is likely due to an increased rate of hospitalization because these patients make more medication errors, are less compliant with prescribed drug regimens, and have great difficulty working through the cumbersome health care system.[17]
   Simple words, short sentences, large type, and use of "white" or unprinted space are useful techniques when preparing written materials for low literacy patients. Complicated medical or technical words should be replaced with simpler choices as previously described. Comic-strip formats may be useful for presenting drug information or demonstrating techniques to patients with low health literacy skills.[18]
   However, it is important when using comic-strips or other types of illustrations that the materials do not appear to be condescending. The objective for a picture is the same as for written materials, to communicate an important concept. Therefore, pictures should focus on desired behaviors rather than on drug facts, and the information should be both culturally sensitive and relevant to the patient situation.[19,20]
   The Foreign-Speaking Patient. The patient who does not speak English or understands very little English somewhat resembles both the hearing-impaired and the low literacy patient. This patient will have difficulty understanding both the verbal and the written communication provided by the pharmacist. The patient's name and dress may indicate that they are originally from another country and are not native English-speaking patients. The patient may respond in a foreign language or with a heavy accent to her English. The patient may seem confused or may respond inappropriately, either verbally or with inappropriate body language.
   Suggested techniques to improve counseling include:
   - Nonverbal cues and body language to communicate ideas to the patient
   - Speak slowly; use simple, basic terminology
   - Substitute numbers and calendars for written instructions
   - Pictograms and auxiliary labels containing pictures or draw pictures for the patient
   - Ask open-ended questions to see if the patient has understood your communication
   - Reinforce information with accompanying family member whose English is more proficient

   If a large percentage of the pharmacy's patient population speaks the same language, the following steps would be worth investigating:
   - Learn the language or, at least, learn some key words
   - Employ a translator, live or computerized; use printed instructions in other languages or manufacturers' videos in other languages

   Comprehension Difficulties. Patients who have poor comprehension, whether it is caused by a psychiatric illness or mental retardation, are unable to process the information communicated and respond appropriately. Clues to the nature of the barrier may include psychiatric medications in the patient profile, patient address that indicates the patient lives in an institutional setting, inappropriate behavior, dress, or responses. While the patient barrier may be readily apparent, some patient behaviors may be easily confused with other types of barriers and will be evident only with time and repeated interactions with the patient.
   Suggested techniques to improve counseling include:
   - Patience, kindness, and extra attention to the nonverbal message since patients usually interpret nonverbal messages well
   - Rephrase or carefully repeat when necessary; speak slowly and face patient

- Reassure patient as needed
- Ask for feedback from patient to assess level of understanding
- Keep it simple; use no jargon
- Prioritize the information to be given, stress the most important points, break into small segments of information
- Use association to daily activities
- Use calendar or containers to help organize and remember when to take medications
- Use demonstrations when appropriate
- Include caregiver or family member in conversation when possible

Counseling Children and Adolescents

The USP Pediatrics Advisory Panel and its *Ad Hoc* Advisory Panel on Children and Medicines have developed a position paper entitled *Ten Guiding Principles for Teaching Children and Adolescents About Medicines.*[21] These principles encourage activities that help children and adolescents to become active participants in their own health behavior, particularly with regard to medication use. The basic principles are provided in Table 97-4.

Suggestions for talking to children about their medications include:

- Talk to parents and children about how to protect young children from accidental poisoning and what to do if it occurs.
- When children are old enough to understand, speak directly with them about their medicines. Tell children what you expect them to do and why.
- Encourage children to ask you questions about their illness and treatment.

Health care professionals are often unsure of what information is appropriate to share with pediatric patients. Table 97-5 provides examples of questions children have about their medications classified by age. This provides some guidance about the type of information that is appropriate at different ages.

Table 97-4. Ten Guiding Principles for Teaching Children and Adolescents About Medicines

1. Children, as users of medicines, have a right to appropriate information about their medicines that reflects the child's health status, capabilities, and culture.
2. Children want to know. Health care providers and health educators should communicate directly with children about their medicines.
3. Children's interest in medicines should be encouraged, and they should be taught how to ask questions of health care providers, parents, and other caregivers about medicines and other therapies.
4. Children learn by example. The actions of parents and other caregivers should show children appropriate use of medicines.
5. Children, their parents, and their health care providers should negotiate the gradual transfer of responsibility for medicine use in ways that respect parental responsibilities and the health status and capabilities of the child.
6. Children's medicine education should take into account what children want to know about medicines, as well as what health professionals think children should know.
7. Children should receive basic information about medicines and their proper use as a part of school health education.
8. Children's medicine education should include information about the general use and misuse of medicines, as well as about the specific medicines the child is using.
9. Children have a right to information that will enable them to avoid poisoning through the misuse of medicines.
10. Children asked to participate in clinical trials (after parents' consent) have a right to receive appropriate information to promote their understanding before assent and participation.

From Doak CC, Doak, LG, Root JH. *Teaching Patients with Low Literacy Skills.* Philadelphia: JB Lippincott, 1996.

Table 97-5. What Children Want to Know about Medicines at Different Ages

Grades K-1

1. Why some medicines are only for children
2. How they can tell the difference between medicines for children and medicines for adults
3. The therapeutic purposes of medicines
4. Dose forms and ways of taking medicines
5. Importance of complying with the treatment regimen
6. The side effects of some medicines
7. That whether a medicine helps is not related to its color, size, or taste

Children Grades 2–5

1. What the ingredients (active and inactive) are in medicines
2. How medicines work and where medicines go in the body
3. How doctors know that a medicine works
4. Why there are different medicines for different illnesses
5. Why the same medicine can be for different illnesses
6. Why there are different medicines for a single illness
7. Why you should not take other people's medicines
8. How to ask questions of health care professionals about medicines
9. How to read labels
10. Difference between licit and illicit ("good" and "bad") drugs

Children Grades 6–8

1. Difference between prescription and OTC medicines
2. Meaning of dependency and addiction
3. How medicines are made
4. Why medicines come in different forms
5. Reasons for a special diet and time schedule when taking a medicine
6. Potential for drug interactions with other medicines and foods
7. Lack of a relationship between the efficacy of a medicine and its source or price
8. Difference between brand and generic medicines
9. Difference between medicines, botanicals/herbals, and homeopathics
10. How to select an appropriate over-the-counter medicine
11. *For children born outside of the US or whose parents are recent immigrants,* differences between medicines produced in their country of origin and medicines produced elsewhere

Concepts are based on information obtained in 1996 in focus groups of schoolchildren grades K-8 in Baltimore, MD, New York City, and Worcester, MA.
Adapted from Doak CC, Doak, LG, Root JH. *Teaching Patients with Low Literacy Skills.* Philadelphia: JB Lippincott, 1996.

Counseling the Elderly Patient

The most rapidly growing segment of the population, the elderly, present a great number of challenges to the communication skills of a pharmacist. The elderly patient may have several functional barriers. Vision and hearing are often impaired, and the patient may have difficulty removing child-proof tops, self-injecting insulin, or applying creams and ointments. Many elderly have low literacy skills as previously discussed. Additionally, cognitive impairments become more common with increasing age. As patients age, chronic conditions and the number of medications prescribed increase. Many of the techniques previously discussed with other barriers are useful when counseling elderly patients. In addition, pharmacists should consider the following:

- Additional time may be required to address the needs of the patient.
- Written information and compliance reminder aids are particularly helpful with large numbers of prescription products.

Studies indicate that an effective way to provide counseling to elderly patients is to provide small pieces of specific information coupled with a reminder aid and verbal reinforcement of the information.[23] It is also important for pharmacists to

consider their own feelings about aging. One recommendation to increase empathy for elderly patients is to consider what the patient and the world were like when he or she was younger and to remember that the patient was not always old.[24]

Emotional Barriers

Regardless of the type of emotion the patient exhibits, dealing with a highly emotional patient is challenging for the pharmacist. Often the pharmacist is uncomfortable with the emotions expressed by the patient and responds inappropriately by ignoring the issue at hand or by focusing on trying to solve the patient's problem. When the pharmacist recognizes that a patient is in an emotional state, it is important to deal with the emotional barrier first. Discussing the patient's current medication needs will be ineffective while the patient is distracted by other issues. It is important, at the very least, to acknowledge the patient's concerns.

The most effective way to address patients' emotional concerns is to use empathic responses, also called reflective responding. Use of this technique requires that the pharmacist truly listens to what the patient is saying, both in words and nonverbal communication. Additionally, to be successful using this technique, the pharmacist must have a desire to understand and help the patient.

It is important to understand the meaning of empathy, a concept that is often confused with sympathy. When expressing sympathy, the pharmacist feels sorry for the patient. Empathy is a neutral process in which the pharmacist identifies with the feelings of the patient. This is sometimes described as putting yourself into the other person's shoes. It is not necessary to actually have experienced the same situation or emotion, but rather to try to understand how the patient feels. Using empathy tells the patient that the pharmacist is interested in him, and it is a positive step in building the pharmacist-patient relationship. Over time, the patient is more willing to voice questions and concerns to the pharmacist thereby improving the quality of care the pharmacist can provide.

Expressing empathy to the patient is accomplished through the use of a reflective response. A reflective response is the pharmacist's way of communicating to the patient his or her understanding of the patient's feelings. It acknowledges the patient's feelings and usually has a calming effect on the patient that may allow the pharmacist to proceed with the counseling session.

How to Formulate a Reflective Response

The starting point for formulating a reflective response is to mentally paraphrase what the patient has expressed and to state that for the patient. Examples of phrases that often begin a reflective response include the following:

- "It sounds like . . . "
- "I gather that . . . "
- "What I hear you saying is . . . "
- "It seems that . . . "
- "In other words . . . "
- "If I understand you correctly . . . "
- It appears that you are saying . . . "

Use of this type of response tells the patient that the pharmacist is listening and is trying to understand the patient's concerns. It also tells the patient what the pharmacist thinks he or she is feeling. This allows the patient the opportunity to reply affirmatively or gesture that the pharmacist has correctly understood the situation. If the pharmacist has misinterpreted the patient's feeling, he or she will usually correct the pharmacist's misimpression.

What Reflective Responses Are Not

It is often easier to understand a good reflective response by looking at statements that are not truly empathic. The most common errors in attempting to express empathy are to offer advice or judge the patient. Some examples will illustrate the most common errors pharmacists make in attempting empathic responding.

Mr. Roberts, a regular patient in the pharmacy (looking worried and upset): *"My doctor says I might need to have surgery if this drug doesn't work."*

Pharmacist 1: *"Oh, there is no need to worry. I'm sure this medication will work and everything will be fine."*

Pharmacist 1 makes a judgment about the patient's concerns and tells the patient that he is wrong to be concerned. This response may actually make the patient feel worse and lets him know that the pharmacist does not understand his concerns.

Pharmacist 2: *"You should get a second opinion from another doctor before you think about having surgery. Maybe it won't really be necessary."*

Pharmacist 3: *"You shouldn't think that far ahead. Maybe the medication will work and you would have worried for nothing."*

Pharmacist 2 and 3 provide advice to the patient about what he should do but do not acknowledge his current feelings and concerns. Advice, even when it is appropriate, should be deferred to a later time in the conversation if at all.

Pharmacist 4: *"I know how you feel. My mother just went through the same experience. But it all ended up okay."*

Pharmacist 4 is engaging in deflecting behavior. This pharmacist takes the focus from the patient to himself. While it may seem appropriate to give an example of a similar experience that tells the patient you have experienced the same feelings, this type of response brings the pharmacist's feelings into the conversation rather than focusing on the patient concerns.

Pharmacist 5: *"Have you asked your doctor about one of the new medications for this condition?"*

When pharmacists feel uncomfortable dealing with the patient's emotions and concerns, they frequently concentrate on facts and question asking. While information gathering is important in a patient counseling session, it is not appropriate at this point in the conversation when calming the patient is the primary goal.

While each of these responses seems like a sincere attempt to be helpful to the patient, none of them is a reflecting response. Remember that the primary purpose of empathic responding is understanding and acknowledging the patient's feelings not solving the patient's problem. Examples of appropriate reflecting responses for Mr. Roberts include:

Pharmacist: *It sounds like you are worried about the possibility of having surgery.*

Pharmacist: *I can see that you are concerned about whether the new medicine will work so you won't need surgery. Let's take a few minutes to talk about how to use the new medicine so that you can get the best possible effect from it.*

These responses acknowledge the patient's worry and the pharmacist's understanding of why he is worried. The second response continues after addressing the patient's concern to offering patient counseling and the benefit to the patient in participating in that process. Ultimately, the purpose of empathic responding is to move the patient to a mental and emotional state that will allow the pharmacist to continue with the patient counseling session.

It takes time and practice to become proficient in using reflective responses. Pharmacists may choose to practice these techniques on family, friends, and patients with whom they already have good relationships prior to attempting these techniques on difficult patients.

When Reflective Responses Don't Work

Obviously, reflective responses will be unsuccessful if the pharmacist is not skillful at this process. As stated previously, this skill can be improved through practice. Sometimes, the process will not work regardless of the skill of the pharmacist. The patient's emotional state may be too highly charged to respond to a brief interaction with a pharmacist. The patient may be irrational due to psychiatric illness or the influence of drugs. The pharmacist must maintain a cool demeanor and utilize assertiveness techniques when required. When it is obvious that these techniques will be unsuccessful, the pharmacist may terminate the interaction.

THE ANGRY PATIENT—Perhaps the most common and difficult emotional situation a pharmacist faces on a daily basis is the angry patient. Patients may be angry when they arrive at the pharmacy for a variety of reasons—time spent at the doctor's office, concerns over health or health care costs, or frustration over dealing with the complexities of the health care system, just to name a few. It may be helpful to recognize that anger is a secondary emotion.[16] The patient may begin by feeling fear, hurt, anxiety, or frustration over events not under the person's control. The most effective techniques to deal with patient anger are assertive.

Assertiveness is a neutral expression of one's personal rights, feelings, and beliefs that does not violate the rights of others. It sets boundaries for what behavior is acceptable. Assertiveness techniques that may be useful in dealing with patients who are angry or aggressive include the following:

- Language ownership–This is the demonstration of owning your feelings and emotions. Rather than using nonspecific terms, speak in the first person. For example, when speaking to a verbally abusive patient, don't respond with:
  "Everyone one in the pharmacy hates it when you talk to them in that tone."
  To use ownership language, say *"I feel angry and uncomfortable when you speak to me in a condescending tone and use inappropriate words."*
- Specificity–Clearly state what your needs and expectations of the other person are. For example, when speaking to a patient who has made several unreasonable demands, don't respond with:
  "You are being totally unreasonable."
  To use language specificity, say *"It is not appropriate to ask me to refill a prescription that is not authorized for refills without an approval from your doctor. That would be a violation of pharmacy laws."*

WHEN PATIENTS REFUSE PATIENT COUNSELING

Patients may decline the offer of patient counseling because they don't value taking the time to participate in the counseling process. Other patients may be rushed for time or distracted by other concerns that prevent them from listening to information about their prescription medications. When this happens, the pharmacist should be sure to give the patient written counseling materials along with the phone number of the pharmacy. The patient should be encouraged to call the pharmacy to discuss any concerns that she has at a more appropriate time. The pharmacist may offer to make an appointment with the patient for counseling over the telephone at a later date.

CONDUCTING A PATIENT MEDICATION INTERVIEW

In order to provide the best possible patient care, a pharmacist must collect information from the patient about current and past medication use as well as medical conditions and life-style information (Fig 97-2). This information serves as a database for the pharmacist to help patients achieve the best possible outcomes of drug therapy. This process has several purposes for the pharmacist and patient:

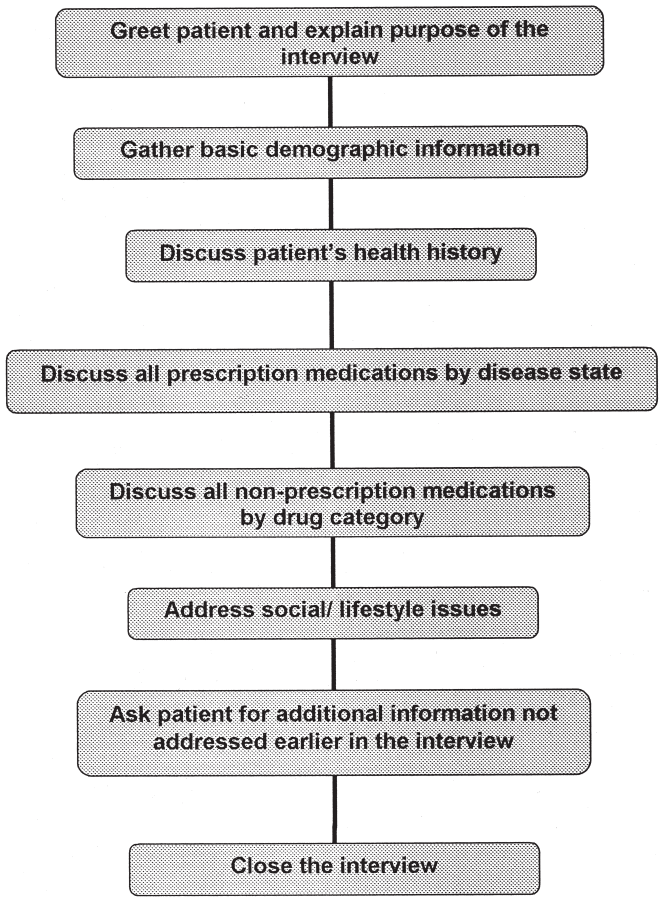

Figure 97-2. Steps in a patient medication history interview.

- Helps to establish the pharmacist-patient relationship
- Provides a basis for assessing the appropriateness and effectiveness of past and present medications
- Assists the pharmacist in solving current drug-related problems and preventing future problems

It is preferable to conduct medication interviews by appointment since this process will take a minimum of 20–30 minutes and possibly longer for patients who have extensive medication histories. The interview should take place in a private setting due to the confidential nature of information to be discussed. Some pharmacists prefer to give the patient a blank medication profile and ask the patient to fill out the form and bring it to the interview. If this technique is used, the pharmacist should work through the form with the patient to confirm and complete the information provided by the patient.

Utilizing a standard format when conducting medication interviews ensures that important information is not overlooked in the process. A logical structure for the patient interview is suggested below.

Steps in the Patient Medication Interview

1. *Greeting and purpose of the interview*
   The patient should be greeted and the pharmacist should make introductions if the patient is not already known to the pharmacist. The patient should be put at ease with some small talk. The

purpose of the session and the benefits to the patient should be outlined. The patient should be assured that the information gathered will be held in confidence.

2. *Gathering of basic information*
   Basic information such as complete name, address, phone number, birth date, all regular health care providers, insurance information, and occupation should be gathered.
3. *Patient's health history*
   The patient should be asked about all current and past medical conditions including the symptoms experienced and the duration of the illness. Female patients of child-bearing age should be asked if they are pregnant or breastfeeding. Allergies and the type of reaction the patient experienced upon exposure to the substance should be determined.
4. *Prescription medication use*
   Each medical condition identified above should be addressed in turn. The patient should be asked to describe all medications in current use including the name, strength of the drug, prescriber, dosage form and route of administration, dosing schedule including how the patient adheres to the prescribed regimen, the patient's perception of how well the medication works, adverse effects that the patient has experienced and the steps taken to relieve those effects. The patient should also describe all past medications used for a particular condition and the reasons why the medication was discontinued. The medications used for each condition should be discussed in turn.
5. *Nonprescription medication use*
   The patient should be asked to describe the use of all products purchased without a prescription. This includes all typical over-the-counter products as well as dietary supplements and herbal products. Patients often have difficulty remembering these products and their use. Prompters that the pharmacist might use include asking in turn about the major categories of products. For example, "Mrs. Jennings, do you take any products to treat symptoms of cough, cold, or allergies?" The pharmacist should ask the same follow-up questions about how the products are used that are asked for the prescription products.
6. *Life-style issues*
   Asking patients about life-style issues as well as the use of recreational drugs is best left until the end of the interview when the patient has become comfortable with the pharmacist and the process. The pharmacist should explain that use of these products may affect drug therapy and a clear understanding of the extent of use of these products is necessary for the best patient care. Remind the patient that this information is strictly confidential. The patient should be given the option of refusing to provide this type of information. The patient should be asked about use of tobacco products and alcohol as well as recreational drugs.
7. *Closing the interview*
   After completing the systematic collection of information, the pharmacist should offer the patient the opportunity to add any additional information he or she wishes to share or to ask any questions. The pharmacist should reiterate that all information collected will be held in confidence unless there is a need to discuss some of the information with another health care provider in the course of providing care for the patient. The pharmacist will need time to review the information and formulate any recommendations that should be made to the patient. A follow-up appointment should be scheduled with the patient for this purpose. The patient should be thanked for taking the time to complete the interview.

SUMMARY

In summary, the pharmacist-patient relationship is an important one in health care. The relationship that is built on effective communication and trust and established over time may be related to better patient health outcomes. This chapter explained the communication process, introduced the concept of patient empowerment, described pharmacist counseling and communication skills, reviewed a model patient counseling session, a model medication history process and presented steps and techniques for counseling patients who present to the pharmacy with barriers. It is imperative that future health care professionals and pharmacists understand the need for effective communication and the link with patient health behavior.

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http://www.usp.org
http://www.askme3.org/
http://www.plainlanguage.gov/

CHAPTER 98

Patient Compliance

Daniel A Hussar, PhD

The important advances that have been made in the understanding of the etiology of many disease states, and the development of many new therapeutic agents, have made it possible to cure or provide symptomatic control of many clinical disorders. However, accompanying the increasing sophistication relative to diagnostic and therapeutic knowledge and skills has been the recognition that in many circumstances, drugs are not being used in a manner conducive to optimal benefit and safety. In many situations, efforts to maintain or improve health fall short of the goals that are considered attainable, and frequently, the failure to achieve the desired outcomes has been attributable to patient noncompliance or partial compliance.

With regard to the provision of health care, the concept of compliance can be viewed broadly, as it relates to instructions concerning diet, exercise, rest, return appointments, etc, in addition to the use of drugs. However, it is in discussions concerning drug therapy that the designation *patient compliance* is employed most frequently. It is in this context that it will be used in this discussion, and compliance can be defined as the extent to which an individual's behavior coincides with medical or health instructions/advice.

Compliance with therapy implies an understanding of how the medication is to be used, as well as a positive behavior in which the patient is motivated sufficiently to use the prescribed treatment in the manner intended, because of a perceived self-benefit and a positive outcome (eg, enhanced daily functioning and well-being). Some have recommended the use of the terms *adherence* or *concordance* rather than the designation *compliance;* however, the latter term continues to be the most widely accepted and used.

The term *persistence* is also used to identify the duration of time over which a patient continues to take prescribed medication.

Problems concerning patient compliance with instructions have been recognized for years and, indeed, Hippocrates once cautioned, "Keep watch also on the fault of patients which often makes them lie about the taking of things prescribed." Twenty-three centuries later, attaining patient compliance in the use of their medications continues to represent a formidable challenge for health care providers.

When the complexity of the patient's illnesses and the actions of potent therapeutic agents are taken into account, the physician, pharmacist, and other health professionals easily can become preoccupied with the diagnosis of the disease state as well as the selection and implications of drug therapy and assume that the patient will follow the instructions provided. After all, since the medication is being provided to improve and/or maintain the patient's health, why would the patient not follow instructions? Yet, studies continue to show that a large percentage of patients, for a variety of reasons, do not take their medication in the manner intended.

Although some patients make a conscious decision to deviate from the prescribed regimen (ie, *intentional* noncompliance), many intend to take their medication according to instructions and, in some cases, even may be unaware that their use of medication differs from what the prescriber intended.

The term *patient noncompliance* suggests that the patient is at fault for the inappropriate use of medication. Although this is often the case, in a number of situations, the physician and pharmacist have not provided the patient with adequate instructions or have not presented the instructions in such a manner that the patient understands them. The most basic questions regarding drug usage must be addressed—Has the patient been provided with adequate instructions? Does the patient understand how the medication is to be taken? Nothing should be taken for granted regarding the patient's understanding of how to use medication, and appropriate steps must be taken to provide patients with the information and counseling necessary to use their medications as effectively and as safely as possible.

NONCOMPLIANCE

Types

The situations most commonly associated with noncompliance with drug therapy include failure to have the prescription dispensed or renewed, omission of doses, errors of dosage, incorrect administration, errors in the time of administration, and premature discontinuation.

Some patients for whom medication has been prescribed do not even take their prescriptions to a pharmacy, and some others who do take their prescriptions to a pharmacy fail to pick them up when they are completed. In a survey[1] of consumers, 2% responded that they had brought prescriptions to the pharmacy but failed to pick them up. The most common explanations for not taking the prescriptions to a pharmacy or not picking them up are that patients feel that they have recovered from the condition or otherwise don't need the medication, they think they have a similar medicine at home, they don't like to take medicine, the cost is too high, or they forget to pick up the prescription from the pharmacy. In the many situations in which infection is associated with fever and local discomfort, patients already may be taking nonprescription medications, such as acetaminophen. The ability of these agents to provide some, if not complete, relief of the symptoms of early infection may lead some patients to conclude that the condition is improving, or better, and that it is not necessary to have a prescription dispensed.

The omission of doses is one of the most common types of noncompliance and is more likely to occur when a medication is to be administered at frequent intervals and/or for an extended period of time. Errors of dosage include situations in which the

amount of an individual dose or frequency of administration is incorrect.

Examples of the incorrect administration of medication include not using the proper technique in using metered-dose inhalers and, in some cases, giving medication by the wrong route of administration. Errors in the time of administration of the drug may include situations in which medication is administered in an inappropriate relationship to meals. Certain drugs—eg, tetracycline, alendronate (Fosamax)—should be administered apart from meals to achieve optimal absorption. The time of day at which a drug is administered also may be important in the use of some medications; eg, diuretics are best administered in the morning.

The premature discontinuation of treatment occurs commonly with the use of antibiotics as well as medications used in the treatment of chronic disorders such as hypertension. Patients must be apprised of the importance of taking the medication in the manner instructed, even though their condition may be asymptomatic or, as in the case of infections, the symptoms may have subsided soon after the initiation of therapy.

Studies reflect a wide variation in the degree of noncompliance. Many reports indicate that at least one-third of patients failed to comply with instructions, and for patients with chronic illnesses on long-term treatment regimens the results suggest a rate of noncompliance of approximately 50%.

Consequences

The importance and scope of the difficulties that result from the failure to use medications in the manner intended have resulted in the National Council on Patient Information and Education designating noncompliance as *America's other drug problem,* and others have described it as an "invisible epidemic."[2] Others have noted that noncompliance may be the most significant problem that faces medicine today[3] and that "knowledge of patient compliance is of critical importance in interpreting drug response, whether it be in the individual patient or in a clinical trial."[4] In response to concerns regarding mismedication among elderly patients, including observations that 55% of this patient population is noncompliant, the Office of the Inspector General conducted a study to determine why elderly people fail to follow prescription medication regimens.[5]

"Drugs don't work if people don't take them." This observation made by former Surgeon General C Everett Koop in his keynote address at a symposium on *Improving Medication Compliance,*[6] provides a clear statement of one of the consequences of noncompliance. In many cases noncompliance results in *underuse* of a drug, thereby depriving the patient of the anticipated therapeutic benefits and possibly resulting in a progressive worsening or other complications of the condition being treated.

Noncompliance also may result in the *overuse* of a drug. When excessive doses are employed or when the medication is given more frequently than intended, there is an increased risk of adverse reactions. These problems may develop rather innocently, as when a patient recognizes that he has forgotten a dose of medication and doubles the next dose to make up for it. Some other patients appear to believe that if the one-tablet dose that has been prescribed provides some relief of symptoms, two or three tablets will be even more effective.

Numerous hospital admissions and nursing-home admissions are related to noncompliance. In a study of 315 consecutive medical admissions of elderly patients to a community hospital, 28% were medication-related—17% because of adverse reactions and 11% because of noncompliance.[7] A review of published studies of drug-related hospital admissions noted that 11 reports indicated that 22.7% of adverse drug reaction hospitalizations were induced by noncompliance.[8]

Hypertension is the most frequently studied disease with regard to compliance. Although educational and screening programs have significantly reduced the number of individuals who are unaware that they have hypertension, it is thought that most of the more than 50 million Americans with high blood pressure do not have their condition under good control. For those hypertensive patients for whom treatment has been prescribed, many do not have their blood pressure under effective control, and a major reason for the failure to control hypertension is noncompliance with regimens that would work if administered as intended. Noncompliance is one of the most commonly missed diagnoses, and the manner in which patients use their medication should be evaluated before the therapeutic regimen is changed. In one study it is reported that the underuse of antihypertensive medications may be associated with hospitalization that could have been prevented if patients had complied with their treatment regimens.[9]

The statins (eg, atorvastatin [Lipitor], simvastatin [Zocor]) have been shown to significantly reduce morbidity and mortality in patients with coronary heart disease and in patients with hyperlipidemia, when they are used on a continuing basis. However, in two recent studies, compliance with statin therapy declined more than 25% in the first 6 months after the original prescription, with further declines in compliance occurring the longer the patients were followed.[10,11]

Noncompliance has major implications for those with HIV infection/AIDS. The complexity of the treatment regimens used in the treatment of HIV infection/AIDS and its complications results in a "pill burden" that is often associated with noncompliance. Surveys have demonstrated that approximately one-third of the patients missed doses during the 3-day period prior to the surveys. The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents include the following observations:

> "Adherence is a key determinant in the degree and duration of virologic suppression. Among studies reporting on the association between suboptimal adherence and virologic failure, nonadherence among patients on HAART (highly active antiretroviral therapy) was the strongest predictor for the failure to achieve viral suppression below the level of detection."[12]

An additional concern is that the irregular treatment that results from noncompliance appears to accelerate the emergence of resistant strains of HIV.

It has been observed that about one-half of patients with schizophrenia are noncompliant in using their medications and experience a relapse of symptoms within a year of initiation of antipsychotic treatment. The inadequate control of schizophrenia has, in some situations, been associated with violent actions.

One report[13] has called attention to the hazards of noncompliance with antiepileptic drug regimens. In examining autopsy records pertaining to 11 cases of unattended, unexpected deaths of epileptic patients, no antiepileptic drugs were found in 4 patients and subtherapeutic concentrations were noted in 6 others. It is suggested that a number of these deaths may have been preventable had there been better compliance with the instructions for using the medication(s).

Similarly, a leading cause of death in transplant patients, some of whom had waited for years for a donor organ, is the rejection that results from noncompliance in using immunosuppressant medication.[14]

The economic consequences of noncompliance also are alarming, and some have estimated that the costs associated with noncompliance in the US exceed $100 billion a year. The cost of noncompliance and the capacity of improved compliance to reduce health-care expenditures are the subject of a review of a number of studies in which it is observed that the benefits realized from improved compliance outweigh, in some cases far outweigh, the costs of programs designed to improve compliance."[15]

Noncompliance also may take other forms. The problems associated with drug misuse and abuse, whether unintentional or deliberate, are well recognized. Although usually not thought of in terms of noncompliance, drug-abuse problems sometimes result from excessive use of medications that have been prescribed for existing clinical disorders.

Another implication relates to the storage of drugs that are not used completely during the intended period of treatment. Keeping these drugs may result in their inappropriate use at some later time. Accidental poisonings have resulted, and stockpiled medications have been used to commit suicide.

The recognition that noncompliance is so prevalent has raised questions regarding the attention this variable has received in clinical studies of therapeutic agents. For example, an analysis of the sources and the amount of overt and hidden bias in reports of double-blind studies of nonsteroidal anti-inflammatory drugs published between 1966 and 1985 revealed that only 13% of the studies measured compliance.[16] The potential changes in therapeutic response resulting from noncompliance dictate that close attention be given to this aspect of the study of the action of therapeutic agents.

Although the consideration of the consequences of noncompliance should focus primarily on the problems that may develop, there also should be an awareness of situations in which some patients may benefit from being noncompliant. Designated by one investigator[17] as *intelligent noncompliance,* it is noted that certain individuals have a rational basis (eg, avoiding adverse effects) for altering the dosage of their medication, and that good treatment outcomes are still attained. However, the fact that certain patients may benefit from not complying with a treatment regimen must not be considered a reason for health professionals to be less diligent in detecting noncompliance and initiating the appropriate corrective measures, as any situation in which noncompliance occurs requires careful evaluation.

Detection

Like the diagnosis of medical disorders, detection of noncompliance is a necessary prerequisite for adequate treatment. In addition, like many diseases, compliant or noncompliant behavior is not stable and may change over time, necessitating the regular use of detection methods to measure this behavior as part of the assessment of treatment efficacy.

The ideal detection method would measure compliance at the time and place of the medication-taking (or other treatment) event. Direct observation of the patient would come closest to providing this ideal measure of compliance. However, this method usually is not practical.

Current detection methods include indirect measures, such as self-report, interview, therapeutic outcome, pill count, change in the weight of metered-dose inhaler canisters, medication-refill rate, insurance prescription claims databases, and computerized compliance monitors, and direct measures, such as biological markers, tracer compounds, and assay of body fluids. In general, the direct methods of detection have a higher sensitivity and specificity than the indirect methods. However, all of these methods have their limitations. To help overcome limitations of the assessment methods and to provide corroborative information, it is recommended that at least two different detection methods be used to measure compliance.

INDIRECT METHODS—Self-reports and interviews with patients are the most common and simplest methods of attempting to determine compliance with therapy. However, many studies have demonstrated that even the most skilled and highly refined interviewing techniques substantially overestimate medication compliance. In spite of the limitations of interviews, asking carefully constructed questions (eg, "Most people have trouble remembering to take their medicine. Do you have trouble remembering to take yours?")[18] in a nonthreatening manner will help to identify some noncompliant patients.

Pill counts are another detection method used to measure compliance and frequently are used in clinical drug studies. A patient's compliance with a medication regimen can be assessed by the difference between the number of dosage units initially dispensed and the number remaining in the container on a return visit or during an unscheduled home visit. However, *pill dumping* (ie, attempts by patients to misrepresent their compliance by discarding medication) is common, and several studies have shown that return counts grossly overestimate actual compliance rates.[19,20]

The achievement of treatment goals sometimes has been used as a measure of a patient's compliance. When a particular treatment is associated with a successful outcome (eg, normal blood pressure, glucose concentration, or intraocular pressure), satisfactory compliance with the regimen may be inferred. However, patients may *load-up* on medication or comply with other treatment regimens (eg, diet) just before their return visit. Such behavior has been called the *toothbrush effect,* after the way people brush their teeth just before seeing a dentist. The toothbrush effect can invalidate almost completely the health-outcome strategy, as well as certain other detection methods (eg, determination of drug concentrations in a body fluid).

Computerized compliance monitors are the most recent and reliable of the indirect-detection methods, but their cost may preclude their use in most practice settings. The Medication Event Monitoring System (MEMS) is a microprocessor housed in the cap of the medication container. Each time the patient removes the cap, the time and date are recorded. Data are retrieved by connecting the microprocessor unit to a computer. The data not only provide an indication of individual dosing patterns, but also allow correlations with clinical events. Such data might be useful to the clinician in understanding why treatment has not been fully successful. Although the computerized monitors provide no direct information on whether or how much medication was actually taken, their use helps to supplement other methods. For example, in one study[21] in which pill counts indicated near-perfect compliance, the monitor in the cap showed that fewer than half of all cap openings occurred at the prescribed interval of 12 $\pm$ 2 hr.

In a study designed to compare multiple measures of compliance with the use of HIV protease inhibitors, it is noted that compliance may be underestimated by MEMS and overestimated by pill count and interview.[23] These investigators also combined these three measures to determine a composite adherence score (CAS) that was more clearly related to clinical outcome than any of the three measures used individually.

DIRECT METHODS—Biological markers and tracer compounds indicate patient compliance over an extended period. For example, measurement of glycosylated hemoglobin in patients with diabetes mellitus gives an objective assessment of metabolic control during the preceding 3-month period. Tracer compounds—small amounts of agents with long half-lives such as phenobarbital—have been added to drugs in some studies and measured in biological fluids as pharmacological indicators of compliance.

Finally, compliance also has been measured through determination of drug concentrations in patients' biological fluids. However, the usefulness of data on drug concentrations in biological fluids is limited because (1) concentrations of drugs are affected by individual differences in absorption, distribution, metabolism, and excretion, and low or erratic drug concentrations are not necessarily an indication of noncompliance[22]; (2) drug concentrations do not provide data regarding the timing of doses consumed; and (3) brief intake of rapidly cleared drugs before testing can produce results that show adequate drug concentrations, erroneously suggesting regular medication use.

The Noncompliant Patient

Efforts have been made to demonstrate the relationship of noncompliance to a number of variables such as age, education, occupation, socioeconomic status, personality factors, physiological variables, and the number, types, and severity of illnesses. Although certain patterns have been noted in some studies, the results, in general, have been inconsistent, and it continues to be difficult to identify which patients are most likely to be noncompliant.

A distinction has been made between attitudinal and behavioral compliance, since often the attitude and behavior of a patient may be incongruent. For example, patients fully may intend to take the medication according to instructions but actually not do so because they are forgetful or really do not understand the instructions. On the other hand, some patients may have no intention of complying but nevertheless do so.

Some individuals are intentionally noncompliant, and this further underscores the complexity of the challenge to develop strategies to improve compliance. Although considerable progress has been made in recognizing and addressing the problems associated with noncompliance, an observation made in an early discussion of this subject continues to be valid today—"It has not proved possible to identify an uncooperative type. Every patient is a potential defaulter; compliance can never be assumed."[24] In a recent commentary on the challenge of attaining compliance, the authors observe: "Bluntly, we are very human physicians in corruptible institutions treating fallible patients. Everyone takes shortcuts. This is the ragged edge of medicine in the 21st century."[25]

Considerable attention has been directed toward the sociobehavioral determinants of compliance, and a number of models based on behavioral principles have been described.[26] A *health-belief model,* which initially was developed[27] to explain preventive health behaviors such as obtaining immunizations and prophylactic dental care, was revised subsequently[28] to apply to compliance with prescribed medical regimens. A *third-generation* model was then proposed[3] that focuses more specifically on health decisions. This *health-decision* model combines decision analysis, behavioral decision theory, and health beliefs to yield a model of health decisions and resultant behavior. The components of this model and the manner in which they are interrelated are outlined in Figure 98-1.

With respect to the relationship between health beliefs and compliance, if compliance is to be achieved, patients must believe that

They actually have the illness that has been diagnosed.
The illness could cause severe consequences with regard to their health and daily functioning.
The treatment prescribed will reduce the present or future severity of the condition.
The benefits of the regimen prescribed outweigh the perceived disadvantages and costs of following the recommended action.

In addition, there must be a stimulus to trigger the advocated health behavior, which can be either internal (eg, concern about the disease) or external (eg, interaction with the physician or pharmacist).

Patient education and counseling initiatives should be designed to encourage the beliefs noted above, particularly since many patients believe that "you only need to take medication when you are ill and experience symptoms" and/or "you need to stop taking medication once in awhile or else your body becomes dependent on it or the medication will become less effective."

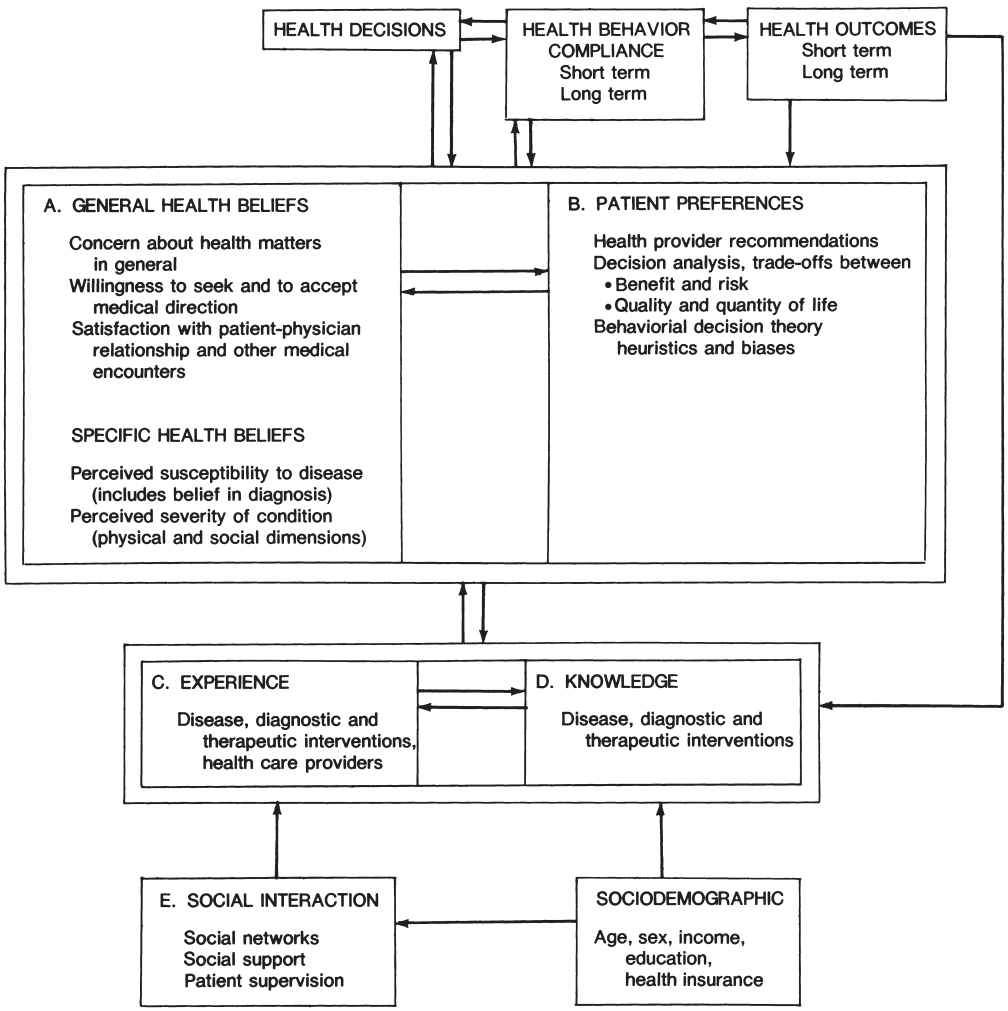

Figure 98-1. The health-decision model, combining the health-belief model and patient preferences, including decision analysis and behavioral decision theory. (From Eraker SA, et al. *Ann Intern Med* 1984; 100:258.)

There are also other *patient factors* that may contribute to noncompliance. Patients who live alone are less likely to comply than those who live with another family member who can take an interest in and/or supervise their therapy. The increasing problems of drug abuse and addiction have increased the awareness and concern about becoming dependent on agents that are prescribed for legitimate medical reasons. Although drugs that carry a potential for abuse and development of dependence often are prescribed and used too casually, some patients develop a fear of dependence regarding use of any drug that is to be employed for a prolonged period. To avoid such a possibility or to prove to themselves that they are not dependent, they may interrupt or stop therapy or use the medication in smaller amounts.

Numerous other factors have been suggested to contribute to patient noncompliance, and the most important of these are considered in the following discussion.

FACTORS ASSOCIATED WITH NONCOMPLIANCE

In addition to the patient factors previously considered, a number of other determinants of patient compliance have been cited. Some of the more important and/or commonly considered factors are discussed below. Although the relationship of some of these factors to the occurrence of noncompliance has not been proven, there should be an awareness of the potential implications in selected patients.

Disease

The nature of the patient's illness may, in some circumstances, contribute to noncompliance. In patients with psychiatric disorders, the ability to cooperate as well as the attitude toward treatment may be compromised by the illness, and these individuals may be more likely than other patients to be noncompliant. Several studies of patients with conditions such as schizophrenia have shown a high incidence of noncompliance, and this is thought to be due, in part, to a distorted view of reality that does not allow these patients to recognize their illness as well as the need for treatment.

Patients with chronic disorders, particularly conditions such as hypertension and hypercholesterolemia, which often are not associated with symptoms are also more likely to be noncompliers. Patients understandably tend to become discouraged with extended therapeutic programs that do not produce cures of the conditions. Even when cures can be anticipated as a result of long-term therapy, problems still can occur, as exemplified by patients with tuberculosis who frequently become noncompliant as the treatment period continues.

It might be anticipated that patients who experience significant symptoms if the therapy is discontinued prematurely will be more attentive to taking medication correctly. However, few studies have demonstrated a correlation between disease severity and compliance, and it cannot be assumed that these patients will comply with their therapeutic regimens. The relationship between the degree of disability caused by a disease and compliance is defined better, and it can be expected that increased disability will motivate compliance in most patients.

Therapeutic Regimen

MULTIPLE DRUG THERAPY—It generally is agreed that the greater the number of drugs a patient is taking, the higher is the risk of noncompliance. For example, many elderly patients are taking five or six or more medications several times a day at different times. In addition, some elderly patients may experience lapses of memory that make noncompliance even more likely. Even when specific dosage instructions for the medications are provided, problems still can occur.

The similarity of appearance (eg, size, color, or shape) of certain drugs may contribute to the confusion that can exist in the use of multiple drugs. It is desirable that there be an awareness of the physical characteristics of the drugs used, so that the patient will not be taking, for example, only small white tablets.

The observations in an editorial[29] provide a perspective that is helpful in understanding the challenge for the patient who is to take a number of medications.

> "A common consequence of too many pills is organizational breakdown. Given a regimen of four pills once a day, one pill twice a day, three pills three times daily, and two pills four times daily, compliance suffers. Even the best intentions struggle under such complexity. Day-to-day pill-taking becomes a little like a church dinner, at which no one takes exactly the same foods or the same portions. An assortment of dishes bewilders the senses. Except for the most compulsive patient, a regimen of many pills many times a day breeds more variety than regularity. Reducing pills and reducing intervals helps minimize the randomness of taking drugs. Potluck becomes a balanced diet."

Although combination drug products have certain disadvantages, their use may help improve compliance with therapy, since only one product need be administered rather than several. Therapy usually should not be initiated with a combination product but rather with the individual agents. Once the optimal dosages of the individual drugs have been determined, if they correspond to the amounts included in the combination, these products can be used to advantage.

FREQUENCY OF ADMINISTRATION—The administration of medication at frequent intervals makes it more likely that the patient's normal routine or work schedule will have to be interrupted to take a dose of medication, and in many cases the patient will forget, not want to be inconvenienced, or be embarrassed to do so.

In a study in which compliance was observed to improve from 59% on a three-times-a-day regimen to 75% on a twice-a-day regimen to 84% on a once-a-day regimen, the investigators noted that "probably the single most important action that health-care providers can take to improve compliance is to select medications that permit the lowest daily prescribed dose frequency."[30]

The attitudes of patients toward their illnesses and treatment regimens also should be anticipated and addressed. In most situations, it is reasonable to expect that patients will favor, and be more inclined to comply with, a dosage regimen that is simple and convenient.

DURATION OF THERAPY—The potential for noncompliance is greater when the treatment period is long. As noted earlier, a greater risk of noncompliance should be anticipated in patients with chronic disorders, especially if discontinuation of therapy is not likely to be associated with prompt recurrence of symptoms or worsening of the illness. Noncompliance with regimens for the treatment of tuberculosis is a major reason for the development of resistance to multiple antitubercular agents and is a very important problem for many patients with this infectious disease.

ADVERSE EVENTS—The development of unpleasant effects of a drug is a likely deterrent to compliance. In an AARP survey of people 45 years of age and older, 40% of the respondents stated they had experienced some form of side effect during medication use.[31] Of this 40%, 50% responded that they stopped taking the medication as a result of the side effect. Of the respondents who were 65 years of age and older, only 47% informed their physicians of the discontinuation.

In some situations it may be possible to change the dosage or use alternative drugs to minimize adverse events. However, in other cases such alternatives may not exist, and the benefits expected from therapy must be weighed against the risks. Particularly disconcerting are those situations in which the development of adverse events makes patients feel worse than they did before therapy was initiated, as often occurs in hypertensive patients.

The adverse events (eg, nausea, vomiting, hair loss) associated with the use of many antineoplastic drugs are sufficiently distressing to a number of patients with cancer that they do not take their medication in the manner intended. The reduction in the quality of life resulting from effects such as severe nausea and vomiting may be of such importance to some individuals that they do not comply with a regimen that in some cases may even offer the hope of being curative.

The ability of certain drugs to cause sexual dysfunction is a reason for noncompliance by some patients, with the antipsychotic agents, antidepressants, and antihypertensive agents being implicated most frequently.

Even a *warning* about possible adverse events may result in some individuals not complying with instructions. It is inadvisable for patients being treated with sedatives or other agents with a central nervous system depressant effect to consume alcoholic beverages, because of the possibility of an excessive depressant response. However, there should be a realistic recognition that some patients, if faced with a mandate not to drink while on drug therapy, will choose not to take their prescribed medication. Although problems of combined alcohol-drug usage are well known, this situation continues to present a challenge of effectively communicating with the patient so that optimal benefit can be achieved at minimal risk.

PATIENTS MAY BE ASYMPTOMATIC OR SYMPTOMS SUBSIDE—It is understandably difficult to convince a patient of the value of drug therapy when the patient has not experienced symptoms prior to initiation of therapy. Such is often the case in the treatment of hypertension, and the lack of previous symptoms coupled with the probable lack of appearance of symptoms if therapy is discontinued contributes to the high rate of noncompliance in these patients.

In other circumstances patients may feel better after taking the drug and feel that they no longer need to take it once the symptoms subside. Situations frequently occur in which patients do not complete a full course of antibiotic therapy once they feel that the infection has been controlled. This practice increases the likelihood of a recurrence of the infection and increased resistance of the microorganisms causing the infection, and patients must be advised to take the full course of antibiotic therapy.

COST OF MEDICATION—Noncompliance may occur with the use of drugs that have a relatively low cost; however, it might be anticipated that patients may be even more reluctant to use the entire prescribed quantity of more-expensive agents. The expense involved has been cited by some patients as the reason for not having prescriptions dispensed at all, whereas in other cases the medication is taken less frequently than intended or prematurely discontinued because of the cost.

Concerns regarding the consequences of noncompliance or partial compliance that result because patients are not able to afford their prescribed medications are an important reason for the high level of attention that has been devoted to the development of Medicare coverage of prescription drugs for outpatients, as well as initiatives to import medications from Canada and other countries in which they are available at lower costs.

ADMINISTRATION OF MEDICATION—Although patients may fully intend to comply with instructions, they may inadvertently receive the wrong quantity of medication because of incorrect measurement of medication, use of inappropriate measuring devices, or incorrect use of medication-administration devices. The inaccuracy of using teaspoons to administer liquid medications is well known and is compounded by the possibility of spillage and asking the patient to measure a fraction of a teaspoonful. This problem has been long recognized, but problems still occur. The importance of providing the patient with measuring cups, or calibrated droppers for the use of oral liquids is evident.

Some patients do not use metered-dose aerosol inhalation devices correctly, and this could result in inadequate control of the conditions (eg, asthma) for which their use are intended. The provision of oral instruction by the pharmacist has resulted in better patient understanding and performance of the correct steps for inhaler use.

TASTE OF MEDICATION—Medication taste problems are encountered most commonly with the use of oral liquids by children. Getting a child to take a dose of medication may be such a difficult task for a parent that doses may be missed or administration of the drug discontinued as soon as the parent sees any sign of improvement. Experiences such as these have resulted in initiatives to flavor liquid medications so that they are acceptable to children. FLAVO R has used more than three dozen flavors in the development of a medication-flavoring formulary system that has been used successfully in pharmacies around the country. This system also has been extended for use in medications prescribed for pets.

Compliance problems relating to the taste of medication are not limited to children. Objections to the taste of liquid potassium chloride preparations often are raised; a number of patients discontinue taking the medication for this reason.

Patient/Health Professional Interaction

The circumstances surrounding the visit of a patient with a physician and pharmacist and the quality and effectiveness of the interaction of these health professionals with the patient are major determinants of the patient's understanding of, and attitude toward, the illness and therapeutic regimen. One of the patient's greatest needs is psychological support provided in a compassionate manner, and it has been observed that patients are more inclined to comply with the instructions of a physician they know well and respect and from whom they receive information and assurance about their illnesses and medications.

The patient-physician interaction has been described as a negotiation between two active and equal participants with a strategy that includes the elements of "putting the ill at ease," respect, positive attitude, information, translation, feedback, patient response, and negotiation. Respect for the patient and a realistic appraisal of the circumstances of the individual patient are essential if therapeutic goals are to be achieved.

In a discussion of the influence of the patient-physician relationship on compliance, the following observation was made:

> "Our only true influence on the patient is based on the strength of our professional relationship with that patient. And it is this relationship that is central to improving patient compliance with both medication and treatment regimens."[32]

These observations are equally important with respect to the interaction between the pharmacist and the patient. The following factors are among those that could influence compliance adversely if inadequate attention is given to the scope and quality of the interaction with the patient.

FAILURE TO COMPREHEND THE IMPORTANCE OF THERAPY—A major reason for noncompliance is that the importance of the drug therapy and the potential consequences if the medication is not used according to instructions have not been impressed upon the patient. Patients usually know relatively little about their illnesses, let alone the therapeutic benefits and problems that could result from drug therapy. Therefore, they establish their own beliefs and expectations with respect to their drug therapy. If the therapy does not meet these expectations they are more likely to become noncompliant. Greater attention to educating patients about their conditions as well as the benefits and limitations of drug therapy will contribute to better compliance with therapeutic regimens.

POOR UNDERSTANDING OF THE INSTRUCTIONS—Prescriptions that state that medication should be taken *as directed* can be the source of misunderstanding as well as serious consequences. Even when instructions are more specific, confusion still may occur, and there have been many errors of interpretation of instructions that the prescriber considered to be clear. For example, many prescriptions are written and labeled to indicate how many doses are to be taken each day with no

additional clarification as to how the doses are to be scheduled. How should instructions to take one tablet three times a day be interpreted? Does this mean every 8 hr, or with meals, or possibly some other schedule? If the drug is to be given with meals or at a specified time before or after meals, it usually is assumed that the patient eats three meals a day. Yet this is not always the case. In one study,[33] patients being treated with medications with instructions to take them three times a day were interviewed with respect to the times at which they administered the individual doses of medication. Of 137 patients, only 1 was administering the medication at regular 8-hr intervals between doses, and 79% of the patients reported taking all three doses within 12 hr, leaving a dosage interval of 12 hr or more.

A patient may be knowledgeable about the dosage and the specific times at which the medication is to be administered but not understand the meaning of *auxiliary* instructions. Some patients have received prescriptions for a tetracycline derivative in a container to which is affixed an auxiliary label with a precaution about exposure to sunlight. However, in the absence of additional explanation, some have concluded that it is the medication that needs to be protected from sunlight (and have placed the container in the refrigerator) and have not recognized that the information applies to an adverse event for which *they* are at risk.

Pharmacists should be certain that patients are familiar with special considerations pertaining to the particular dosage form dispensed, such as the importance of not chewing or crushing controlled-release capsules or tablets. In one report the death of a patient is suspected to be due to chewing diltiazem extended-release capsules (Cardizem CD) because she thought the capsules were too big to swallow whole.[34]

In some cases the uncertainty or confusion on the part of the patient is such that medications are given by the wrong route of administration (eg, instilling oral pediatric antibiotic drops into the ear for an ear infection or administering suppositories by the oral route).

A patient being prepared for an electrocardiogram was observed to have 20 transdermal nitroglycerin patches at various locations on his body. Although he had understood the instructions to apply one patch a day, no instruction had been provided regarding their removal.

Although not a complete listing of all factors that result in noncompliance, those discussed give an indication of the difficult challenge of assuring optimal drug therapy.

IMPROVING COMPLIANCE

It often is assumed that health professionals recognize the importance of noncompliance and will take the steps necessary to achieve the compliance of their patients with the instructions provided. However, this assumption may not always be valid. In one study, physician compliance with public health recommendations for tuberculosis control was evaluated.[35] The study revealed poor compliance by physicians with recommended policies for the prevention of tuberculosis in health-care workers, thereby raising concerns about the personal risk of tuberculosis for these physicians, as well as questions about how effectively such physicians will promote preventive actions among their patients. An accompanying editorial[36] noted that "one might wonder how much patient noncompliance is fostered by a less than enthusiastic endorsement by the health-care provider." For strategies to improve compliance to be effective, health professionals must not only believe that noncompliance is an important problem, but also be willing to make a greater commitment to the steps that will help their patients be compliant.

A number of strategies to enhance compliance have been proposed. Inherent in many of the factors considered is the matter of communication of the physician and pharmacist with the patient. This communication is, in many cases, not only incomplete and ineffective, but often there is also the impression that physicians and pharmacists are too busy or not interested in talking with the patient. Improving communications must be considered the key to increasing compliance and some of the approaches and recommendations directed toward this goal are reviewed in the following discussion. Pharmacists have a particularly valuable opportunity to encourage compliance since their advice accompanies the actual dispensing of the medication, and they usually are the last health professional to see the patient prior to the time the medication is to be used.

Identification of Risk Factors

All patients should be viewed as potential noncompliers. A first step in efforts to improve compliance should be to recognize individuals who are most likely to be noncompliant, as judged by a consideration of the risk factors noted earlier. These factors should be taken into account in planning the patient's therapy so that the simplest regimen that is, to the extent possible, compatible with the patient's normal activities can be developed.

Development of Treatment Plan

The more complex the treatment regimen, the greater is the risk of noncompliance, and this must be recognized in the development of the treatment plan. The use of longer-acting drugs in a therapeutic class, or dosage forms that are administered less frequently, also may simplify the regimen.

The treatment plan should be individualized on the basis of the patient's needs, and when possible, the patient should be a participant in decisions regarding the therapeutic regimen. Compliant patients see themselves as active members of the team involved in their care, not as passive victims of a disease and the health-care system. Involving patients in the development of a treatment plan will help them view the regimen as something that increases their control and options, rather than something that is done to them.

To help reduce inconvenience and forgetfulness, the regimen should be *tailored* so that the doses of medication are administered at times that correspond to regular activities in the patient's daily schedule. When prescriptions are written, the instructions should be as specific as possible.

Instructions such as "*as directed*" or other directions that are subject to misinterpretation should be avoided. Even such seemingly specific instructions as *one tablet three times a day* often are misinterpreted, as discussed previously. Where possible and with a recognition of the patient's normal routine, the specific times of day at which the patient is to take the medication should be indicated.

The APhA and the American Society of Internal Medicine have developed a statement on prescription writing and prescription labeling (Appendix A). Not only do the guidelines provide important information and suggestions, but the statement reflects the type of interdisciplinary cooperation that also must be achieved in practice if patient needs are to be served best.

The prescription can be used as the organizing instrument of instruction. However, "most often the prescription slip simply is handed over as the closing act of the encounter, while the patient or parent is outward bound."[37] The prescription should signal the start of an alliance, and it behooves the physician to emphasize its importance.

Many prescriptions that patients receive from their physicians are never dispensed. Little progress has been made in detecting and correcting these occurrences, further emphasizing the need for more-effective communication and a closer working relationship between physicians and pharmacists.

Patient Education

One of the findings of the report of the Office of the Inspector General is "education is the best way to improve compliance."

However, former FDA Commissioner David Kessler has expressed concern that "the nation also is facing a communications gap that has serious implications for the public health. This gap extends from what patients want to know about their medicines to what they actually learn from their physicians and pharmacists."[38] He further observes that "physicians . . . need to re-examine the amount of information they give their patients and the way they deliver it. In addition, they need to acknowledge that pharmacists should have a larger role in patient education and advise their patients to expect counseling when they fill their prescriptions."[38]

Many factors influence the effectiveness of educational efforts and a patient's development of compliant behavior. Decisions must be made as to what information should be provided to patients about their illnesses and drug therapy. It must be recognized that when the information is too comprehensive or detailed or is presented inappropriately (eg, a discussion of adverse events that alarms the patient), the patient actually may be discouraged from taking the medications. Thus, compliance may be compromised rather than enhanced.

In discussing an illness or drug therapy with a patient, a distinction should be made between *information* and *education*. Patients may receive information but not understand it and use it correctly, whereas education implies understanding and behavioral change. Patients should be encouraged to participate in the discussion, and when possible, they should be brought in on the decision-making process.

The goal of patient education is to provide information that the patient is able to understand and use. The anticipated benefits of the therapy should be explained, as should the importance of complying with the provided instructions. Complex terms and unnecessary jargon that can interfere with patient understanding should be avoided. Patients should be asked to repeat the instructions for administering their medications to show that they understand them, and they also should be encouraged to ask questions. At the least, the questions noted in Table 98-1 should be addressed. It is recommended by the National Council on Patient Information and Education (NCPIE) that these questions be discussed each time a patient obtains prescription medication.

ORAL COMMUNICATION/COUNSELING—Communication between the pharmacist and patient regarding the use of medication can be both oral and written. Although it may be supplemented and reinforced by written instructions, oral communication is the most important component of patient education because it directly involves both the patient and the pharmacist in a two-way exchange and provides the opportunity for the patient to raise questions. For such communication to be most effective it should be conducted in a setting that provides privacy and is free of distractions.

Although many pharmacies do not presently have a separate patient consultation area, this is a desirable goal. Not only will this emphasize to the patient the importance the pharmacist attaches to the information being discussed, but it also will strengthen further the recognition of the pharmacist as one who is contributing to the patient's health care.

Medication often is obtained in a manner that does not lend itself to oral communication. For example, the pharmacist may receive a telephoned prescription from a physician that is to be delivered to the patient's home or picked up at the pharmacy by a relative or friend. In these circumstances, when appropriate, the pharmacist might call the patient to discuss the use of the medication.

The effect of pharmacist counseling on patient compliance has been evaluated in a number of studies. Studies assessing pharmacist counseling of patients with hypertension have demonstrated a significant increase in the patients' knowledge of hypertension and its treatment, their compliance with prescribed therapy, and the number of patients whose blood pressures were maintained in the normal range.

A *compliance clinic* has been described[39] in which pharmacists endeavored to improve the compliance of patients referred to the clinic by physicians. Six of the 14 patients seen on a regular basis demonstrated a significant reduction in emergency room visits, and 8 patients exhibited reduced hospitalizations, as determined by a comparison of pre- and postclinic records. In addition to the therapeutic benefits most patients will experience as a result of improved compliance, there is a considerable cost savings to be achieved as a result of the reduced hospitalization.

WRITTEN COMMUNICATION—The emphasis on oral communication should not be interpreted to indicate that written communication is not important. Although at the time of the visit to the physician or pharmacist patients may understand how the medication is to be used, later they may not remember the details relating to administration of the drug. Therefore, specific instructions for use should be placed on the prescription label.

It is also desirable and sometimes required to provide supplementary written instructions or other information pertaining to the patient's illness or drug therapy, and many pharmacists provide patients with medication instruction cards or inserts. Information that pertains to the specific medication/formulation being dispensed is preferred to information that applies to a therapeutic class of agents or a general statement that applies to all dosage forms of a particular medication. The provision of supplementary written information appears to be most effective in improving compliance with short-term therapeutic regimens (eg, antibiotic therapy). For drugs used on a long-term basis, written information as a sole intervention has not been shown to be sufficient for improving patient compliance.

Although the supplemental instructions and information may be thorough and well written, it must be recognized that many patients cannot read. Millions of adults in the US are functionally illiterate (ie, they cannot perform the basic reading tasks required to function in society) and millions more are only marginally literate. In one study[49] of more than 2600 predominantly indigent and minority patients, 42% were unable to comprehend directions for taking medication on an empty stomach. Written instructions and information also must be viewed as one-way communication unless patients are permitted to discuss and ask questions about their therapy. Therefore, oral and written communication should be used to complement each other, and both should be viewed as important components of the effort to educate patients regarding their drug therapy.

AUDIOVISUAL MATERIALS—The use of audiovisual aids may be particularly valuable in certain situations because patients may be better able to visualize the nature of the illness or how their medication acts or is to be administered (eg, the administration of insulin, the use of a metered-dose inhaler). An increasing number of health-care professionals have used such aids effectively by making them available for viewing in a patient waiting area or consultation room and then answering questions the patient may have.

CONTROLLED THERAPY—It has been proposed that hospitalized patients be given the responsibility for self- medication prior to discharge. Usually, patients go from a complete dependence on others for the administration of their medication while hospitalized to a situation in which they are given the full responsibility when discharged, often with the assump-

Table 98-1. Patient Questions Regarding Medication[a]

1. What is the name of the medicine, and what is it supposed to do?
2. How much of the medicine should I take, when should I take it and for how long?
3. What foods, beverages, and other medicines should I avoid while taking it?
4. What are the possible side effects, and what should I do if they occur?
5. What written material is available about the medicine?

[a] Questions that patients should ask, as recommended by the NCPIE.

tion that they know about their drugs because they were taking them in the hospital. Similarly, many ambulatory patients who are expected to be responsible for their own treatment have not been provided with adequate information.

The suggested arrangement would permit patients to start using the medications on their own before discharge, so that health-care professionals can more directly identify problems or situations that might undermine compliance, and answer patient questions.

Special programs for providing information about medication are needed for some individuals including sight-impaired and hearing-impaired patients. Some pharmacists prepare prescription labels in Braille for the blind and use a telecommunication device for the deaf (TDD) to communicate with hearing-impaired patients over telephone lines. The Medifier is a molded plastic device (in four sizes) into which a prescription vial is placed. A clear lens magnifies the print on the label so that patients with vision problems can read the instructions.

Patient Motivation

Many health care professionals assume that patients who are knowledgeable about their illness and therapeutic regimen are likely to be compliant. Although this premise is valid for many patients, increased patient knowledge does not necessarily alter patient behavior and compliance. Therefore, there must be an awareness of the need to motivate patients to use the knowledge they have acquired to achieve optimum benefit from their therapy.

Information must be provided to patients in a manner that is not coercive, threatening, or demeaning. The best intentioned, most comprehensive educational efforts will not be effective if the patient cannot be motivated to comply with the instructions for taking the medication. In addition to counseling the patient and providing specific written instructions, supplying cues for appropriate behavior *(prompting)* may be of value in motivating the patient to be compliant. Cues may be verbal or nonverbal, with examples of the latter including the use of special packaging or reminder systems.

The physician-patient interaction has been characterized as a *negotiation*. This concept may be extended further by the development of *contracts* between patients and health-care providers in which the agreed-upon treatment goals and responsibilities are outlined. As summarized in a review,[3] contracts offer "a written outline of expected behavior, the involvement of the patient in the decision-making process concerning the regimen and the opportunity to discuss potential problems and solutions with the physician, a formal commitment to the program from the patient, and rewards . . . which create incentives for achieving compliance goals." Although such a structured approach will not be needed with most individuals, it may be effective for patients who have not responded to other initiatives to ensure compliance.

Noncompliance is the greatest challenge in the control of tuberculosis, and the difficulties currently encountered in the management of this infection have prompted one clinician to make the following observations: "Sometimes it takes a little imagination. Give them a cup of coffee. Talk to them. Pay them an honorarium to come in and take the medicine. If the public doesn't want drug-resistant TB, and if bribing people is the way to get them to take their medicine, then I say bribe them."[41]

Compliance Aids

LABELING—The importance of the accuracy and specificity of the information on the label of the prescription container has been noted. Auxiliary labels that provide additional information regarding the use, precautions, and/or storage of the medication also will contribute to the attainment of compliance. The inclusion of pictograms in labeling and patient information leaflets has been demonstrated to have a positive effect in the acquisition and understanding of information regarding medications prescribed for patients with limited literacy skills.[43]

MEDICATION CALENDARS AND DRUG REMINDER CHARTS—Various forms, such as medication calendars, have been developed and are designed to assist patients in self-administering drugs. In addition to their use in helping patients understand which medication to take and when to take it, the forms on which patients are to check the appropriate area for each dose of medication they take, can be evaluated by the pharmacist or physician when the patients return for more medication or have their next appointment.

SPECIAL MEDICATION CONTAINERS, CAPS, AND SYSTEMS—Several types of medication containers have been developed to help patients organize their medications and to monitor self-administration of the drugs. An example is the 28-compartment MEDISET container that contains four compartments for different time periods (ie, morning, midday, evening, bedtime) for each day of the week. The Med Light Tablet Organizer also has 28 compartments as well as an alarm and flashing light.

Specially designed caps for prescription containers also have been developed to facilitate compliance, and include features such as a digital timepiece that displays the time and day on which the last dose of medication was taken, and an alarm and flashing light when it is time to take the next dose. Containers/caps that contain all or some of these features include The Prescript Time Cap, The Pill Timer, and Remind Cap Closures. The use of microelectronic medication monitors (Medication Event Monitoring System) in the caps of prescription containers has been described earlier.

For patients with vision impairment or who otherwise have difficulty reading information on prescription labels, products such as Talking Rx, ScripTalk, and Aloud Talking Prescription Labels have been developed to play a prerecorded message when activated. Instructions for using the medication are recorded in a small electronic unit or microchip that is attached to the bottom of the container or embedded in a label.

Although these special prescription containers, caps, and systems are not needed by most patients, they may be effective in achieving compliance by patients who forget doses or who are confused by the complexity of the regimen.

COMPLIANCE PACKAGING—The manner in which medication is packaged also has an influence on patient compliance. A *compliance package* has been defined as a prepackaged unit that provides one treatment cycle of the medication to the patient in a ready-to-use package, and a comprehensive review of the use of such packaging as a patient education tool has been published.[43] This type of packaging usually is based on blister packaging using unit-of-use dosing and is designed to serve as a patient-education tool for health professionals and to make it easier for patients to understand and remember to take their medications correctly at home. Specially designed packaging for oral contraceptives was one of the first initiatives of this type and has been valuable in increasing patient understanding of how these agents are to be taken.

Special packages of certain corticosteroids (eg, *Medrol Dosepak*)also have been designed to facilitate the use of steroids in dosage regimens that may be difficult to understand or remember.

The Medicine-On-Time system is an example of a packaging system that provides unit-of-use dosing with specific labeling in a plastic card that is set up like a calendar. In addition to simplifying the use of medications for patients who self-administer their medications, these systems also have been very useful in the distribution and administration of medications in assisted-living and other patient-care facilities.

A possible negative effect of drug packaging on patient compliance is seen with the use of the child-resistant containers. Some patients, particularly the elderly and those with conditions like arthritis and parkinsonism, have difficulty opening some of these containers and may not persist in their

efforts to do so. There also may be difficulty opening some foil-packed drugs. Pharmacists should be alert to problems of this type and, when appropriate, suggest use of standard containers or caps.

DOSAGE FORMS—New dosage forms of certain drugs also have been developed, in large part in recognition of problems of noncompliance. For example, the development of longer- acting, controlled-release dosage forms of numerous medications (eg, calcium channel blocking agents) has permitted less frequent administration of these agents, which facilitates compliance. The use of transdermal delivery systems permits less-frequent administration of the drugs (eg, nitroglycerin, fentanyl) given by this route.

Monitoring Therapy

SELF-MONITORING—Patients should be apprised of the importance of monitoring their own treatment regimen and, in some situations, the response parameters. The attention to the responsibility that patients must personally assume also has been considered in consumer publications, as illustrated by an article in *Good Housekeeping* titled "If your medicine isn't working. . . . It may not be the medicine at all. It could be *you*!"[44]

PHARMACIST MONITORING—The pharmacist's role in minimizing noncompliance does not end when the prescription is dispensed. The pharmacist is in an excellent position to detect noncompliance pertaining to drugs used in the management of chronic conditions, such as hypertension and diabetes, by being alert to situations in which the frequency of requested refills is not consistent with the directions for use. Pharmacist follow-up with telephoned or mailed refill reminders has been found to increase compliance.

One approach in which both health professionals and patients have collaborated effectively in reviewing/monitoring the use of medication has been the *brown bag* program. The Administration on Aging and National Council on Patient Information and Education (NCPIE) have encouraged older consumers to put all their medicines in a bag and take them to their health professional for a personalized medicine review.

DIRECTLY OBSERVED TREATMENT (DOT)—Even when many of the steps described earlier have been taken, noncompliance may still result. For example, there is great concern about the high rates of treatment failure in patients with tuberculosis and the increasing prevalence of drug-resistant tuberculosis. In one study that used self-administered treatment, 39% of patients were lost from the study with a 6-month antitubercular regimen and 49% with a 9-month regimen.[45] In contrast, in a study that used a 6-month regimen of directly observed treatment (ie, giving patients their medications and seeing that they are swallowed), fewer than 10% of the patients were lost to further treatment.[46] A commentary advocating the use of directly observed treatment regimens for patients with tuberculosis observed that "we can't afford not to try it."[47]

Many of the recommendations for improving patient compliance are included in a comprehensive set, *Recommendations for Action to Advance Prescription Medicine Compliance* that has been developed by NCPIE (Appendix B). A meta-analysis of 153 studies published between 1977 and 1994 that evaluated the effectiveness of interventions to improve patient compliance with medical regimens has been published.[48] The authors conclude that "no single strategy or programmatic focus showed any clear advantage compared with another. Comprehensive interventions combining cognitive, behavioral, and affective components were more effective than single-focus interventions."

CONCLUSION

Considerable time, effort, and expense often have gone into the diagnosis of a patient's illness and the development of a treatment program. Yet the goals of therapy will not be reached unless the patient understands and follows the instructions for use of the drugs prescribed. One also cannot help but wonder how often patients have been categorized as treatment failures and have had their therapy changed, possibly to more potent and toxic agents, when the reason for the lack of response or an unanticipated altered response was noncompliance.

Despite the increasing attention directed to the issue of noncompliance, the problem continues to be prevalent. Although not uniformly successful, the approaches taken and suggestions advanced in an effort to improve compliance have contributed substantially to recognition of the problem and provided a valuable base on which to develop modified or new approaches to the problem. Certain approaches that involve a significantly increased commitment of time on the part of health-care professionals may be viewed by some as impractical. Yet can this increased commitment of time compare with the time and money that are currently being wasted as a result of noncompliance?

The improvement of compliance will result in a situation in which all parties benefit. Most importantly patients benefit from the enhancement of the efficacy and safety of their drug therapy. Pharmacists benefit because there is an increased recognition and respect for the value of the advice and service that they provide. Pharmaceutical manufacturers benefit from the favorable recognition that accompanies the effective and safe use of their drugs as well as from the increased sales resulting from the larger number of prescriptions being dispensed. Finally, society and the health care system benefit as a result of fewer problems associated with noncompliance. Although an increase in compliance will result in more prescriptions being dispensed and a higher level of expenditures for prescription medications, this increase in costs will be more than offset by a reduction in costs (eg, physician visits, hospitalizations) attributable to problems due to noncompliance.

For too long patients have been deprived of close attention to, and monitoring of, their drug therapy. An excuse that health-care professionals are too busy to advise patients regarding their drug therapy cannot be accepted; the highest priority must be assigned to taking the steps to ensure that patients will use their medications in the appropriate manner.

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Statement on Prescription Writing and Prescription Labeling[a]

APPENDIX A

INTRODUCTION

Historically, the pharmaceutical and medical professions have devoted considerable time and effort to the development and rational utilization of safe and effective drugs for the treatment and prevention of illness. Today, that successful effort continues, helping to achieve the highest standards of health in the world for the American people. But in order to gain maximum benefit from the use of drugs while minimizing their adverse side effects, prescribers and pharmacists must maintain effective communications not only among themselves, but with their patients as well. The directions for drug use and other information which prescribers indicate on prescription orders and which pharmacists transfer to prescription labels are critical to safe and effective drug therapy. In order to assure that this information is conveyed clearly and effectively to patients, the following guidelines have been developed by the American Pharmaceutical Association and the American Society of Internal Medicine.

GUIDELINES FOR PRESCRIBERS

The following guidelines are recommended for prescribers when writing directions for drug use on their prescription orders:

1. The name and strength of the drug dispensed will be recorded on the prescription label by the pharmacist unless otherwise directed by the prescriber.
2. Whenever possible, specific times of the day for drug administration should be indicated. (For example, *Take one capsule at 8:00 am, 12:00 noon, and 8:00 pm* is preferable to *Take one capsule three times daily*. Likewise, *Take one tablet two hours after meals* is preferable to *Take one tablet after meals.*)
3. The use of potentially confusing abbreviations, ie, *qid, qod, qd,* etc, is discouraged.
4. Vague instructions such as *Take as necessary* or *Take as directed* which are confusing to the patient are to be avoided.
5. If dosing at specific intervals around-the-clock is therapeutically important, this should specifically be stated on the prescription by indicating appropriate times for drug administration.
6. The symptom, indication, or the intended effect for which the drug is being used should be included in the instructions whenever possible. (For example, *Take one tablet at 8:00 am and 8:00 pm for high blood pressure,* or *Take one teaspoonful at 8:00 am, 11:00 am, 3:00 pm, and 6:00 pm for cough*.)
7. The Metric System of weights and measures should be used.
8. The prescription order should indicate whether or not the prescription should be renewed and, if so, the number of times and the period of time such renewal is authorized. Statements such as *Refill prn* or *Refill ad lib* are discouraged.
9. Either single or multi-drug prescription forms may be used when appropriately designed, and pursuant to the desires of local medical and pharmaceutical societies.
10. When institutional prescription blanks are used, the prescriber should print his/her name, telephone number and registration number on the prescription blank.

GUIDELINES FOR PHARMACISTS

1. Pharmacists should include the following information on the prescription label: name, address and telephone number of pharmacy; name of prescriber; name, strength and quantity of drug dispensed (unless otherwise directed by the prescriber); directions for use; prescription number; date on which prescription is dispensed; full name of patient and any other information required by law.
2. Instructions to the patient regarding directions for use of medication should be concise and precise, but readily understandable to the patient. Where the pharmacist feels that the prescription order does not meet these criteria, he should attempt to clarify the order with the prescriber in order to prevent confusion. Verbal reinforcement and/or clarification of instructions should be given to the patient by the pharmacist when appropriate.
3. For those dosage forms where confusion may develop as to how the medication is to be administered (for example, oral drops which may be mistakenly instilled in the ear or suppositories which may be mistakenly administered orally), the pharmacist should clearly indicate the intended route of administration on the prescription label.
4. The pharmacist should include an expiration date on the prescription label when appropriate.
5. Where special storage conditions are required, the pharmacist should indicate appropriate instructions for storage on the prescription label.

CONCLUSION

Communicating effective dosage instructions to patients clearly and succinctly is a responsibility of both the medical and pharmaceutical professions. Recent studies documenting the low order of compliance with prescription instructions indicate that poor communication between the medical and pharmaceutical professions and poor comprehension by the public may be causative factors.

The American Pharmaceutical Association and the American Society of Internal Medicine believe that the guidelines as stated above will serve as an initial step toward patients achieving a better understanding of their medication and dosing instructions. The two associations urge state and local societies representing pharmacists and prescribers to appoint joint committees for the purpose of refining these guidelines further as local desires and conditions warrant. The associations believe that such cooperative efforts between the professions are essential to good patient care and that significant progress can be made in other areas by initiating discussions between the two professions concerning common interests and goals.

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[a] By American Pharmaceutical Association/American Society of Internal Medicine (revised March 1976).

NCPIE Recommendations for Action to Advance Prescription Medicine Compliance

APPENDIX B

ADVANCING COMPLIANCE: NCPIE PANELS MAKE RECOMMENDATIONS

In December 1994, the National Council on Patient Information and Education (NCPIE) sponsored a conference, "Advancing Prescription Medicine Compliance: New Paradigms, New Practices." The most important objective of this conference was to produce realistic recommendations for advancing compliance across health care professions and practice settings.

To develop recommendations, commissioned speakers addressed prescription medicine compliance issues relating to: physicians, pharmacists, nurses, manufacturers, patients, managed care organizations, NCPIE and other groups. Each speaker suggested what could be done to improve compliance. Six complementary working groups then used the speakers' ideas as a springboard in developing recommendations for each group and for groups in collaboration. These were then presented to the full conference for participants' response and consideration.

The following recommendations are directed to the varied organizations and individuals who can advance compliance; however, many recommendations apply to more than one category under which they are listed:

1. Physicians and Medical Schools

   - Involve the patient in treatment decisions.
   - Monitor compliance with prescribed treatment at every patient visit; follow up outside of scheduled visits as appropriate. Give the patient an alternate contact person at your office if you might be unavailable when he/she calls between visits.
   - Document patient compliance using a compliance-monitoring form that can be incorporated into the patient's record.
   - Coordinate patients' medication regimens with health professionals providing remote site care, including visiting nurses, physician assistants and nurses in satellite clinics or offices, and pharmacists working with patients in care facilities or in the pharmacy.
   - Include patient communication skills in medical training and continuing education curricula.
   - Train physicians to communicate with other members of the health care team to ensure continuity of care.

2. Pharmacists, Pharmacy-Providers and Educators

   - Become proactive about gathering and providing medicine information. Ask questions that stimulate dialogue, discuss care plans with patients, and use information about patients to make better decisions.
   - Provide compliance monitoring and documentation for at least one at-risk patient per month. Share your findings with the patient and with his/her other health care providers.
   - Work with management to redesign facilities to increase pharmacist/patient contact, and to provide a private counseling area.
   - Incorporate patient communication skills and new teaching methods into undergraduate courses and continuing education programs.
   - Work with other health professional schools/organizations to develop interdisciplinary compliance education programs.
   - Integrate behavioral and clinical sciences in educating pharmacists about compliance.

3. Individual Nurses and Educators

   - Integrate into each patient encounter an educational assessment of patient medicine knowledge.
   - Collaborate with other health care providers, including prescribers and pharmacists, about patient compliance issues.
   - Develop programs to increase nurses' knowledge and skills for compliance-enhancement.
   - Include compliance questions in examinations for professional degrees, licensing, and continuing education.

4. All Health Professionals

   - Individualize patient care, including medication management, considering factors such as age, culture, gender, attitudes, and personal situation.
   - Specifically ask patients about use of over-the-counter drugs, including vitamins and dietary supplements.
   - Engage in a dialogue with patients and involve them as partners in the treatment process. Explain why you think a treatment plan is most appropriate for your patient.
   - Use written materials to reinforce oral counseling, not as a substitute for it.
   - Respect a patient's right to confidentiality when sharing medication compliance experience with the patient's other health care providers, including nurses, pharmacists, physicians, and physician assistants.

5. Pharmaceutical Manufacturers

   - Individually and as an industry, develop a public service advertising campaign promoting patient medication compliance with therapy.
   - Support health professionals' education to develop effective communicators in a patient-centered health care system.
   - Recognize and promote role models who can demonstrate improved compliance from a patient-centered approach.
   - Provide NCPIE's "Get the Answers" brochure with all responses to consumer information requests or "800" program responses.
   - Support interdisciplinary teams that provide patient education and programs for compliance and health promotion.

6. Patients

   - Become an active participant in making treatment decisions and solving problems that could inhibit proper medicine use.
   - Talk to your health professionals about why and how to use your prescription medicines. Give them information about your medicine use (prescription and over-the-counter medicines, vitamins and dietary supplements) and health. If you stop or change a prescribed treatment, tell them and explain why you did this. Get the answers to any questions you have.
   - Recognize, accept, and carry out your responsibilities in the treatment regimen.

7. Managed Care Organizations and Hospitals

- Use existing databases to profile the extent of medicine noncompliance among your health plan members.
- Develop and implement programs for patient compliance support (e.g., group support programs, educational interventions, monitoring clinics, compliance packaging aids, and brown bag reviews). Keep health care providers informed about these programs so they can refer appropriate patients as part of an individualized compliance regimen.
- Develop and implement innovative programs that teach patient's responsibility for and involvement in his/her health care.
- Identify, implement, and evaluate compliance-promoting organizational practices and policies.
- Review drug use policies, such as formulary policy guidelines, from a patient compliance perspective. Revise policies accordingly to facilitate compliance.
- Develop and implement computerized systems that allow departments to share clinical patient information electronically.

CHAPTER 99

Drug Education

Michael Montagne, PhD

Drug use occurs in virtually every society and culture. Whether the use of a particular drug is for a medical or a nonmedical reason, problems resulting from use often arise. Preventing drug use problems is a major concern of most societies, and it usually is highlighted when specific outbreaks of problems or inappropriate use occur. As pharmacy is the profession to which the control of drugs is attributed, it should be involved intimately with those activities aimed at preventing or reducing drug use problems. In fact, the pharmaceutical profession should be providing the leadership and directing the research in this area. It is unfortunate that, on the whole, pharmacy has been lacking in its social responsibility for the chemical substances it develops, promotes, and dispenses.

Most pharmacists are aware of the important problems that potentially can occur with the appropriate use of prescription medications, such as adverse reactions and drug interactions. Many pharmacists also are knowledgeable about potential problems inherent in self-medication with a nonprescription drug, though they probably are less familiar with the use of herbal remedies and homeopathic medications in the same context. Few pharmacists, however, are aware of potential problems that can arise with social-recreational drug use. Regardless of the situation, the problem of poisoning or overdose by a drug should be delegated to poison-control centers and hospital emergency rooms. The individual pharmacist, particularly one working in a community setting, may not feel capable of consulting or educating a particular drug consumer in these problem areas.

Most societies are in great need of learning more rational and appropriate uses of all types of drugs and of gaining control over the products (drugs) of their own technology. Humans have learned how to create (extract and/or synthesize) drug products, yet humans have not learned fully how to use these products in an optimal manner. The primary importance of drug education is its benefit to the drug user (patient or consumer); such education can improve the appropriateness of drug taking behaviors to achieve optimal health and well-being. At the center of any educational effort is the provision of drug information, the strategy with which pharmacists and pharmacy students are most familiar. In today's highly complex, technological world, the availability of current and precise information allows one to understand, to make better choices, and to prevent or solve problems.

The individual best suited to assist people in preventing drug use problems and in achieving optimal, desired experiences from their drug taking is the pharmacist. The pharmacist is an accessible source of high-quality information and educational programs and should be concerned with a person's drug-taking behavior. Whether it be the use of a prescription medicine or an herbal remedy to achieve or maintain a state of health, the use of a drug for its socially oriented effects in a recreational setting, or the ingestion of a chemical substance to enhance a religious or aesthetic experience, the perspective presented herein considers the pharmacist to be the leader in efforts to prevent or limit drug use problems.

In this chapter, the basic principles of drug education are presented with the underlying premise that these principles and strategies are applicable to any type of drug use. Although information about, and inherent problems resulting from, specific types of drug taking might vary from drug to drug or among reasons for use, the fundamental approach to educating people and fostering changes in drug use is the same. The word *drug* refers to any substance, other than food, which by its chemical or physical nature, alters structure or function in a human being, resulting in physiological, behavioral, or social changes. This includes all medicinal agents (whether defined legally as prescription or nonprescription), herbal and home remedies, alcohol and caffeine (and other substances that are often considered *food* by consumers, but are used for their pharmacological activity), substances used primarily in a nonmedical context, and even poisons.

Many approaches have been developed for designing drug information and drug education programs in medical settings, and many of these are described in other chapters of this book. The majority of the examples in this chapter, therefore, come from the realm of *drug abuse* prevention. These techniques and strategies, and their basic principles, are also applicable to educating patients about medicines or providing drug education programs in any context. It is important to realize that, conversely, ideas, strategies, and programs from the field of patient drug education can be relevant to the development of programs on the nonmedical use of drugs, and some examples of this broader view of drug education are provided.

DRUG USE AND DRUG EDUCATION

Human beings engage in a great variety of drug taking behaviors, but one of the most important and rudimentary considerations involves the definition of what constitutes a drug and which situations characterize drug taking. In a 1972 nationwide survey of drug use, adults and youths were asked to indicate which substances they regarded as drugs.[1] More than 80% of the respondents regarded substances such as heroin, cocaine, marijuana, and psychotherapeutic agents to be drugs. One should realize, however, that a small proportion of the general public (5–20%, depending on the specific drug) did not regard these substances to be drugs. Alcohol and tobacco were regarded as drugs by less than one-third of the respondents. Most of the adolescent respondents (84%) did not consider tobacco to be a drug, although we might expect that if the survey were repeated today, the results would be different.

The key point is that individuals can hold different beliefs or perceptions about which chemical substances they regard as being drugs. In fact, this type of survey can be a useful and interesting exercise in a drug education program. The audience is shown a list of chemical substances and asked to indicate which ones are drugs and which ones are not. Not only can this exercise, and its results, provide the educator with a better idea of the opinions and level of drug knowledge of an individual or group, but it also can be used as a focal point for discussion at that time or subsequent sessions. The belief that certain substances may be drugs is important in understanding why and how people use such substances, and it should be a primary consideration in the development of any drug education program.

The nature and extent of certain types of drug taking vary by drug, availability (or accessibility), and the reason for use. In the medical realm, drug taking may be initiated by the patient, as in self-medication, or it may be directed by another person, usually a physician, who writes a prescription for it. Studies of self-medication are limited. The research done in this area indicates that self-diagnosis, rather than making contact with the health-care delivery system, occurs in the majority of illness episodes and that self-medication occurs from 60% to 90% of the time in these situations.[2] Studies of nonprescription-drug consumption indicate that, in general, approximately one-third of a population could be defined as current users of such substances and that from 25% to 60% of a population may be users of such drugs during any specific period.[2] The prevalence of nonprescription drug use is even higher in the older adult population (ranging from 50% to 90%), in addition to their extensive use of prescription drugs.[2]

The recent Slone Survey studied medication use of all types at the population level.[3] This study determined that during 1998–99, 81% of adults had used at least one medication in the week prior to the study interview; 50% used at least one prescription medication; and 7% used five or more. The highest prevalence of medication use was among older women; 57% used at least five medications and 12% used at least ten. Herbal products were used by 14% of the population, and 16% of prescription users also used an herbal concurrently. Vitamin and mineral supplements were used by 40% of the population.

When a drug is prescribed for a patient, health professionals expect that the drug will be taken precisely as directed. Compliance with medication regimens is another type of drug taking considered of major importance in a successful treatment plan. There have been many studies in this area (see *Compliance* chapter for a thorough review); their results have shown that anywhere from 5% to 90% of patients may be noncompliant in some manner. Although there is a wide variation in noncompliance, caused by various factors as well as the research design of particular studies, the rate of noncompliance, in general, probably ranges from 33% to 50% in any given population. This situation represents a different behavior; many patients are not taking drugs when they should be.

Drug taking also occurs in a nonmedical context. Although cigarette smoking has declined steadily among adults, tobacco use has increased in young people during the past few years.[4] The prevalence of alcohol use has remained stable for many years, but there is an increase in binge drinking among young adults, especially college students.[4] Nationwide surveys of drug use, conducted by the National Institute on Drug Abuse in 2001, found that 18% of youths (less than 18 years), 35% of young adults (18–25 years), and 25% of adults (26 years or older) were current users of tobacco, whereas 20% of youths, 58% of young adults, and 56% of adults were current users of alcohol.[4]

The nonmedical use of most other types of psychoactive drugs has declined during the past decade, but there have been increases in the use of some substances over the past couple of years.[4] The nonmedical use of marijuana, cocaine, and some psychedelic drugs (eg, LSD) has increased in the past 2 years in all age groups, but especially in the 12–17 age group. The greatest increase in the use of a specific nonmedical drug has occurred with marijuana. The nonmedical use of prescription psychotherapeutic drugs also has increased in the past year.

The misuse of drugs, including the development of an addiction, also has increased in the past couple of years.[4] Among 12–17 year olds, the misuse of or dependence on any drug (including alcohol) has increased from 7.7% to 7.8%; among 18–25 year olds, from 15.4% to 18.4%; and for people 26 years of age and older, from 4.8% to 5.4%. Alcohol is the biggest problem, by far, followed by marijuana and then the nonmedical use of a prescription psychotherapeutic agent (primarily pain relievers). Drugs are also the cause of almost one-half of all poisoning episodes (see *Poisons* chapter), a type of drug taking behavior that is usually unintentional, except in cases of suicide.

Drugs clearly are used appropriately in certain situations for beneficial reasons, are not used in some instances when they should be, and are used inappropriately on many occasions. In all three circumstances, though most often in the last two examples, problems can result from drug use. The prevention or recognition and management of problems resulting from drug use are the main reasons for developing and providing drug education programs.

Two additional aspects of drug use important in assisting drug users are their type of drug use behavior and their reasons or motivations for use. The focus of many drug education programs is on the drug itself and not the behavior (drug use). This has led to programs that focus on illegal drugs, but not legal drugs; on "hard" drugs, but not "soft" drugs; and on the pharmacology of the drug, but not on how that drug is used. Instead of focusing on these ill-defined or irrelevant terms, the focus of drug education should be on behavior, how and why the drug is being used. A typology of drug taking behaviors was developed by the National Commission of Marijuana and Drug Abuse,[1] and it can be very useful in orienting both the educator's and audience's focus on drug use, rather than on a drug (Table 99-1). Reasons or motivations for using drugs are the key to understanding why individuals use drugs. These reasons also should be addressed in developing and offering drug education programs (Table 99-2).

Drug education in a medical context has occurred for some time. The earliest health promotion movement occurred in the 19th century, and educational activities were an important part of the effort. Patient counseling always has been a part of the health professional's role, though the assumption of this role has varied from time to time, especially within pharmacy. The principle strategies have been to provide either drug information or drug education to patients through verbal interaction. Structured educational programs have been developed throughout the 20th century, but it was only after World War II that concerted efforts to develop and implement health education programs began to occur in public health. In the 1950s and 1960s, several attitudinal and behavioral approaches were studied to expand the traditional information-based approach and improve on the effectiveness of information only programs. At the beginning of the 21st century, the behavioral approach has become popular in health education programs, and the use of the mass media has increased dramatically.

Early efforts in education about nonmedical drug use consisted of negative portrayals of drugs and moralizing about drug use in the classroom and through the mass media, with little objective information being presented. Such an approach unfortunately still can be found in many contemporary drug education programs. These early efforts evolved into the drug education programs of the late 1960s and early 1970s, which claimed to provide relatively objective information, mostly pharmacological in nature, to children in the health, social science, or some other part of a school's curriculum. In most of these cases, the information was provided, but ways of using and incorporating it into one's life-style were not presented and discussed. Several studies in the 1970s found that informational programs in this area aroused the student's curiosity about drugs and increased the likelihood of experimentation with drugs.[5,6]

Table 99-1. Typology of Drug Taking Behaviors

TYPOLOGY OF DRUG TAKING BEHAVIORS
Intensity - how much (single dose)
Frequency- how often (dosing schedule)
Duration - how long (length of use)
Experimental
Short-term, non-patterned trial
Variable intensity but minimal frequency
Reason: curiosity about effects
May be a shared social activity or individual
Low risk to individual and society
Limited long-term problems
Social-Recreational
Patterned use
Variable intensity, frequency, and duration
Social setting of use
Reason: for effects or group acceptance
Voluntary act
May not escalate, but can lead to habit formation
Low-high individual risk (differs by drug and dose)
Low-moderate societal risk
Circumstantial-Situational
Patterned use
Variable intensity and frequency, limited duration
Reason: task-specific and usually self-limiting
Achievement of effect to cope with symptom, condition, situation, or need
Personal (individual) use (setting)
Moderate risk to individual (dose-dependent)
Moderate societal risk
Can lead to escalation in drug taking behaviors (Self-medication hypothesis)
Intensified
Long-term patterned use (duration)
At least daily use (freq.) with moderate-high intensity
Reason: Achievement of relief from symptoms, situation, personal problems, possibly to prevent withdrawal
All settings
Drug is a part of everyday life
Moderate-high risk for individual (dependence)
Moderate-high risk for society
Compulsive
Long-term patterned use (duration)
High intensity and frequency
Reason: Dependence and loss-of-functioning, lifestyle
Drug and Its Use Become Central Focus of Life
High individual and societal risk

From National Committee on Marijuana and Drug Abuse, 1972.

There came, consequently, a shift in educational programming toward the goal of enhancing social competencies (ie, a person's communication and interpersonal skills and ability to make decisions and to solve problems). The reasoning was that a stable, well-adjusted, socially competent individual surely would have little need for drugs, and in those cases when drugs were used, it would be only socially approved substances in socially accepted and appropriate ways. Such programs usually were effective in enhancing these competencies, but the subsequent influence on drug taking was usually negligible. It was soon realized, however, that the effectiveness of these programs indicated a general lack of social competency training in the family, schools, religious settings, and other places. These programs have value in an educational plan, but mostly when incorporated with drug information, alternatives to drugs, recognition of drug use problems, and other related activities.

In the mid-1970s, in the US, several *responsible drug use* programs were created, mainly in response to the dominant approach, which implied that a successful drug education program would result in abstinence from socially disapproved drugs, and of course, a reduction in drug use problems. The *responsible drug use* movement accepted the notion that people will always want to take chemical substances, and so programs were designed to foster appropriate drug taking behaviors, rational decision-making in the use of drugs, and skills for preventing or recognizing drug use problems.

Programs employing the responsible drug-use approach ranged from responsible drinking-awareness activities, to drug-overdose first-aid training, to the suggestion that some individuals who had alcohol-use problems could reintegrate social drinking into their lives after chemical dependency treatment and counseling. Such programs, however, were not of value to all individuals and groups who engaged in drug taking, and the relative utility and effectiveness of these programs still are not well known.

A few researchers and educators more recently have suggested a rather different drug education and drug prevention approach in which drug taking is considered a *natural behavior*.[7] In this context, educational programs focus on the need to alter one's state of consciousness in an acceptable way and to use drugs in a responsible manner consistent with one's lifestyle. The drug taker is alerted additionally to the importance of values and the influence of societal attitudes on drug taking. These two notions are extremely important in presenting programs or for counseling patients with regard to drug use.

Differences in opinion about and the actual use of many drugs may vary considerably between different individuals and groups. Tobacco (nicotine) and coffee (caffeine) were considered dangerously toxic and addictive substances in earlier times, whereas few people today call either a drug, although renewed interest in combating cigarette smoking has led to the labeling of nicotine as being as addictive as heroin.

In some societies, alcohol is the social drug of choice by adults, whereas marijuana is the social drug of the young people despite its being socially unaccepted or illegal. In other societies, alcohol use is forbidden, whereas marijuana use is socially accepted. As a result of these differences, specific needs for information, education, or consultation to resolve problems in drug taking may not be met; it might be that what we are now doing in the name of stopping the drug problem *is* the drug problem.

Table 99-2. Reasons/Motivations for Drug Use

For drug's effects (therapeutic or otherwise)
Accessibility and availability of drugs
Peer pressure/ modeling/social acceptance
Genetic predisposition
Suggestibility
Curiosity
User set (personality, past experiences, attitudes and perceptions, expectations, motivations for use)
Information, instructions, and accounts of drug effects and experiences (including other users, mass media and advertising)
Meanings of drug effects
Labels for describing drug effects (symbols, metaphors)
Inherent behavior in humans
Rituals of preparation, administration, use
Religious reasons
Social and communication networks
Group/social interaction dynamics
Prior mood and body state
Symptom sensitivity
Coping response
Physical and social setting
Social-cultural background of user
Political and social control
Body image/ideology
Escape
"I don't know" & "As an excuse" (for other behavior)

In the 1980s, there was a backlash against the *responsible drug use* approach and a reorientation of prevention efforts from a supply-reduction strategy (ie, preventing or limiting the supply and flow of drugs at the source) to a demand-reduction strategy (ie, preventing or limiting the need, and thus actual use, of drugs in an indigenous population). Popular contemporary trends are the *Just Say No* campaign and the use of the mass media to inform and educate. The refusal skill technique (eg, *Just Say No* campaign) is an abstinence-based approach, which was developed in the area of smoking prevention research. The use of peers in educational programs also increased in the 1990s. Much of the effort started in the field of alcohol education as attempts were made to move away from authoritarian, moralistic programs with abstinence as a goal to peer-facilitated strategies based on the concept of self-discovery and the fact that alcohol use is socially approved and engendered in most societies, even if it is an illegal activity for certain segments (eg, by age) of the population. Regardless of these trends, *fads*, or new approaches in drug-education programming, there are a few basic principles that always should be considered.

BASIC PRINCIPLES OF DRUG EDUCATION

Various strategies and techniques exist for use in counseling and educating patients, but before these are considered, the process through which learning takes place is reviewed. The process of learning occurs in three domains or in three different ways[8] (Fig 99-1). The basic domain is cognitive, where facts and information are assimilated. A person's knowledge is built through a process of acquiring, understanding, retaining (memory), and reinforcing specific bits of information. The next domain (affective) involves the formation of attitudes such as feelings, beliefs, perceptions, emotions, and appreciations. These are constructed through an interactive process, combining knowledge (from the cognitive domain) and real-life experiences during which the person's knowledge is applied and evaluated to see if it fits that of reality. The behavioral domain (eg, actions, decision-making, physical abilities) is developed from what the person knows and feels, in conjunction with the nature and requirements of their social environment.

Values may affect all domains of learning. One's viewpoint, ethical orientation, or way of life influences drug taking,[9] and it also influences educators as they develop and provide programs. The classic philosophical approach is to consider beliefs and decision-making in one of two ways. The deontological approach focuses more on the action or motive behind the decision, whereas the teleological approach focuses more on the results or consequences of the action or decision.

Decisions to give or take drugs can follow the same philosophical lines of thought. In health care, for instance, the outcome or result of therapy usually is more important than the nature of the therapy itself. In many cases, a vast array of drugs is used to continue the patient's life (the primary *result* of therapy) even when the drugs themselves lead to various negative effects and problems, sometimes worse than the disease itself. Medical and drug research in the past also followed the teleological approach. The emphasis was on the results of research (ie, finding a drug that would cure a disease) and less on what happened to the patients in the experiment. Contemporary clinical drug trials are much more ethical, but the emphasis on results or the outcome of therapy still remains.

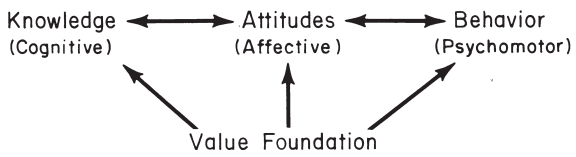

Figure 99-1. Domains of learning.

The influence of values also can be seen in the development and provision of drug education programs. As described by Dembo,[10] the two current views or frames of reference in drug prevention and treatment differ in their emphasis on drug use. The positivist view focuses on drug use problems and drug education attempts to alter the user's attitudes and behaviors in the direction of total abstinence. The interactionist view stresses the importance of sociocultural and environmental factors leading to drug taking as a valued activity, and drug education focuses on the development of social sanctions and rituals to prevent or limit dysfunctional drug taking. Each viewpoint would result in the development of perhaps different types of drug education programs.

The importance of values in drug taking and drug education even has been considered a primary facet in the development of programs. One approach is known as values clarification, which was developed as a strategy to improve an adolescent's general social skills and which has been adapted to drug education and drug prevention programs.[11] The idea behind values clarification is that an individual's beliefs and ability to make decisions are influenced greatly by values. The clearer these values and the process of valuing are, the more self-directed and consistent the individual is in making optimal decisions and choices in life. The values-clarification strategy has become an important part of some drug education efforts.

The main problem that educational theorists and researchers have had is in determining what and how much of what is learned in one domain influences the learning process in another domain. There is a dominant notion, based in part on common sense, that the provision of drug information will improve appropriate drug-taking behaviors in most situations (eg, increased compliance, responsible self-medication, or decreased social-recreational use). Various research in different areas of drug education suggests that this relation *does not necessarily* hold true.

Many studies on patient package inserts (PPIs), for instance, have found that this form of printed information can lead to reliable gains in drug knowledge, but they seem to have little effect on how patients use a drug.[12] Although the patients' knowledge and understanding (cognitive domain) of the drug and drug regimen were improved, their initial decisions regarding drug therapy, their intention of using the drug (attitudinal domain), and their actual compliance with the regimen were not changed greatly. The same also holds in educating people about nonmedical drug use. The relation between what a person knows about the nonmedical use of drugs and whether a person actually uses drugs in such a way is not very strong, according to most of the research in this area.[13] This body of research also suggests that the relation between knowledge, attitudes, and behavior is unclear and may be weak or inconsistent for some individuals or in some drug taking situations.

On the other hand, some studies of drug knowledge, attitudes, and behavior in the area of social-recreational drug use have shown a relationship between these three domains in some educational situations. The strongest relationship seems to exist between attitudes and behaviors with regard to smoking behavior (and to a limited extent, alcohol use), but even this appears to be a complex and difficult connection to describe and predict in educational efforts. Interactions with individual patients in practice settings also might show that improving patients' knowledge about their drug therapy, in fact, directly influences their compliance behavior. It is obvious that some things we know do influence our attitudes about them, and what we feel about them will influence how we act toward them.

The relationships illustrated in Figure 99-1 are assumed to exist, but not necessarily for everyone in all possible situations, and the relations are shown to occur in either direction. The most important point to realize is that for achieving a particular type of effect, the best approach is to focus on the domain of learning where the desired effect or change should occur. If the

goal of the educator's efforts is a negative attitude toward the use of certain drugs, then the educational program should focus its activities more on attitudes and less on increasing drug knowledge or on discouraging drug taking. If the goal of the program is to prevent or limit certain types of drug use, the focus should be on building skills and directing behavior away from use and not so much on increasing drug knowledge or on developing attitudes against drugs and their use.

Truly effective drug education occurs by individualizing the learning process to the particular needs of the patient or consumer. The pharmacist should become aware of a particular person's situation and be ready to help as needed. Not only is this a part of effective counseling and drug education, but most people indicate that this approach (ie, being considered as a unique human being) is what they desire and expect in interactions with health professionals.

Individualized attention, not surprisingly, is also one of the major factors in a consumer's selection and patronage of a particular pharmacy. In terms of drug education, then, the best way to approach the learning process is to:

Assess the person's level of knowledge and provide relevant information in those areas where there is a deficiency.
Counsel the person and encourage positive attitudes toward the appropriate and controlled use of drugs.
Evaluate the person's drug taking and general health over time to verify appropriate patterns of use and optimal outcomes from use and to reinforce positive attitudes and behaviors.

This individualized approach also raises an extremely important concept that has attracted much attention recently: the importance of literacy in reading and understanding health and drug information. About 18% of the US adult population reads at the 5th grade level or lower, and almost half of the population reads at less than the 10th grade level, with the average reading level at the 8th to 9th grade.[14] It is imperative that health and drug counselors and educators become more aware and educate themselves about this major problem.

The concepts and principles presented in this chapter apply to people who use a chemical substance for a medical or nonmedical reason in any setting. The delineation of educational effects or outcomes is most productive when it is based on the idea that people learn and act on what they know in different ways.

EFFECTS AND OUTCOMES OF DRUG-EDUCATION PROGRAMS

The most important concept, which surprisingly often is not stated explicitly in educational programs, is the behavior or problem that is the target of the educational or prevention effort. This is unfortunately the case with most drug education programs. There is sometimes a general sense of what should be achieved, but the specific results or outcomes are not clearly delineated. Several different, though not necessarily mutually exclusive, goals for drug education programs are:

An increase in drug knowledge
A change in attitudes about drugs and their use
An improvement in social functioning (eg, social competency), which might lead to better decision making in drug taking situations
A change in drug use in general
A change in the use of specific types of drugs
A reduction in the occurrence of specific drug-use problems

Once the overall goals of the program are determined, more specific results and outcomes may be identified and characterized.

This degree of generality appears to occur most often in educational programs on the nonmedical use of drugs. Most programs list a primary goal of prevention of drug abuse, but the question of what constitutes *abuse* of a chemical substance usually is not well defined. This results in the adoption of complete abstinence from drug use as the goal of the educational or the prevention program.

What, then, are the effects and outcomes of drug education programs? The most effective type, in relation to one specific level of learning, addresses drug knowledge. The provision of drug information, and the receipt and understanding of that information, leads to increases at the cognitive level most of the time; patients or consumers show an improvement in their knowledge about drugs, as measured by some cognitive test. This increase in knowledge, however, may not lead to a change in attitudes or behaviors. For instance, the effectiveness of PPIs and other programmed medication instruction sheets are variable. Studies of PPIs by the Rand Corporation provided a better idea of the use and effectiveness of patient drug information.[12] The principle findings of those studies were that:

PPIs are likely to be read widely.
PPIs are used as reference documents by many patients.
PPIs lead to reliable gains in drug knowledge.
PPIs seem to have little effect on how patients use a drug.
PPIs do not, in general, lead patients to report more side effects.
PPIs are unlikely to change the frequency with which patients contact their physicians.
Patients find written drug information helpful.
The amount of explanation provided in a PPI makes little difference in how much information patients understand or remember.
The simplicity with which a PPI is written has little effect on understanding.

Other studies, as well as comprehensive reviews of the literature in this area, have arrived at similar conclusions.[15,16] In a medical context, the provision of drug information often leads to measurable gains in knowledge about drugs, but corresponding changes in drug taking (eg, improved compliance or more appropriate self-medication) may not occur, especially if learning also does not take place in the attitudinal or behavioral domain.

Drug education programs directed at these other domains of learning most often have their effect in those specific domains. The general lack of effectiveness of drug information programs in improving compliance motivated educators to develop other techniques. In the area of compliance, several attitudinal and behavioral strategies have been developed (see *Compliance* chapter). For example, health beliefs have been found to influence an individual's decision making about seeking health care and complying with prescribed therapy. In educational efforts, the Health Belief Model[17] has been used to design specific techniques and strategies, which have been found to be effective in increasing compliance in some patients. Behavior modification techniques also have been effective in helping patients to adhere to dieting plans, to comply with complex or difficult therapeutic regimens, and even to stop smoking.

In the area of nonmedical drug education, the informational approach also has been found to have a short-term effect on drug knowledge and little effect on nonmedical drug use. The interesting and somewhat unfortunate exception is that the provision of information or lecturing solely on the pharmacology of the *drugs of abuse* was found in some studies actually to increase students' curiosity and their desire to experiment with these substances.[5,18] In these studies, drug use increased slightly for a short time after the educational program, and then it fell back to the level measured before the educational activity. Early efforts using fear-arousal messages and scare tactics were found to have an immediate effect, when compared with the provision of factual information or discussions of attitudes, but the effect usually only lasted for a short period. The consensus of researchers is that fear as a part of punishment is not an effective approach, but positive reinforcement might be effective in some programming efforts.

From a meta-analysis of 143 adolescent drug prevention programs, Tobler[19] concluded that of all the different approaches only the peer counseling programs were effective in producing changes in all three domains of learning and, most important, these types of programs were the only ones to prevent or reduce significantly nonmedical drug use in adolescents. Programs using alternatives to drugs were found to be

effective in reducing drug use for *high-risk'* adolescents. In general, this large-scale analytical review found that multimodality programs were much more effective than programs that used only a single approach or strategy. A review and analysis of 35 drug-education programs, which employed specific outcome measures, found that the *new generation* of prevention strategies may produce more positive and fewer negative results than did the older drug-information approaches.[20] Even when positive changes were noted in a particular program, those changes were usually small and short term. Other studies and reviews have arrived at similar conclusions; most educational programs, regardless of the approach or strategy, seem to produce changes in drug knowledge, but few are capable of leading to significant changes in drug taking behaviors.[21]

Some educators, however, have argued and shown through research that the relation among knowledge, attitudes, and behavior might be a complex one, and although changes in the cognitive domain can occur quickly, changes in attitudes and behaviors take longer to be internalized by the learner and put into everyday, real-life practice.[22]

Strategies and approaches that have been developed more recently have not been shown to be more effective. The refusal-skills approach (eg, *Just Say No*) appears to be most effective in smoking prevention, but even then, the effect is short term. Mass-media approaches to drug education and prevention also have been shown to have a noticeable, short-term effect on drug use, especially in terms of smoking prevention. The use of written drug information, as a supplement to the media content, seems to improve slightly the effectiveness of the mass media.

DRUG EDUCATION IN A MEDICAL CONTEXT

The range of audiences for medical drug education programs can vary from the one-to-one interaction with an individual patient to comprehensive programming for groups of people or whole communities. Drug information and consultation are educational activities that pharmacists have been using for some time. Providing information, presenting drug education programs and consulting with patients and health professionals represent the major prevention efforts requiring pharmacy involvement (see Appendix A).

Drug taking in a medical context often is influenced or directed by a health professional. The drug educator should not forget this audience in planning and developing drug education programs. The primary group is the drug prescriber, mostly physicians. Research has shown that prescribing behaviors are influenced by numerous factors, including: prescriber education and training; drug advertising and promotion; interactions with colleagues; control and regulatory mechanisms in health care; and the demands of patients and society.

These factors should be considered in developing programs to educate physicians and others about drugs and to improve the appropriateness of their prescribing behaviors.[23] Drug information newsletters and other services, counter detailing and screening pharmaceutical representatives, in-service seminars and presentations and drug utilization review with feedback and consultation are the most commonly used approaches to improve drug knowledge and change prescribing practices.

The actual education of patients about their prescribed medications covers a wide range of complex and involved strategies (see Appendix A). At one end of the spectrum, a drug information sheet (also called a study instruction sheet), education card, or PPI is given to the patient along with the medication. Information sheets in languages other than English, and in a pictorial format for those who cannot read, also have been designed. Programmed instruction sheets, which provide both information and auto-tutorial learning with reinforcement, also have been developed and used in pharmacy. The value and effectiveness of sheets is variable, with the greatest degree of learning occurring in the cognitive domain.

Written drug information obviously is important, and used by many patients. The best manner to provide such information, however, may not be through mandatory distribution of standardized information, but by individualization of the information to the patient's needs. Supplementing written information with verbal counseling usually increases its effectiveness and utility. The *Omnibus Budget Reconciliation Act of 1990* (OBRA 90) mandates patient counseling. The pharmacist also may help patients' informational needs by being aware of and providing some of the many consumer-oriented drug books now on the market.

Experience suggests that the vast majority of patients' questions and needs can be answered fairly immediately from one's knowledge and experience. The optimal distribution of drug information should be based on the old adage: the right information, in the right form and amount, to the right person or place at the right time.

One concept that has emerged recently as an effective learning strategy is social support. Some programs have been designed to include social support in the educational process, and this concept even can be applied to individual counseling situations in health-care settings. The pharmacist and a significant other, such as a spouse, family member, or friend, help in motivating the patient toward a positive health behavior by monitoring drug use, noting problems, and reinforcing appropriate drug taking behaviors. In the context of motivation, another technique, called motivational interviewing, has been developed in patient education. Motivational interviewing is a patient-centered counseling approach for initiating behavior change by helping patients resolve ambivalence or confusion in understanding their treatment regimens. It is an approach that helps patients to increase their motivation to change.

Another strategy involves the use of behavior modification to assure appropriate drug use. This problem solving process employs the observation of behavior, cueing (some type of motivator or reminder to initiate behavior), and rewards to define and modify behavior in a specific way. The patient learns about the medical condition and drug regimen, and then implements a self-management program related to his particular therapy. The patient becomes a partner in the planning of therapy, and consequently feels responsible for following the agreed-upon regimen. These two techniques, social support and behavior modification programs, have been found to be effective in improving patient compliance with medication regimens.

There is one type of drug taking behavior for which few educational programs have been developed. Self-medication and related practices involving home remedies have not been well studied in the past, and consequently, ideas and theories for how to change and improve self-medicating behavior are limited. Some investigators are working on the application of the *Health Belief Model*[17] to situations involving self-diagnosis and self-medication. For the most part, educational activities in self-medication have consisted of drug information, usually in the form of consumer-oriented books on drugs. A perusal of the health and medical sections of local bookstores should give the reader an idea of the range and quality of this information.

Basic principles in the provision of drug information apply to the evaluation and use of these materials as well, before they are suggested or distributed to consumers. In addition to consumer-oriented books and materials, the only other strategies developed in this area are simple, structured educational presentations on self-medication trends, fads, and problems, and the use of algorithms or flow charts to assist consumers in their decision making.[24]

DRUG EDUCATION IN A NONMEDICAL CONTEXT

Various programs have been designed to provide information and education on drug taking in a nonmedical context (see Appendix A). The classic approach is to provide drug-specific

(eg, pharmacology) and drug-related (eg, drug laws or alternatives) information to individuals or groups. The affective or attitudinal approach consists of training in communication skills, values clarification, self-esteem and coping with stress. Informational and affective strategies often are combined in a single program or a series of workshops.

The behavioral approach focuses on the building of skills, such as refusal skills to counter peer pressure, assertiveness, decision making and problem solving, or employs behavioral modification techniques to help identify and change inappropriate behaviors. Comprehensive programming involves complex, multisession educational experiences that are designed to have an effect on all domains of learning. Examples of these types of programs include peer-counselor and teacher training, curricular design in school settings, and community-based approaches such as parenting and parent–child interaction workshops and the use of the local mass media.

Research has shown that the best point in a curriculum to begin or to expand *drug abuse* education programming is approximately at the fifth- or sixth-grade level.[5] Student populations may differ greatly from one school setting to another, thus necessitating the use of a needs assessment survey to determine their level of experience and understanding. Drug-related information (eg, drug laws, alternatives to drugs) also should be presented and discussed as part of any drug education program, particularly if the program goal is abstinence from drug use.

Social competencies are those skills and abilities that promote healthy personal and social functioning. It has been suggested that people who are not socially competent (ie, those with low levels of trust, confidence, self-esteem, identity, directionality, and interpersonal skills) are more likely to engage in inappropriate drug use. On the other hand, the socially competent person is more likely to make better decisions about drug use, prevent problems from drug use, or recognize such problems and solve them. In fact, the strategy of enhancing social competencies is a major part of Alcoholics or Narcotics Anonymous.

The training of gatekeepers and other key people to assist in recognizing drug use problems and in referring people to appropriate health and social agencies has been the focus of some educational programs. Gatekeepers are those individuals to whom a person might turn for help in dealing with drug use problems. Such individuals can be family members, school personnel, religious leaders, local officials, criminal-justice workers, bartenders (with regard to alcohol use problems), civic organizations, and health professionals. Pharmacists perhaps are qualified best to be gatekeepers for individuals who have drug-use problems.

Being a gatekeeper essentially means being able to recognize potential or actual drug-use problems, being empathic in understanding the different attitudes or motivations that might have led to the problem, and being able to assist the person in solving the problem or making a referral. Such skills are not difficult to learn and actually enhance one's ability to help family, friends, patients, and even one's self with all kinds of problems.

DEVELOPING DRUG-EDUCATION PROGRAMS

The provision of drug education programs occurs to varying degrees, according to the motivations of the pharmacist and the nature of the pharmacy-practice setting. Many factors should be considered in developing a drug education service:

What types of educational programs can be provided?
How involved the pharmacist is willing to become, given the constraints of personal knowledge and skills, space, time, manpower, availability of resources, and financial considerations?

It is good practice to define the exact role one plans to assume as a drug educator, including the specific programs and services to be provided. This provides a framework upon which skills and abilities may be built and acts as a point of reference from which to work. It also delineates how and what to promote, and makes it clear to patients and consumers what is being offered.

It is important to recognize that each pharmacist becomes a drug educator to a different degree of involvement. One pharmacist may wish to provide only verbal and written information at his pharmacy, whereas another may be willing to give structured drug education presentations before groups of people. Neither should be forced to do more or less. In essence, the type of education required by the patients and consumers must be determined, and a personal educational style best suited to meet those needs must be developed.

In using any particular educational strategy or program, the pharmacist should be familiar with its goals and content, the target audience for whom it is intended, its biases and flaws, the results of any evaluation studies performed on it, its known effect on actual use and practical considerations such as costs, time and manpower requirements, materials and equipment, and extra training.

Whether an individual or group effort, drug education activities require an interactive and structured approach, such as described by the framework illustrated in Figure 99-2. This general approach is useful during education of individual patients in practice settings or during presentation of formal programs before groups of people. The approach basically delineates the important steps one should consider in the conceptualization, development, and implementation of any activity intended to educate patients and consumers about drugs.

The first step is the identification or presentation of a specific question, problem, or need. This might consist of anything from a patient's noncompliance with prescribed drug therapy to a community's need for comprehensive programming in the area of alcohol use and alcoholism. The problem is identified and defined through interaction with the pharmacist. Once the need has been stated and defined, appropriate strategies can be selected and combined into a specific educational or prevention program. The activity may be as simple as the provision of written and verbal drug information to the patient, or it might be as complex as a multisession drug education program involving various strategies. The effect of the activity that has been implemented always should be monitored and evaluated to assure relevance and usefulness in fulfilling the need. In the instance of an ineffective strategy or program, then, the pharmacist can add or drop specific strategies to improve the overall program.

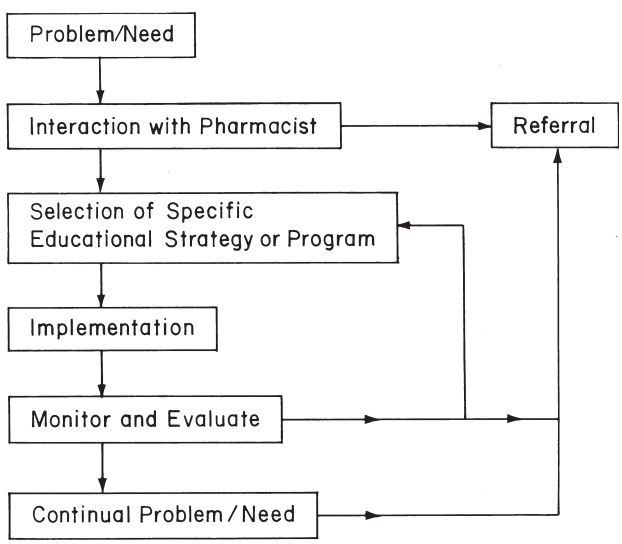

Figure 99-2. Pharmacist-oriented approach to drug education.

Table 99-3. Guidelines for Developing a Drug Education Program

I. Identify Audience and Educational Need or Problem
   1. Receive request for program
   2. Determine need or problem and individual or group at risk
II. Set Goals and Objectives for the Program
   1. Clarify needs, interests, and expectations
   2. Determine outcomes
   3. Define specific goals and objectives
   4. Identify specific topics and content areas based on needs and objectives
   5. Determine focus and philosophical approach
III. Develop Resources and Materials
   1. Identify sources of information and gather and evaluate these materials
   2. Identify key people with expertise
   3. Prepare new materials
IV. Select Appropriate Educational Techniques
   1. Choose teaching approach and strategies
   2. Identify educational setting, time-frame, equipment, and other technical needs
V. Design, Implement, and Evaluate the Program
   1. Structure the program format
   2. Make a complete outline
   3. Pretest components, content, and educational approach
   4. Implement the program
   5. Evaluate and refine

If there is a continual need or problem or if the pharmacist feels that the nature of the stated problem is outside of his or her area of expertise or comfort, a referral should be made.

A stepwise approach also should be used in developing drug education programs, but the educator must realize that a list of guidelines (Table 99-3) represents only those decisions and activities that should be considered in the planning and developmental stages. These guidelines, and program outlines and curricula from other sources, must never be used in a cookbook fashion, with little or no critical thought about what is being done.

Flexibility in program design and tailoring the program to the individual needs of the audience are most essential for a successful educational endeavor. One procedure for improving the match between the audience's needs and expectations and the educational program's content and approach is to perform a needs assessment. A short questionnaire is prepared to elicit the needs, suggestions, and expectations of the target audience, as well as the demographic information on the group's characteristics. The results from such a survey then are used to design the content and format of the educational program.

In addition to the program's content and educational materials, there are a few technical matters that need to be considered (Table 99-4). The provision of drug information and drug education programs always entails the use of time, money, and equipment. More complex and involved programs often are more effective in changing drug taking behaviors, but they also can be more costly and time consuming. The provider of a drug education program also must make certain that specific types of equipment (eg, audiovisuals or computers) are available and in good working order for the program. Finally, in most situations, the consent or permission of the audience or their representative, such as in school settings, is necessary prior to the actual implementation of any educational activity.

Developing and providing educational services involves four steps: design, implementation, evaluation, and promotion. Each step should be directed by the specific situation. The design of educational services consists of assessing patients' needs, collecting and developing resources and program materials, being trained in their appropriate use, and planning their distribution to the target person or audience.

Patient or consumer needs may be determined by recalling past experiences with specific problems, being aware of the mass media and the concerns of consumer-advocacy groups, and surveying the local population for current and future needs. Many pharmacists periodically have used patient-need surveys (which simply can consist of a single page of general, open-ended questions soliciting a written response from the person or a listing of services and programs that the person can check off) to assist them in the design process. They have found that besides being useful for that purpose, it also builds greater trust and loyalty among their patients and gives the pharmacist an idea of what the patients think about the pharmacy and pharmacist in general.

Once the educational services are defined and developed, they can be implemented whenever a need or problem arises. On many occasions, the pharmacist might have to take the initiative, particularly if it is perceived there are potential drug-use problems occurring in a person or in the community. Most of what is involved in implementation has already been described. Local and regional resources (eg, drug information and poison-control centers, mental health and chemical-dependency facilities, hospitals, libraries, bookstores, and media centers) should be identified beforehand to determine what services or information they can provide, and to know when they are available and how to reach them if necessary. One should consider evaluating the educational services used to make sure that they are both ef-

Table 99-4. Technical Aspects of Drug Education Programs

APPROACH	GROUP SIZE	AUDIENCE	TIME	COSTS	OUTCOMES
Cognitive only	any number	nonspecific heterogeneous unless content specific	short	low except material costs	short-term gains in knowledge
Affective (Social Competencies)	small groups (<20)	nonspecific or target groups	short	low	short-term changes in attitudes
Cognitive and Affective	small to medium size (depends on activities)	nonspecific or target groups	short to medium (depends on content)	low	short-term changes in knowledge and attitudes
Skills Building	small groups (<15)	focused on specific skill or activity homogeneous	time consuming multi-session	high*	significant changes in attitudes and reductions in drug use (medium to long-term impact)
Comprehensive Programming	small groups directly large groups indirectly for certain activities (mass media)	very focused on specific goals or tasks homogeneous for direct programs heterogeneous for indirect programs	very time consuming multi-session	high*	significant changes in attitudes and reductions in drug use, esp alcohol, tobacco, and marijuana

*High cost involves personnel, materials, and multi-media, all over multiple sessions, so dependent on number of sessions in the specific program.

fective and efficient and that the information and services provided are understandable and of use in meeting the problem or need. Evaluations can be performed in the same manner as the aforementioned patient-need surveys.

The pharmacist also should consider the promotion of educational programs and services, so that the patients and consumers become aware of and use them. The promotion of such services is similar, in concept, to the promotion of any product or service. Detailed descriptions may be found in any reference book on marketing, advertising, or business practices. There are many specific techniques that can be used in promotion. Some are free of cost and involve only a small amount of time, whereas the willingness to spend more time and money leads to more intricate and diverse promotional schemes. One comprehensive way is through the local mass media. It is not difficult to contact the local town or neighborhood newspaper, local TV or radio station, and local cable networks and ask for a news story or even request an interview that would describe the new educational services that will be provided to the community.

If the services are significantly new in nature or potentially beneficial to the community, such as presenting structured drug education programs, free news stories and public service announcements about these services and their provider could result. Word-of-mouth communication from current users of the services also is important. It is good to end an episode involving counseling and education with the statement, "If you, or anyone else you know, needs further help or information, please don't hesitate to contact me." Advertising in the phonebook and through the media, and placing signs in the pharmacy's window and at key spots around the community also may be effective.

Single-page consumer-oriented drug information sheets may be produced for distribution. Assistance for the printing of such materials may be obtained from local agencies and businesses as a show of community support. There is also the accepted practice of promoting a new service by informing lay people or community groups about them. Through a process of diffusion, this information is shared with a larger number of people who come in contact with those who have been informed. In most communities, key people or groups include teachers and counselors at local schools, the Jaycees and Chamber of Commerce, the PTA, women's clubs, consumer groups, governmental agencies, social and welfare organizations, chemical-dependency agencies, and other health professionals in the area.

FUTURE EFFORTS

The nature and focus of most drug education and drug prevention programs will not change greatly in the near future. Numerous different strategies and techniques have been developed, but what is really needed are more concerted efforts to design and evaluate programs in a rational manner. In a philosophical way, our ability to prevent drug use problems can be improved in several ways. Drugs should not be categorized as being "hard" or "soft," licit or illicit, or addictive or nonaddictive, but instead it should be stressed that the use of any chemical substance carries with it a certain potential for the development of problems, depending on the pattern and setting of use, the reason for use, past experiences with the drug, and various additional social and pharmacological factors. Future efforts should focus more on preventing or limiting drug use problems.

Some educators[25] have even argued that a health promotion, rather than the more traditional disease prevention, approach should be used. Also, a need exists to become more cognizant of attitudes, values, and motivations—especially those that differ from our own—in people's drug taking, because these factors are most important in recognizing and characterizing the nature and the extent of drug-use problems. For instance, some educators have argued that it is time to view drug use as a motivated, adaptive behavior that is pursued in the consummation of valued experience, and then to develop strategies and programs based on this notion.[7,10]

In practical terms, the success of future programs and activities depends on a clearer and more coordinated effort in using the strategies and techniques that have been developed and tested. Health professionals, the family, schools, and communities should combine their efforts and integrate drug- education strategies into ongoing activities, instead of just adding them onto irrelevant courses and programs. Attitudinal strategies and basic drug information should be combined in educational programs. The various structured and prepackaged materials and techniques should be selected and synthesized into programmatic formats that best meet the needs of the target audience.

It is important to identify individuals or groups at high risk for developing drug-use problems and to focus educational and prevention efforts on their needs. Finally, a humanistic approach, in which drug taking is considered a natural kind of behavior and in which an awareness of different values is stressed, should be brought into educational programming. Regardless of the degree of involvement, it is time for pharmacists and the pharmaceutical profession to provide more drug education programs for their patients and all of society.

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APPENDIX A

Specific Strategies and Programs in Drug Education[a]

COGNITIVE (INFORMATION) PROGRAMS

Drug Information

Corry JM, Cimbolic P. *Drugs: Facts, Alternatives, Decisions*. Belmont, CA: Wadsworth, Belmont CA, 1985.
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Computer-Assisted Instruction

Gustafson DH et al. *Ann Rev Publ Health* 1987; 8: 387.
Anon. *Healthcare CAI Directory*. Alexandria VA: Stewart Publ., 1991–2002.

Drug Information Services

Montagne M et al. *Am J Hosp Pharm* 1980; 37: 1211.
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Snow B. *Drug Information: A Guide to Current Resources*. Lanham MD: Scarecrow Press, 1999.

Health Literacy

Doak CC, Doak LG, Root JH. *Teaching Patients with Low Literacy Skill*. 2nd ed. Philadelphia PA: JB Lippincott, 1996.
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Zimmerman M, Newton N, Frumin L, Wittet S. *Developing Health & Family Planning Print Materials for Low-Literate Audiences: A Guide*. Seattle WA: Program for Appropriate Technology in Health (PATH), 1989.

AFFECTIVE (ATTITUDINAL) PROGRAMS

Interpersonal Skills

Begin S et al. *Traditional Ties: Cultural Awareness and Listening Skills*. White Plains, NY: Longman, 1992.
Tindall WN, Beadsley RS, Kimberlin CL, Speziale HS. *Communication Skills in Pharmacy Practice*. 4th ed. Philadelphia PA: Lippincott Williams & Wilkins, 2002.

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CHAPTER 100

Professional Communications

Amy Heck Sheehan, PharmD
Steven R Abel, PharmD, FASHP

Communication is a vital skill, necessary for success in personal and professional settings. Pharmacists often serve as the guardians of appropriate drug therapy. Therefore, communicating effectively is key to reinforcing the value of the pharmacist within the health care system. Pharmacists communicate with patients and a wide variety of health care professionals on a daily basis. The type of information that is communicated may be the same. However, the knowledge level and expectation of the audience dictate the delivery of the message. Regardless of knowledge or expertise, pharmacists cannot actively participate in patient care unless they can communicate effectively.

Pharmacy career options have expanded into multiple, different settings including hospital, community, managed care, academia, and industry. In all of these settings, communication is critical. Whether verbally responding to a physician's question during patient care rounds, providing an educational program to nursing staff, or publishing results of a research project in a biomedical journal, communication skills are paramount to effective pharmacy practice. This chapter will discuss appropriate professional communication skills related to verbal and written drug therapy recommendations, oral presentations, formulary communications, published manuscripts, poster presentations, professional and personnel issues, and communicating with the media.

COMMUNICATING WITH HEALTH CARE PROFESSIONALS

Verbal Communications

Regardless of the practice setting, verbal communication is the most common type of communication that pharmacists utilize. It is common for a pharmacist to be approached by several different individuals (with varying backgrounds), regarding a multitude of situations, in a single day. As practitioners, pharmacists should be encouraged to remember that any type of question or interaction, regardless of how informal it may seem, is an important method of professional communication. Whether responding to a question concerning compatibility of intravenous medications from a nurse, a drug dosing question from a physician, or a request about the adverse effects of a medication from a patient; all of these interactions require excellent verbal communication skills. The most common verbal communications that pharmacists engage in involve responding to drug therapy questions and receiving verbal drug orders.

RECEIVING DRUG THERAPY QUESTIONS

A major challenge in responding to requests for drug therapy recommendations is determining the unique situation that prompted the request. Often, the original request posed by a requestor does not represent the actual information needed.[1,2] Requestors of information are sometimes unclear when asking questions pertaining to specific-patient needs. This most likely occurs because they are not aware of the specific information that pharmacists need to provide a comprehensive response. Therefore, pharmacists should recognize this potential challenge and use appropriate listening and questioning skills to collect pertinent background information to determine the exact context of the question. Questions that often appear simplistic in nature at first glance may actually be more complex when all appropriate background is considered. If pertinent background is not determined and the pharmacist does not have a clear understanding of why the question is being asked, patient care could be jeopardized. For example, if a physician asks a pharmacist a question regarding the dose of a medication, inaccurate and potentially harmful information may be provided if patient-specific factors such as age, weight, and renal or hepatic function, are not considered.[1]

Consider the example of a middle-aged man who approaches a community pharmacist and asks the question "Is Advil good for muscle pain?"[2] At first glance this appears to be a relatively simple question. Advil contains ibuprofen, which is a common over-the-counter (OTC) analgesic. Therefore, it would appear that a reasonable answer to the man's request would be "yes". However, what if the pharmacist further questions the man about his medical history to determine why he was asking this question? After further questioning, the pharmacist realizes that the man had recently started lovastatin therapy. This additional background information suggests that the patient may be experiencing symptoms of lovastatin-induced myopathy. Instead of answering the question at face value, the pharmacist in this situation is able to identify a potential drug-related adverse event by collecting important background information to determine "why" the man was asking the question.

The previous example illustrates the importance of questioning strategies to collect pertinent background information and determine the true information need. Pharmacists should apply the appropriate skills to ask logical background questions in a reasonable sequence to clarify each question. This is especially important when confronted with an impatient requestor who may not realize the value of gathering background information.

When receiving drug-related information requests from health care professionals, it is particularly useful to ask the information requestor if his or her question is about a specific patient.[1,2] This allows the pharmacist to ascertain key patient data

immediately and usually prompts the requestor to describe more information about the patient. Another helpful questioning strategy is to use open-ended questions.[2] Open-ended questions cannot be answered by one-word, short answers; but require responses with detailed descriptions, and enhance information exchange about the context of the question. In the previous example about Advil and muscle aches, an appropriate open-ended question could be, "Can you describe your muscle pain to me?" This question allows the patient to provide more details about the circumstances surrounding his question. There are situations however, when the pharmacist will need to ask direct questions to obtain certain types of factual information like patient age, weight, or current medications. For pharmacists to gain a clear understanding of the actual question, a mixture of different types of questioning strategies should be used.

In addition to asking appropriate questions, it is important to have strong listening skills. Pharmacists should avoid all possible distractions when gathering background information. If the interaction is in person, the pharmacist may use nonverbal cues such as facial expressions, eye contact, and other forms of body language to interpret the requestor's response to his or her background questions. Communicating over the telephone is inherently more difficult, and in these situations, pharmacists must be especially skilled in gathering background information. It is very important to ask for clarifications when necessary to ensure a complete understanding of the situation. Finally, an important last step to collecting appropriate background information is to repeat the question or request to verify the inquiry. This will help clarify any discrepancies between the requestor and pharmacist. Pharmacists should remember that it is their professional responsibility to collect pertinent background information to fully understand the true information request. Providing drug therapy recommendations without a complete understanding of the pertinent background is simply negligent. Table 100-1 is a list of important background questions to consider when receiving a drug-related request. These questions allow the pharmacist to formulate the most appropriate response. Care also should be taken to identify when a response is needed. Providing timely and accurate responses establishes the value of pharmacists as drug therapy experts.

RESPONDING TO DRUG THERAPY QUESTIONS

After a complete and accurate response to the request is developed, communicating the information clearly and concisely is critical. Utilization of appropriate information resources, data analysis, and formulation of responses is beyond the scope of this chapter. However, the reader is referred to *Drug Information: A Guide for Pharmacists* for more information on this topic.[1]

In the clinical pharmacy practice setting, verbal communications may be more common than written communications. Therefore, it is very important for pharmacists to have the necessary skills to communicate information verbally in an effective manner. Oral responses are generally preferred because they are more personal than written responses, and they allow for prompt clarification of information that may be unclear. Verbal responses may also be favored in situations that are of high priority (emergency situations when a prompt response is needed) or when a sensitive issue is being discussed. It is important to note that when pharmacists effectively communicate drug information in a face-to-face manner, they promote the profession of pharmacy by being recognized as valuable members of the health care team. However, when information is communicated orally, the risk for misinterpretation exists.[3]

When communicating important drug therapy information, one should always make sure to identify him- or herself professionally as pharmacist. This provides the requester with confidence that a professional with appropriate educational background is responding to their request. If responding to a question that was posed during a previous interaction, it is recommended to review briefly what the initial drug therapy question was for the purpose of refreshing the memory of the requester. For questions that are specific to a certain patient, the patient should be identified to avoid any potential confusion.[3]

When verbally communicating the specifics of the response, the pertinent facts should be stated, limitations to the literature should be acknowledged, and a final conclusion and recommendation should be provided.[1,3] Pharmacists should make sure to focus on the key points in a clear and concise manner and reinforce the major point again at the end of the conversation. All relevant information should be presented. However, describing large amounts of minor details should be avoided. It may be helpful to write a brief outline using bullet points with the major issues to be communicated. This helps to ensure that pertinent information is not forgotten and that the information is communicated in a clear and concise manner. Once the response has been communicated verbally, verification should be made to make sure that the information provided to the requestor was sufficient to meet his or her needs. An offer to provide written documentation of the response should also be made.[3] Proper methods for documenting drug therapy recommendations will be reviewed later in this chapter.

Displaying confidence is obviously very important during the delivery of the response. If the pharmacist does not appear confident in his or her response, the requester may certainly have reservations about the information provided. Additionally, the vocabulary and terminology that is used should be appropriate for the given audience. For example, when communicating with a physician, professional terminology should be used and all medical terms should be pronounced correctly. However, when communicating with a patient, terminology that a layperson can easily understand should be used. Finally, follow-up questions should be expected and addressed in advance to save valuable time.

Table 100-1. Questions to Consider When Collecting Pertinent Background Information

What is the requestor's name, profession, and affiliation?
Does the question pertain to a specific patient?
Do I have a clear understanding of the question or problem?
Do I know if the correct question is being asked?
Do I know why the question is being asked?
Do I understand the requestor's expectations?
Do I know pertinent patient history and background information?
Do I know what unique circumstances generated the question?
Do I have insight about how the information I provide will actually be used?

Adapted from Calis KA, Heck AM. In: Malone PM, Mosdell KW, Kier KL, eds. *Drug Information- A Guide for Pharmacists*, 2nd ed. Stamford, CT: Appleton and Lange, 2001.

USING THE TELEPHONE FOR COMMUNICATION

Pharmacists are often asked to respond to questions and provide drug therapy recommendations using the telephone. Therefore, all pharmacists should be familiar with professional phone etiquette. Face-to-face interactions are preferred, as they are more personal; however, in many situations telephone interactions are necessary.

Regardless of the professional setting, the telephone should always be answered by providing a greeting that identifies the pharmacist's name and affiliation (eg, "Pharmacy Department, this is John, a pharmacist, speaking"). It is also helpful for pharmacists to have a pen and paper readily available before answering the telephone to document any notes that are necessary during the conversation. Many pharmacists find it helpful to write down the exact date and time that a call is received. The hold option should always be used when asking someone to wait

on the telephone line. This maintains a professional setting and avoids the potential for the caller to overhear background conversations while waiting for the pharmacist to return to the telephone line. Repeating information to clarify any discrepancies is also especially important to avoid any confusion.

FOLLOW-UP AND DOCUMENTATION

Follow-up is extremely important to maintaining professional practice. This allows pharmacists to verify if their recommendations were taken and to investigate patient outcomes while demonstrating dedication to patient care. Additionally, pharmacists can learn from their experiences and develop more confidence when they conduct regular follow-up to drug therapy recommendations.[1]

Although verbal recommendations do not always include a formal written response, it is important to document oral drug therapy recommendations for several reasons including in the event that legal questions arise. Documentation also reinforces the usefulness of pharmacists to other health care professionals and contributes to pharmacist workload assessment. Proper methods for documenting drug therapy recommendations in patient medical charts are reviewed in the next section of this chapter.

RECEIVING VERBAL DRUG ORDERS

Pharmacists may be asked to receive medication orders over the telephone. A licensed prescriber, or an agent of the prescriber, can communicate a patient-specific order directly to the pharmacist. This process challenges the pharmacist to dictate the information necessary to accurately fill the prescriber's order, as well as quickly ascertain if the prescription will be an appropriate medication for the patient.

The pharmacist should ask the prescribing party to identify him or herself and to provide the appropriate contact information to verify authenticity and to ensure a method of contact in case follow-up questions are necessary. Asking questions and directing the conversation can assist the pharmacist in controlling the rate and extent of information exchange. Patient-specific information must be obtained along with a complete and accurate description of the medication regimen. The patient's medication order should always be verbally repeated back to the prescriber to verify accuracy. Repeating information to clarify any discrepancies is especially important when taking verbal medication orders from a prescriber over the telephone. The Institute for Safe Medication Practices (ISMP) recommends that all verbal orders and telephone prescriptions be repeated back to the prescriber to reduce the likelihood of medication errors.[4] It should also be documented that the verbal order was repeated back to the prescriber. Verbal drug orders may not be the ideal means of communicating drug therapy orders, but this method is sometimes employed for urgent institutional orders or as a means of convenience in community settings. Verbal drug orders emphasize the importance of excellent communication skills to allow accurate and rapid decision-making processes.

Written Communications

DOCUMENTATION OF PATIENT CARE IN THE PERMANENT MEDICAL RECORD

OBRA-90 legislation set forth the requirements for patient education and maintenance of records, which reflect the thought process of the pharmacist as it relates to patient care. For practitioners who previously did not formally document their therapeutic recommendations, OBRA-90 formalized the requirement for completion of that task. The OBRA-90 legislation requires that pharmacists maintain a database inclusive of patient diagnosis, pertinent demographics, and perhaps most importantly that documentation regarding input into patient care may be located such that review by an impartial, external reviewer will clearly identify the intent of the pharmacist's actions in terms of patient care.

The American Society of Health-System Pharmacists (ASHP) has recently published guidelines on documenting pharmaceutical care in patient medical records.[4] In developing these guidelines, it was emphasized that recommendations made by pharmacists on behalf of their patients should be documented in a permanent manner, such that information is accessible to all health care professionals caring for the patient.[4] These recommendations may include the patient's medication history, allergies, consultations to other health care professionals regarding drug therapy management, verbal orders, order clarification, drug-related problems, drug-therapy monitoring findings, and patient education. It is stressed that documentation by pharmacists should incorporate a standard format and be written in a legible, clear, and complete manner.[4]

The Weed method of documentation has been most utilized and accepted by health care professionals including pharmacists.[5,6] The Weed method consists of the development of a patient problem list and SOAP note, which organizes written patient care communications into subsections related to Subjective, Objective, Assessment, and Plan components for the identified problem(s). In addition to the components, each chart note should be appropriately titled (eg, Pharmacy Note), dated, timed, and signed with the appropriate professional designation of the pharmacist (eg, RPh) along with the method for follow-up contact from the recipient (eg, pager or telephone number). The components of each of the sections of a soap note are included in Table 100-2.

The authors have expanded this methodology to include two additional components, Education and Outcomes. These were incorporated into the authors' formalized documentation program because of the belief that most patients require some type of educational support to optimize therapy and because pharmacists often provide recommendations without identifying the desired specific endpoint in terms of outcomes. Addition of the latter component serves as a mechanism for follow-up to determine whether or not therapeutic goals have been met. It also provides a basis for understanding when care is passed from one pharmacist to another. Figure 100-1 contains an example SOAPEO note.

An alternative method to SOAP charting is Focused Documentation. Focused Documentation is a simplified method of charting, which reduces repetition, uses components reflective of Focus, Data, and Action. In the authors' practice, Focused Documentation is the preferred method for charting except in situations where the physician requests or the pharmacist initiates a comprehensive review of a patient's medication regimen. This may be the case if polypharmacy is an issue, or if a patient demonstrates symptoms consistent with sub- or supratherapeutic response(s) to medications and/or an adverse drug event. An example of Focused Documentation for the above scenario is included in Figure 100-2.

Table 100-2. Components of the SOAP Note[5,6]

S	Subjective: Patient's complaints or symptoms; data provided by family members should be characterized as such.
O	Objective: Patient data including age, sex, race, height, weight, vital signs, results of laboratory and diagnostic tests, and physical exam findings.
A	Assessment: The pharmacist's evaluation of therapeutic alternatives or resolution of drug-therapy problems which may define the necessity for all drugs in the patient's regimen, evaluate the potential for drug interactions, document the appropriateness of the drug regimen and/or evaluate the patient's previous response to pharmacotherapy.
P	Plan: The plan should include specific drug therapy recommendations (drug, dose, route, frequency, duration), monitoring parameters and the necessity for further studies or tests.

Scenario:

AW is a 38YOWM with duodenal ulcer diagnosed this admission following extensive work-up. PMH is significant for epilepsy, controlled since childhood with phenytoin. AW weighs 68 kg and is 5'10" tall. He is employed as a financial analyst in a high-stress, demanding firm. AW reports NKDA. The physician has ordered ranitidine 150 mg PO BID. Ranitidine is a nonformulary drug.

Pharmacist Documentation:

3/9/03 Pharmacy Note
1100
S: AW is a 38YOWM with duodenal ulcer. Dr. Jones has ordered ranitidine, a nonformulary drug.
O: AW receives daily maintenance therapy with phenytoin, to control a seizure disorder.
A: Ranitidine is a nonformulary item. In light of concurrent phenytoin therapy, cimetidine is not considered a viable alternative. Suggest initiating therapy with famotidine.
P: Begin famotidine 20 mg PO BID
E: Educate patient that ranitidine is not available and famotidine has been prescribed as an alternative. Therapy should be administered BID, with a 12-hour dosing interval being most desirable.
O: Control and resolution of patient's duodenal ulcer while avoiding drug-drug interactions.

Figure 100-1. Example of a SOAPEO note.

Formal Presentations

Pharmacists are routinely involved in the delivery of formal presentations, including continuing education and inservice programs. The pharmacist should evaluate the specific needs of the audience and target the level of the educational program accordingly. Pharmacists who know their audience can then prepare specific objectives that include content consistent with the expectations of the recipients. Presentations should be organized based upon the objectives and should not include excessive information that detracts from the key points. Because pharmacists frequently present to other health care professionals, provision of examples, stories, or analogies that include application of the information shared may facilitate the learning process for the participants. Although there is not one approved method for formal presentations, it is clear that "practice makes perfect." The presenter should be certain to prepare his/her talk well in advance of the presentation date, to allow ample time for practice.

In most settings, it is recommended that the presenter use some type of visual aid, which would include slides, overheads or transparencies, or flip charts. Given current technology, the development of a Microsoft PowerPoint presentation is common, as slides can quickly be converted to handouts for program participants. Whether using slides or transparencies, several formatting recommendations exist that have been summarized in Table 100-3.[7]

When properly developed, visual aids should serve as a prompt for the speaker, which should minimize the need for note cards or a complete presentation text. Presenters should be cautioned to speak from their slides or visual aids, but not to read. Other keys to effective presentation include the use of voice inflection to maintain listener interest, incorporating gestures, which accentuate voice inflection, and allowing a pause when emphasizing key points. It is important to dress consistently with the audience. Thus, a formal presentation requires formal (eg, business suit) attire. Nonverbal communication enhances the relationship with the audience. If possible, the speaker should try to move away from the lectern or walk about the front of the room, to make a connection with a greater portion of the audience. Eye contact brings the audience into the presentation. If uncomfortable looking directly at individuals, the speaker should try looking at the top of heads. In a large room, participants will still feel the presenter is making contact with them. In a smaller setting, speakers can try to identify three or four "friendly" faces throughout the audience and use them as a gauge to the presentation as well as a link to the audience.[7]

Most presentations will include time for questions and answers. If time allows, in some settings, it is more effective to allow the audience to interrupt the formal presentation and ask questions instead of waiting until the end. This can enhance the presentation, but the speaker must be careful not to allow excessive time for discussion. Effective presenters should repeat

3/9/03 Pharmacy Note
1100

Focus: Ranitidine, a nonformulary drug, has been prescribed for AW.

Data: AW receives daily maintenance therapy with phenytoin, to control a seizure disorder. Therefore, cimetidine is not a viable alternative.

Action: Begin famotidine 20mg BID. Educate patient regarding alternative therapy and monitor response.

Figure 100-2. Example of Focused Documentation.

Table 100-3. Characteristics of the Ideal Slide/Transparency Text

Horizontal with 2:3 ratio
Content limited to main point
Black or dark blue background
Title in all capitals
Outline format in lowercase
Maximum of seven lines of text
No more than seven words per line
Readable font such as Helvetica or Arial
Limited use of capitals and italics
Graphic slide will have no more than 5–7 bars, columns, or pieces of a pie chart; clear labels or legends in corresponding colors

Adapted from Casella PJ. In: *Writing, Speaking, and Communication Skills for Health Professionals.* The Health Care Communication Group. London: Yale University Press, 2001.

questions to assure that everyone in the audience has heard and understands the inquiry. As in all aspects of health care, if one does not know the response to a question, it is best to admit this freely and offer to follow-up or defer to an expert colleague in the audience who may know the answer. If questions do not relate to the presentation topic, the speaker should respond to the best of his or her ability and redirect the conversation to a point that does relate. The authors recommend the text *Writing, Speaking, and Communication Skills for Health Professionals* to any pharmacist who wishes to strengthen his or her presentation skills.[7]

Formulary Communications

Written communication skills are extremely important for pharmacists who participate in formulary management. A drug formulary can be defined as a continually revised compilation of medications that indicate the current clinical judgment of the medical staff and are readily available for use within an institution.[8] Drug formularies serve the purpose of providing decreased inventory and allow practitioners to gain familiarity with certain drug products. Formularies also promote a decreased risk for medication errors and help the institution provide cost-effective therapy. Ideally, a drug formulary should contain the most cost-effective medications to treat all disease states likely to be encountered within a given institution. A comprehensive review of the issues related to formulary management is beyond the scope of this chapter. However, the most common ways that pharmacists use professional communication skills to contribute to formulary management are through the preparation of drug evaluation monographs (or drug class reviews), medication-use evaluations, clinical pathways, drug alerts, and newsletters. Basic guidelines for the preparation of these documents are listed below.

DRUG EVALUATION MONOGPAPHS

A drug evaluation monograph is an objective, written appraisal of a medication (or class of medications in the case of drug class reviews) under consideration for formulary addition.[9] Drug evaluation monographs are almost always prepared by pharmacists. The following sections are commonly used as a general template in preparing a drug evaluation monograph.[8,9] However, the specific template used by an institution may be modified to meet the institution's needs.

Title: This section includes basic information such as generic and trade names, manufacturer, available dosage forms, and the corresponding national drug code (NDC) numbers, the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification, and any important storage instructions. The AHFS Pharmacologic-Therapeutic Classification number is found in the classification index of the *AHFS Drug Information* reference book. *AHFS Drug Information* is published by the American Society of Health-System Pharmacists and is commonly used as an important reference book for practicing pharmacists. The AHFS Pharmacologic-Therapeutic Classification method indexes medications by pharmacologic and therapeutic effects by assigning numerical values to each drug class. Many institutions use the AHFS Pharmacologic-Therapeutic Classification system to index the medications available on the drug formulary. Use of a classification system helps organize an institution's formulary list.

Description and Pharmacology: This section includes a description of the compound including the therapeutic mechanism of action. Important differences in the pharmacological effects of the monograph drug as compared to current formulary agents of the same class should be discussed as well.

Pharmacokinetics: This section includes a brief review of the available pharmacokinetic data (ie, absorption, distribution, metabolism, excretion), including information about potential pharmacokinetic changes in pediatric and geriatric patients or patients with renal or hepatic dysfunction or other disease states. For this data, a chart format is commonly preferable. This is especially helpful for drug class reviews when several agents within a given drug class are being compared.

FDA-Approved Indications: A list of all the FDA-approved indications and any significant differences between the monograph drug and similar products within the same drug class should be provided. Because many medications are used for indications that are not officially approved by the FDA, it is also important to list pertinent off-label uses of the medication as well.

Clinical Efficacy: A thorough review of available literature pertinent to the efficacy and safety of the requested drug as it relates to the FDA-approved and off-label indications should be presented. Studies that are reviewed should include placebo-controlled and comparative trials, with emphasis on comparative trials when available. It is important to note that clinical trials, which do not assess the safety and efficacy of the drug product, should not be included. For example, pharmacokinetic evaluations in healthy subjects or animal toxicology studies are not appropriate for inclusion in the clinical efficacy section of a drug evaluation monograph. These types of studies may be referenced in other sections of the monograph (such as the pharmacokinetic section or the safety section), but they do not provide clinical efficacy information.

Typically, it is best to follow a general template when abstracting clinical trial data within a drug monograph evaluation. This improves readability, ensures consistency, and allows comparisons to be made between different clinical trials in a relatively simple format. The citation, objective, and study design should always be stated in a clear and concise manner. Detailed information describing the inclusion/exclusion criteria, randomization process, study treatments, and the efficacy and safety assessments should be included in the description of the methods. Within the results section, the writer should report specific numbers to describe the efficacy and safety of the drug. For example, instead of simply reporting a "statistically significant difference between groups," the writer should report the quantitative difference in the outcome measure between study groups (eg, 160 mg/dL versus 110 mg/dL). This allows the reader to interpret the potential clinical significance of the results. In addition to a short conclusion, the writer should provide a brief commentary regarding the potential strengths and limitations that should be considered when interpreting the results of the study. An example of a clinical trial summary that would be appropriate for inclusion in a drug evaluation monograph is shown in Figure 100-3.

Safety and Tolerability: This section should include information regarding manufacturer-labeled contraindications, warnings, and precautions (including pregnancy and lactation information). Adverse event data should be presented in a manner that emphasizes the most common and most serious adverse events, with suggested strategies to prevent or manage these events if they occur. Potential drug-drug, drug-food, drug-laboratory, and drug-herb interactions should also be presented with suggested management approaches. As with all sections of the drug monograph, comparative data should be presented when available.

Medication Error Possibility: Information should be included about potential medication errors that could occur in dosing, medication preparation, medication administration, or concerns with look-alike/sound-alike names. If potential risks exist, methods for preventing medication errors should be introduced.

Dosing and Administration: The recommended doses for specific indications and patient populations (eg, geriatric, pediatric, obese, renal failure) should be clearly listed. If applicable, a description of dosage titration should be included. For parenteral medications, it is important

Citation: Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry* 2002; 63:763-771.

Objective: To determine the efficacy and safety of aripiprazole and haloperidol compared to placebo.

Design: Multicenter, randomized, double-blind, placebo-controlled, parallel clinical trial

Methods: Subjects included men and women aged 18 to 65 years with a primary diagnosis of schizophrenia or schizoaffective disorder who were hospitalized for an acute relapse. A Positive and Negative Syndrome Scale (PANSS) total score of at least 60, with scores of at least 4 on any two items of the psychotic subscale, was required. Additionally, all subjects were required to have documented prior responsiveness to antipsychotic medication. Exclusion criteria included pregnancy, breastfeeding, psychiatric disorders other than schizophrenia or schizoaffective disorder, or a history of violence, suicidal attempts or serious suicidal ideation. Patients were also excluded if they had a clinically significant neurologic abnormality, drug or alcohol abuse, or any acute or unstable medical condition. All subjects underwent a 5-day placebo washout period, and were randomly assigned to treatment if they continued to meet inclusion criteria after the washout. Patients were randomly assigned to one of four treatment groups for four weeks: 15 mg aripiprazole, 30 mg aripiprazole, 10 mg haloperidol, or placebo given once daily after breakfast. Doses were fixed without titration, and patients were hospitalized throughout the trial. PANSS and the Clinical Global Impressions scale were used to measure efficacy. Adverse events were monitored and graded on intensity each week. Extrapyramidal symptoms (EPS) were evaluated using the Simpson-Angus Scale, Barnes Akathesia Scale, and the Abnormal Involuntary Movement Scale (AIMS) on a weekly basis.

Results: A total of 414 patients were randomized for treatment; 102 patients in the placebo group, 102 patients in the aripiprazole 15 mg group, 102 patients in the aripiprazole 30 mg group, and 104 patients in the haloperidol 10 mg group. The 15-mg and 30-mg doses of aripiprazole and haloperidol 10-mg dose showed significant improvements compared to placebo in the PANSS total score (aripiprazole 15 mg –15.5 vs. placebo –2.9, $P < 0.001$; aripiprazole 30 mg –11.4 vs. placebo –2.9, $P = 0.009$; and haloperidol –13.8 vs. placebo –2.9, $P = 0.001$), the PANSS positive subscale (aripiprazole 15 mg –4.2 vs. placebo –0.6, $P < 0.001$; aripiprazole 30 mg –3.8 vs. placebo –0.6, $P = 0.001$; and haloperidol –4.4 vs. placebo –0.6; $P < 0.001$), the CGI-S score (aripiprazole 15 mg -0.6 vs. placebo –0.1, $P < 0.001$; aripiprazole 30 mg –0.4 vs. placebo –0.1, $P = 0.019$; and haloperidol –0.05 vs. placebo –0.1, $P = 0.002$), and the PANSS-derived BPRS core score (aripiprazole 15 mg –3.1 vs. placebo –1.1, $P < 0.001$; aripiprazole 30 mg –3.0 vs. placebo –1.1, $P = 0.001$; and haloperidol –3.5 vs. placebo –1.1; $P < 0.001$). Statistically significant improvements were also reported for the PANSS negative subscale score in the 15-mg aripiprazole group, but not for the 30-mg dose of aripiprazole. Study drop out rates were similar between treatment groups (11% in the haloperidol group, 9% in the aripiprazole 15 mg group, and 8% in the aripiprazole 30 mg group). The most common adverse events associated with aripiprazole were headache, anxiety, insomnia, nausea, dizziness, and vomiting. Fifteen percent of patients in the aripiprazole 15 mg group and 14% of patients in the aripiprazole 30 mg group reported nausea, compared to only 7% and 6% of patients in the placebo and haloperidol 10-mg groups, respectively. Vomiting was reported by 8% and 17% of patients receiving 15 mg and 30 mg of aripiparazole, respectively compared to 10% in both the placebo and haloperidol groups. Aripiprazole was not associated with significant changes in EPS, body weight, serum prolactin levels or ECG readings.

Conclusions: Aripiprazole, at doses of 15 and 30 mg daily, was found to be more effective than placebo and similarly effective to haloperidol 10 mg in patients with schizophrenia and schizoaffective disorder following four weeks of treatment. Both doses of aripiprazole were generally well tolerated.

Comment: Although aripiprazole demonstrated efficacy and safety in the treatment of schizophrenia over placebo in the four-week study, the role of aripiprazole therapy cannot be established at this time due to a lack adequate long-term comparative data. Additionally, the haloperidol-dosing schedule in this study does not reflect current clinical practice (ie, once daily compared to divided into 2 to 3 doses.)

Figure 100-3. Example of a clinical trial summary for a drug evaluation monograph.

to list information about reconstitution techniques, appropriate diluents, long-term stability, and compatibility with other medications. Special administration issues such as infusion rate or the need for in-line filters should also be addressed in this section.

Patient Monitoring Parameters and Patient Information: Information regarding recommended patient monitoring parameters with suggested time intervals for assessments should be presented. Additionally, patient information written in lay terms for the monograph drug should be provided.

Budget Impact: This section should provide a quantitative description of the health system's cost for the new product based on the typical dosage regimen (eg, Q8h × 10 days). The cost per bottle (or package) is not always helpful, because it does not take into account the typical dosage regimen. It is best to provide this data in a tabular format that compares the new product to currently available agents. Additionally, it is helpful to include projected use and how the item will affect the health system's total drug budget.

Summary and Recommendations: The summary should briefly review the pertinent data presented throughout the document including a concise discussion of the drug class and information regarding the efficacy, safety, and cost of the new drug product in comparison to currently available formulary agents. Any important advantages of the

new drug should also be highlighted in this section. Finally, the recommendation should be stated with appropriate rationale. Recommendations for the deletion of alternative agents from the drug formulary should also be included in this section. In some institutions, the summary and recommendation are listed on the front page of the drug evaluation monograph to make it easier for reference and discussion during the Pharmacy and Therapeutics (P&T) Committee meeting.[9]

Authorship: The pharmacist who prepared the monograph should be listed along with the date that the final document was completed. Additionally, pharmacists who served as document reviewers should be listed.

References: All references should be footnoted and listed at the end of the document in the order that they appear within the text. References should be cited using the Uniform Requirements of Manuscripts Submitted to Biomedical Journals.[10]

Some P&T Committees use a one-page summary in lieu of the entire drug evaluation monograph. Pharmacists typically present the summary of the drug evaluation monograph or drug class review verbally during the P&T Committee meeting.[9]

MEDICATION-USE EVALUATION

Medication-use evaluation (MUE) is a continuous improvement method used to evaluate the use of medications within a health system to identify areas for improvement in medication-related outcomes.[8] Medication-use evaluation is frequently completed based upon evidence-based clinical practice guidelines and clinical pathways. In addition, MUE may be based upon approved criteria for use of an individual drug or drugs within a therapeutic class. While MUE is no longer required by regulatory agencies such as the Joint Commission on Accreditation of Healthcare Organizations, it is completed as an ongoing indicator of continuing quality improvement.

There are several key communication issues related to MUE. First, it is imperative that the criteria for MUE are approved by the medical staff and/or any other group of health care providers who are expected to apply the criteria in the care of their patients. Following completion of an MUE, results should be shared through appropriate channels. Within health care organizations, MUE is often a function of the Pharmacy and Therapeutics Committee. The most common communication-related problems in the MUE process generally occur after results have been discussed by the committee. Discussion frequently culminates in recommendations for the improvement of care. These recommendations are often not shared with practitioners, nor is there subsequent assessment to determine the results of the recommended improvements. Thus, the 360-degree cycle associated with study completion and process improvement is not completed, and recommendations for improved care are not implemented. It is essential that the pharmacist assume accountability for completion of this process, in its entirety.

The following sections provide a general template to follow when reporting results of an MUE.

Background: This section should provide background information about why the MUE was conducted. For example, the reason may be that the medication being evaluated has been associated with medication errors, or because the medication may be associated with a serious adverse event. Pertinent literature or national guidelines that support the need for an MUE should also be reviewed. This section should end with a statement describing the primary objective of the MUE.

Methods: A detailed description of exactly how the MUE was conducted should be included. The methods for patient selection, identification, and data collection should be listed; as well as the study time period and sample size. Justification for the selected sample size should be provided. It may be helpful to list the types of data that were collected. For example, if the MUE assessed appropriate use of a particular medication with regards to renal function, serum creatinine would be recorded for all patients.

Results: Detailed results for each type of data that was collected should be presented in a tabular format. The presentation of results should include patient demographics and numerical values for all data.

Summary: The results of the MUE should be briefly summarized, highlighting the most important findings.

Recommendations: Finally, the recommendations to improve medication use should be presented. These should be specific to the health system.

CLINICAL PRACTICE GUIDELINES AND PATHWAYS

Evidence-based clinical practice guidelines have been defined as, "systematically developed statements to assist practitioner and patient decisions about health care for specific circumstances."[11] Guidelines should include specifications for care, which may be disease-based (eg, hypertension, asthma, diabetes) or process-focused (eg, guidelines for the use of serum levels in monitoring aminoglycoside therapy). Clinical pathways reflect the details that support practice guidelines. For example, guidelines which focus on the use of serum levels in monitoring gentamicin therapy might state that patients with an elevated serum creatinine of greater than 2 mg/dL or those receiving daily dosages in excess of 6mg/kg be candidates for serum level monitoring. The corresponding clinical pathway would state the exact manner in which the serum levels should be monitored, such as obtaining the trough level within 30 minutes prior to the infusion of a gentamicin dose, and the peak 30 minutes after the end of a one-half hour infusion.

Clinical practice guidelines and pathways should be specifically and succinctly written, such that there is no confusion regarding the intent of the guideline or the exact process for application of the guideline. Health care organizations with sophisticated information systems (including computer-generated physician order entry) frequently incorporate guidelines and pathways into their software to provide guidance to practitioners in the care of their patients.

DRUG ALERT NOTIFICATIONS

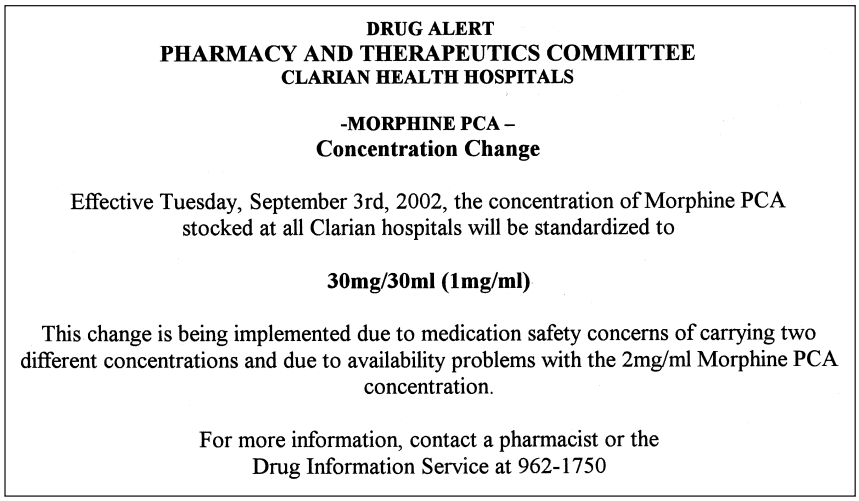
In many cases, there may be situations that require the pharmacy department to alert the medical and nursing staff of an important medication-related issue. Examples requiring drug alert notifications include critical drug product shortages, change in pharmacy procedures, or withdrawal of a drug from the market. Typically, pharmacists are responsible for developing these types of communications. The most effective method is generally the preparation of a one-page communication that clearly states the problem or issue and provides a recommendation for managing the problem. The notification should provide contact information for potential questions or concerns. An example of a drug alert notification is shown in Figure 100-4.

NEWSLETTERS

Most health systems have a pharmacy newsletter that is published on a regular basis to communicate important formulary decisions that have been made by the P&T Committee. As drug therapy specialists, the main writers and editors of pharmacy newsletters are pharmacists. When preparing a pharmacy newsletter the primary factors to consider are the target audience, the primary goal of publication, and professional appearance.[12] The specific format used varies greatly depending on these primary factors. Professional writing strategies will be discussed in detail later in this chapter. Pharmacy newsletters serve a valuable purpose for communicating important information to the medical staff and provide visibility for the pharmacy department.

Writing Manuscripts For Publication

Pharmacists may be involved in writing a wide variety of manuscripts for publication. These include book chapters, editorials, case reports, review articles, and clinical research studies. Publishing these types of manuscripts is essential to enhance communication among peers and advance/promote the



DRUG ALERT
PHARMACY AND THERAPEUTICS COMMITTEE
CLARIAN HEALTH HOSPITALS

-MORPHINE PCA –
Concentration Change

Effective Tuesday, September 3rd, 2002, the concentration of Morphine PCA stocked at all Clarian hospitals will be standardized to

30mg/30ml (1mg/ml)

This change is being implemented due to medication safety concerns of carrying two different concentrations and due to availability problems with the 2mg/ml Morphine PCA concentration.

For more information, contact a pharmacist or the Drug Information Service at 962-1750

Figure 100-4. Example drug alert notification.

profession. Generally, pharmacists are not trained to be writers; for this reason, preparing a manuscript for publication can sometimes appear to be an overwhelming, daunting task. However, publishing is a very fulfilling accomplishment that can lead to professional advancement and recognition.

PREPARATION

Preparation is the first step to any project. Because writing an article for publication is typically a long process, the first hurdle for pharmacists to overcome is the anxiety associated with the project. Because anxiety can sometimes lead to procrastination, it is very important to overcome any apprehensions as soon as possible. A good way to deal with this is to begin the initial preparation process by conducting background research, gathering all necessary resources, and developing an outline for the manuscript.[12] It is also helpful to develop a working plan for completion of the project.[13,14] The writing project should be divided into small sections and attainable deadlines for the completion of each section should be made. Time for working on each section should be planned, similarly to other scheduled daily activities. This strategy can help avoid postponing the writing process due to an already busy schedule.

After all necessary resources have been collected, the items should be organized in a systematic fashion. This will enable the writer to locate references quickly when they are needed during the writing process. This can eliminate frustration and save valuable time later. An outline should also be developed to define the project clearly. When developing an outline, it is best to consider the primary objective of the manuscript and the target audience. Knowing this information will help determine which topics or sections should be included in the manuscript. An effective outline should help make the writing process easier because it determines focus areas. With computer word-processing packages, the outline can be used as a working template for the final manuscript. If the manuscript is intended for a specific medical journal or book, the publishers will customarily have requirements for the various sections that must be included. This will allow organization and provide a framework to follow during the writing process. Many biomedical journals follow *The Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[10] This is a document prepared by a group of editors to provide guidelines for manuscripts that are submitted to medical journals for publication. Table 100-4 lists the general sections that should be included in the publication of a research project.[13]

WRITING THE FIRST DRAFT

Once the outline has been prepared and all information resources have been gathered, the next step is to begin writing. Professional writing is a skill that requires continued practice. Because most pharmacists are not trained writers, this step is often quite difficult. One potential difficulty is finding the time necessary to devote to writing. As stated above, a helpful strategy to manage this problem is to reserve short blocks of time each day that are devoted to writing the manuscript. This approach may be easier for a busy practitioner than to reserve an entire day for completing the project. Progress can be made using short blocks of time, even if the daily goal is to write only one or two paragraphs. During this time, it is helpful to use a technique known as freewriting.[13,14] Freewriting involves taking about 20 to 30 minutes to write your ideas continuously without stopping to check grammar, spelling, or references.[13] Once a few paragraphs have been written in this manner, then content revisions and clarifications can made. In general, is it best to complete a first draft in its entirety before beginning the editing process.[12] However, it is sometimes difficult to avoid becoming engaged in the minor details of correcting grammatical and typographical errors in paragraphs that have already been written. This habit can lead to frustration and slow down the entire writing process. Strategies such as disabling the spelling and grammar check programs of the word-processing program and turning the computer screen off have been recommended to avoid the temptation of making corrections instead of writing new paragraphs.[13,14] Professional writing also follows a certain set of rules that are different from other types of writing.

Table 100-4. Basic Sections of a Research Project Publication[10,13]

Introduction:	Background information to support "why" the project was conducted (written in present tense)
Methods:	Detailed description of all study procedures (written in past tense)
Results:	Detailed description of study findings (written in past tense)
Discussion:	Description of the clinical implications and limitations of the study findings (written present tense)
Conclusions:	A statement of the final conclusions (written in present tense)

General rules for professional writing are listed in Table 100-5.[12] An excellent reference for general stylistic considerations including the rules of proper punctuation and grammar, and avoiding commonly misused words is *The Elements of Style*, written by William Strunk and EB White.[15]

EDITING

After the first draft has been completed, editing is the final critical step. When a manuscript is submitted for publication, or any type of written communication for that matter, it represents an image of the writer. If a written manuscript is full of typographical and grammatical errors, this reflects poorly upon on the author. Because is it sometimes difficult for the author to identify noticeable errors, it is especially useful to ask colleagues to help proofread one's manuscript. Other strategies that have been suggested to aid the editing process include reading sentences out loud slowly, reading sentences in reverse chronological order, and enlarging the font on the computer screen.[13] It is also useful for the author to put the manuscript away from view for several days, and then come back to it at a later date.

REFERENCING

It is very important for authors to be familiar with proper referencing techniques to give credit when appropriate and avoid committing plagiarism. Plagiarism is defined as using the ideas or words of another, in a way that represents them as one's own. Authors should always be vigilant of the potential for plagiarism when writing manuscripts for publication. If copying words verbatim from another authors' work, quotation marks should be used around the material and the appropriate authors should be cited. A good general rule to follow is to use quotation marks around three or more words in a row that are taken directly from a source without modification. If paraphrasing another author, the original publication should always be cited. Specific instructions for citing various types of publications can be found in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*.[10]

Preparing Poster Presentations

Poster presentations are a common method for sharing information at national meetings. At most national pharmacy meetings, there is an opportunity to present research ideas in a poster format. The basic components of a scientific poster are similar to the basic sections of a written research project. These sections include background, methods, results, limitations, and conclusions (see Table 100-4). Posters differ from written manuscripts in the amount of detail presented. With the exception of the background and conclusion sections, posters should not contain full sentences.[16] Information should be presented in at least 18-point font and bullet points and boxes should be used to emphasize the main points. This makes it easier for passersby to read and interpret. There are two different methods to make a poster. The first is to use separate slides (or panels) for each section. This can be done using Microsoft® PowerPoint slides. Alternatively, some word-processing programs allow presenters to make single page posters. These posters still contain different slides for each section, but can be printed as a one-page sheet. This can make the poster easier to transport and arrange at the meeting. The general rules of professional writing discussed above and the importance of proofreading also apply to the preparation of poster presentations. A suggested format for a poster presentation is shown in Figure 100-5.

Written Professional Communication

Given the diverse responsibilities and practice locations of pharmacists, effective written communication is essential. This type of communication encompasses interpersonal interactions among peers and other health care professionals, as well as administrative functions.

ELECTRONIC MAIL

While the introduction of e-mail has greatly facilitated contact and reduced telephone messages for many, this type of communication must be appropriately utilized in the professional environment. Within this environment, e-mail should be for professional use only. Attention should be given to one's chosen e-mail sign-on. If a pharmacist's given name is not utilized for e-mail communication, care should be taken to choose a name that reflects positively on the character of the pharmacist as a professional. Professional e-communication should be utilized in situations where the messenger has concluded that a face-to-face meeting or telephone (ie, direct) communication would not communicate the message more effectively. When communicating by e-mail, it is important to remember that any message may be either saved or forwarded for viewing by others. Accordingly, close attention should be paid to content and format. For example, use of capital letters could be interpreted as "yelling."

The subject line should clarify the intent of the message. The content of messages should be concise but thorough enough to be understood. Given that messages may be printed or shared, one should refrain from including confidential or controversial information. E-mail users are advised to compose professional communications with a word processing program initially, to facilitate spelling and grammar checks. When e-communication is utilized, it is most appropriate to respond within the same business day, but a goal would be to respond in no longer than 24 hours. It is recognized that this may be a challenge, depending on the setting.

MEMORANDA (MEMOS)

Most pharmacists will find a need to communicate with other health care providers via memos, whether or not they have administrative positions. Written memos are frequently used to

Table 100-5. General Rules for Professional Writing

Use proper grammar and spelling
Keep sentences simple and direct
Avoid writing in the first person (eg, I, we, us)
Avoid using the passive voice
Avoid using contractions
Avoid using abbreviations or acronyms
Proofread

Adapted from Malone P. In: Malone PM, Mosdell KW, Kier KL, eds. *Drug Information: A Guide for Pharmacists,* 2nd ed. Stamford, CT: Appleton and Lange, 2001.

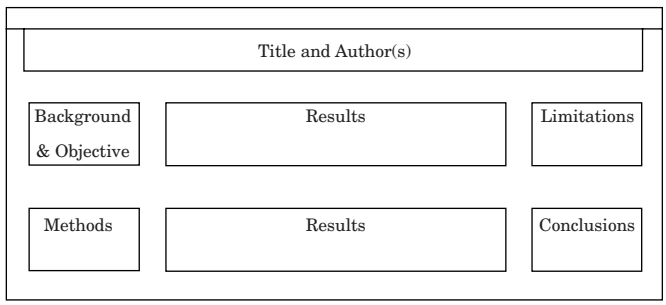


Figure 100-5. Suggested format for poster presentation.

communicate drug information, policy changes, or in the evaluation/discipline of employees. Memos should be formal in format and should be addressed to a specific individual or group of individuals, whenever possible. The format for a professional memorandum is included in Figure 100-6.

COVER LETTERS

Cover letters should accompany applications for employment. As such they offer a written "first impression" to the recipient. Much like e-mail and memos, cover letters should be addressed to a specific individual whenever possible. The cover letter should be written in standard business format, as referenced in any primary or secondary school English text. The first paragraph of the cover letter should include the purpose for writing the letter. For example, the letter may be written to introduce a pharmacist as a candidate for employment. The content would then reflect the pharmacist's background and training and his or her current position. The middle paragraph should contain a brief summary of the key strengths, which make the pharmacist a strong and/or unique candidate for a particular employment opportunity. The last paragraph should close with identification of the mechanism for follow-up. For example, the author may wish to indicate that if the letter recipient does not provide follow-up contact within a two-week time frame, the author will initiate such contact. The letter should also specify the preferred mechanism for contact (eg, e-mail, telephone with specific number).

RESUME

The resume should serve as a one-page summary or snapshot of an individual's education and work experience. Frequently, the resume contains a professional objective, as it is often used to facilitate an employment opportunity. Resumes are designed to highlight professional accomplishments and hopefully entice the recipient to make an offer for an interview. Within today's professional environment, resumes are frequently requested of individuals seeking positions in community pharmacy. Individuals seeking employment within academia, the pharmaceutical industry or hospitals are most frequently requested to submit a curriculum vitae as part of their application package. Figure 100-7 contains an example of potential resume content.

CURRICULUM VITAE

The curriculum vitae is intended to be a comprehensive chronology of the education, training, and work experience which also reflects professional presentations and publications. The health care professional should maintain a curriculum vitae that is inclusive of all types of professional activities. Potential categories for a curriculum vitae are included in Figure 100-8. Some accomplished professionals maintain an abbreviated curriculum vitae that represents the most recent 5 to 10 years of accomplishments.

Date: March 10, 2003

To: Jane A. Doe, PharmD, RPh
Director of Pharmacy

From: Samuel T. Smith, PharmD, RPh
Associate Director of Pharmacy

Re: Staffing Patterns for Outpatient Pharmacy

Figure 100-6. Example of memo header.

Name (centered, top)

Business address — Permanent address (if desired)
Employment objective
Education
Skills
Professional experience (perhaps selected, most relevant)
Other work experience (as applicable)
Activities and honors (most relevant)

Figure 100-7. Content of the resume.

Personnel Communication

Position Description

Pharmacists, particularly those in management positions, are frequently required to write position descriptions for other pharmacists, technicians, and/or other supportive personnel. The position description should delineate the required qualifications, experience, and an overview of job responsibilities. Most position descriptions also include an overview of the required competencies for successful job performance.

The types of positions for which pharmacists might prepare position descriptions include:

Clerical: Individuals who complete tasks including word processing, filing, bookkeeping, and serving as a receptionist.

Service: Individuals involved with equipment and/or building maintenance.

Administrative: Individuals who may complete some clerical functions, with the addition of budgeting/financial management or supervision of clerical staff.

Technical: Individuals involved with product procurement and preparation, along with certain levels of customer interaction

Professional: Including pharmacists, nurses, etc.

Educational requirements may include the ability to read/write English or another language, high school diploma, vocational training, certification, college course work, associate degree, BS degree, advanced degree, or postgraduate training. Required experience should include the number of years and type of experience (ie, directly related to the position). Other related skills might include word processing, accounting, supervision, prescription processing, and perhaps work with automated dispensing systems, to name a few. The position description should include essential duties and the percent of effort that is designated to each duty. Figure 100-9 contains an example position description for a pharmacist.

Name (centered, top)

Business address — Permanent address (if desired)
Education (post high-school, chronological order)
Licensure/certification
Professional experience (list most current first)
Other work experience (as applicable)
Organizational and committee appointments (where applicable)
Affiliations (eg, professional organizations, includes offices held)
Awards/honors
Service (eg, professional, community)
Grants (where applicable)
Presentations
Publications (by category, eg, refereed articles, book chapters)
Date of most recent revision

Figure 100-8. Content of the curriculum vitae.

POSITION DESCRIPTION

AMBULATORY CARE PHARMACIST

PROFESSIONAL PHARMACY SYSTEMS
300 NORTH CARLETON BLVD.
INDIANAPOLIS, IN 44444-4444

Qualifications:

1. Doctor of Pharmacy (PharmD) degree and/or a BS in Pharmacy
2. Minimum of 3 years experience in progressive pharmacy practice
3. Eligibility for and attainment of pharmacy licensure in the State of Indiana
4. Involvement with disease state management programs (eg, diabetes, asthma, hyperlipidemia, anticoagulation) preferred
5. Strong organizational and interpersonal skills
6. Ability to communicate effectively with patients of varying educational backgrounds

Position Responsibilities:

1. Assist with prescription processing and patient education
2. Provide direct disease management services for patients with diabetes, asthma, hyperlipidemia, coagulation disorders
3. Assist in the development and marketing of additional disease management programs to support community-based physician practices
4. Serve as a preceptor for PharmD students completing experiential learning rotations within the practice site

Required Core Competencies:

Knowledge

1. Knowledge of procedures and laws pertaining to the processing and dispensing of prescriptions
2. Knowledge of disease state management including diabetes, asthma, hyperlipidemia, coagulation disorders

Skills

1. Ability to modify disease state recommendations based upon patient lifestyle
2. Ability to individualize education for each patient

Behaviors

1. Monitors indicators of response including disease-based parameters and understanding

Figure 100-9. Example of position description.

2. Provides individualized follow-up for patients to optimize outcomes

It is anticipated that the ambulatory care pharmacist will have responsibilities that mirror the following:

Prescription Processing (50%)

The ambulatory care pharmacist will assist with prescription processing for clinic patients. This activity includes provision of education relative to prescribed therapies and advising patients regarding the appropriate use of over-the-counter and alternative therapies.

Disease State Management (30%)

The ambulatory care pharmacist will provide direct disease state management for patients with asthma, diabetes, hyperlipidemia, and coagulation disorders through established protocols.

Program Development/Marketing (10%)

In conjunction with practice management, the ambulatory care pharmacist will assist with the identification, program development, and marketing of additional disease state management programs.

Experiential Learning (10%)

The ambulatory care pharmacist will assist with supervision of advanced clerkship students from state colleges of pharmacy.

Figure 100-9. *(continued)*

Ambulatory Care Pharmacist Position
Professional Pharmacy Systems
Ambulatory Clinic

Professional Pharmacy Systems invites applications for a full-time pharmacist position in its Indianapolis, Indiana ambulatory clinic site. Applicants should possess a PharmD or BS in pharmacy. Candidates should have a minimum of three years experience in progressive pharmacy practice. Involvement with disease state management programs (eg, diabetes, asthma, hyperlipidemia, anticoagulation) is preferred. The candidate should be able to demonstrate strengths in organization and communication with both patients and other health care professionals. The ability to speak a second language (preferably Spanish) is highly desirable. Salary will be commensurate with qualifications and experience. Review of applications will begin upon receipt and continue until the position is filled. Applicants should send a letter of intent with curriculum vitae and the names and addresses of three references to:

Steven R. Abel, PharmD, FASHP
Pharmacy Director
Professional Pharmacy Systems
300 North Carleton Blvd.
Indianapolis, IN 44444-4444
sabel@professionalpharmacysx.org

Figure 100-10. Example job posting.

JOB POSTINGS

Once a position description has been developed, job postings reflecting abbreviated qualifications and responsibilities for the successful applicant are prepared. Job postings are commonly used to advertise for candidates in local newspapers, professional journals, and/or via the Internet. Position descriptions should include contact information for the individual responsible for recruitment and should also reflect the status of an equal opportunity employer, where applicable. An example position description is included in Figure 100-10.

INTERVIEWING

Interviewing is an essential skill for pharmacists, whether they serve in administrative positions and are responsible for hiring staff that will enhance their services or apply their skills in obtaining a fulfilling professional position. It is important for pharmacists to be aware of the different types of interviews in which they might participate. These include the following:

Structured Interview: An interview that utilizes a predetermined list of questions that are designed to facilitate comparison among the candidates. This format is good for a naive interviewer, because it provides a "script" for the interview process, but it may not offer enough flexibility to allow complete assessment of a candidate's strengths and liabilities.

Unstructured Interview: An interview that is unorganized, spontaneous, and flexible. This format tests the listening skills of the interviewee while challenging the interviewer to remain on task and ascertain pertinent information from the candidate.

Stress Interview: An interview designed to determine the emotional stability of the interviewee. Questions are asked in a direct, sometimes offensive manner in an effort to strike an emotional chord and evaluate the candidate's response.

Behavioral Interview: An interview that is focused on identifying how the interviewee reacted in certain situations. Questions may focus on stressful, frustrating, or positive scenarios. The interviewer asks how the candidate reacted to the scenario, and what they learned or might do differently as a result. The interviewee's past experiences are the focus for specific examples, which offer the interviewer a chance to determine strengths and weaknesses based upon "lessons learned."

Regardless of the interview technique, interviewers and interviewees alike should be prepared to discuss topics including personal interests, education, experience, and career goals. Skills related to interpersonal interactions, communication, and technical/practical competence will also be evaluated. Topics that may not be discussed in an interview are included in Table 100-6.

PERFORMANCE APPRAISAL

Pharmacists will have the responsibility to provide input into or prepare performance appraisals. The primary purpose of the performance appraisal is to enhance employee development. Performance appraisals are also frequently utilized to distribute rewards (eg, salary increases). When communicating with the employee regarding performance, the discussion should focus on four characteristics of good performance criteria. Performance criteria should be achievable, measurable, unbiased, and significant to the work of the individual. It is suggested that performance criteria be developed jointly by the supervisor and employee, including the method for assessment. This approach should make the review process most valuable for the involved parties.

Several general guidelines exist for conducting the appraisal interview. Appraisals should be conducted in a quiet setting that is removed from the general workplace and other employees. The frequency and timing of performance evaluations should be known to the employee. In most settings, evaluations occur on an annual basis (eg, at the end of each year) or on the anniversary of employment. Presentation of the appraisal is critical to its success. Managers should begin their assessment by citing specific examples or instances in which the employee made positive contributions to the site. Criticism is acceptable, but should be offered as opportunities for employee development and should always be presented after at least some positive statements are made. The evaluation should be offered as the manager's interpretation of the available facts. If opportunities for improvement are recommended, these should be delivered in a tactful, but direct manner.

Verbal evaluations should always be supported by paper documentation of performance. The employee and manager should sign the written document. This does not imply that the employee agrees with the assessment, simply that they have read and understand its content. Evaluations should not be changed, but the employee should be offered the opportunity to prepare a written addendum or response that can be appended to the written document and retained in the employee record.

Table 100-6. Inappropriate Interview Topics

Age
Arrest or conviction record
Credit rating
Disabilities
Marital/family status
Military record
Name, national origin, or religion
Request for a photograph

PROGRESSIVE DISCIPLINE

Unfortunately, the process of progressive discipline is a necessary component of most professional work environments. Progressive discipline occurs when there are identified problems with an individual's work habits or performance. There are five steps in the progressive discipline process. The first involves verbal counseling of the employee by the supervisor, with written documentation that the verbal counseling occurred. The written documentation simply serves as a record for the employee's file. The second step in progressive discipline is provision of a written warning. Should performance not improve, there is a follow-up to the written warning issued, which may subsequently lead to suspension and finally discharge. Supervisors should be aware of the process for progressive discipline and should carefully document all events. Without documentation, the poor performer may not be able to be terminated.

When communicating with an employee throughout the progressive discipline process, the supervisor should describe the problem(s) specifically, including the implications of why the problem(s) are of concern to the supervisor and/or within the workplace. The employee should be given a chance to provide his or her explanation, and the supervisor should actively listen during this process. The employee should be asked for input on problem resolution. When completed effectively, the act of progressive discipline should put the onus for improvement on the individual employee. At each step within the progressive discipline process, specific action should be agreed upon, and a date identified for follow-up to review progress. In general, no more than two weeks should pass between discussions. Supervisors should express confidence that the employee can improve, except at discharge. Again, the importance of documentation throughout this process cannot be overemphasized.

POLICIES AND PROCEDURES

Policies and procedures are required in virtually all practice settings. When written properly, policies and procedures should serve as the basis for completion of each function or activity within the workplace. Policies and procedures should be written such that a naive employee should be able to read the policy and procedure and successfully complete a given task. It is virtually impossible for policies and procedures to be too detailed. For example, if a particular task requires use of a com-

puter, the procedure should begin by instructing the participants to turn on the computer using the green switch on the side of the processor. The participant might next be instructed that, once the screen is visible, the cursor should be used to select the appropriate icon for execution of the task, etc. It is common for policies and procedures to be prepared by managers or individuals most familiar with the individual activity. New employees or individuals from other areas within the work environment are frequently utilized to test the depth and detail of written policies and procedures.

COMMUNICATING WITH ADMINISTRATORS

Effective communication with administrators is critical to the success of pharmacists and managers, regardless of the practice setting. It is important to remember that administrators are inundated with information from various sources. Accordingly, communication should be concise and appropriately detailed such that the administrator can effectively understand the situation without being forced to wade through unnecessary paperwork.

Project Proposals

Project proposals require careful thought to detail and are frequently lengthy documents including flow diagrams, policies/procedures, treatment algorithms, etc. Although administrative support is essential to the advancement of any project proposal, it is unrealistic to expect that an administrator will wade through the levels of detail common to most project proposals. Therefore, such proposals should be accompanied by an executive summary that is a maximum of 2 pages in length. The executive summary should enable the administrator to see the "big picture" of the proposal and to refer to the detailed attachments for clarification of key points, without complete review of the proposal. The executive summary should consist of the following subsections (where applicable): goal, target market, required equipment, market research information, action plan, and conclusion.

Presentation of Data

The most common method of sharing data is through presentation of information in tabular format. Unfortunately, this method does not allow the recipient to compare and contrast data for trends, key points, etc. quickly. Alternative methods of data presentation are often overlooked, although they have the potential to augment significantly the display and communicate the intended message more effectively.

For example, line charts, including run and control charts, display discreet data points over time. Bar charts are utilized to compare items. Column charts assist with display of data over time (eg, annual pharmacy expenses 1998–2003). Pie charts, which are commonly utilized display a comparison, but really show the components of a whole at some point of time (eg, static data). Dot charts facilitate evaluation of a relationship between two variables, such as the correlation of years of pharmacy practice experience with a lower incidence of medication errors. An example of the use of a bar chart *versus* a table to display data is included in Figure 100-11.[17]

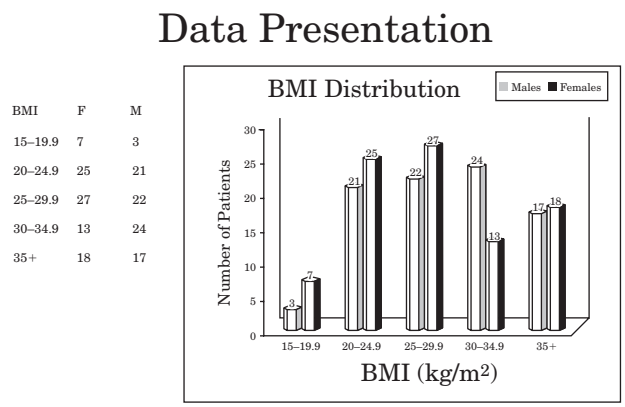


Figure 100-11. Use of a bar chart versus a table to display data.

COMMUNICATING WITH THE MEDIA

In the current information age, public demand for health-related news is greater than ever before. As a result, there is also an increased need for the expertise of health care professionals to help communicate this information accurately. Pharmacists, as drug therapy specialists, are often asked to provide information to the media about drug-related safety and efficacy. Media interviews may be conducted in a face-to-face manner, as the case with television interviews, or via the telephone or e-mail, as in cases of written publications such as newspapers or magazines. Although communication with the media can be very challenging, it is important for pharmacists to communicate accurate information using an effective style and to represent the profession of pharmacy in a positive manner.

Collecting Background Information

When contacted for a potential media interview, the first step is to collect background information before agreeing to an interview. If contacted directly by a journalist, it is best to avoid the urge to respond to his or her questions immediately. General information should be gathered about the nature of the interview such as the name and affiliation of the reporter, the type of interview (eg, television, radio, telephone), when and where the interview will take place, the types of questions that will be asked, and the target audience.[18] This will help the pharmacist determine if he or she is the most qualified person to respond to the reporter's inquiries. For example, if the reporter is asking a policy question, it may be best to defer the questions to an appropriate administrator. Most institutions have a pubic relations department that is responsible for screening requests for media interviews and contacting the most qualified individual to respond. This department should be contacted prior to any media interaction.

Preparation

Once the context of the interview is understood, the next step is to prepare. Although time may be limited, effective preparation is one of the most critical steps to successful communication with the media.[18] As a general rule, it is best to avoid answering impromptu questions without first doing some homework. This is especially the case when pharmacists are responding to the mass media. It is often necessary to gather or confirm the facts and to consult with colleagues before formulating a response to media questions. This helps to ensure that accurate and up-to-date information is communicated.

After sufficient research has been conducted, the pharmacist should determine the major message that they wish to convey.[18] Depending on the situation, there may be more than one message a pharmacist wishes to communicate. During preparation, it is helpful to write down the major message and

list key talking points under each message. Key talking points should include the relevant facts, statistics, or supporting details.[18] This will help refine the major message to only the most important pieces of information. Preparing in this manner is particularly important, because most media interviews are conducted during a very short period of time. There simply may not be enough time for the pharmacist to communicate all of the pertinent details. Therefore, preparing a major message with supporting talking points can make a huge difference in delivery during the interview. If the pharmacist is not appropriately prepared, he or she may run out of time and not be able to communicate the most important facts. In addition, pharmacists should consider the characteristics of the target audience when developing the major message and key talking points; this will help to make sure they are providing relevant information at an appropriate level of understanding.[18] Being organized and prepared is the key to successfully communicating an important message in a clear and concise manner.

Delivery of the Message

Delivery is critical during a media interview. The same concepts that apply when delivering formal presentations should be considered when communicating during a media interview. These include using an open body position, maintaining eye contact with the reporter, using vocal inflections and pauses to emphasize key talking points, exhibiting confidence, and using a relaxed and steady pace.[18] If being interviewed over the telephone, many of these same principles apply. Pharmacists should be aware that interviewers most likely will quote statements that are made. Therefore, it is important to speak is a manner that is both professional and quotable. Pharmacists should never make statements that they do not want to read in print because reporters are not required to respect the statement "this is off the record."[18] If interviewing for information that will be presented in a printed article, it is good practice to request permission to review the article to make any necessary corrections prior to publication.

SUMMARY AND CONCLUSION

Communication is a vital skill for pharmacists, which is utilized multiple times each day, regardless of practice setting. This chapter provides a broad overview of the most common types of written and verbal communication skills that are necessary for successful pharmacists.

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