CHAPTER 1

Scope of Pharmacy

Joseph L Fink III, BS Pharm, JD

Pharmacy is the art and science of preparing and dispensing medications and the provision of drug-related information to the public. It involves the interpretation of prescription orders; the compounding, labeling, and dispensing of drugs and devices; drug product selection and drug utilization reviews; patient monitoring and intervention; and the provision of cognitive services related to use of medications and devices. The American Pharmacists Association describes the mission of pharmacy as serving society as "the profession responsible for the appropriate use of medications, devices, and services to achieve optimal therapeutic outcomes." The Report of the Commission of Pharmacy, *Pharmacists for the Future* (often referred to as the Millis Report), states that "pharmacy should be conceived basically as a knowledge system that renders a health service by concerning itself with understanding drugs and their effects." Thus, pharmaceutical care is a necessary element of total health care.

The current philosophy or approach to professional practice in pharmacy is designated as *pharmaceutical care.* This concept holds that the important role of the pharmacist is "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." Pharmacists, then, are those who are educated and licensed to dispense drugs and to provide drug information—they are experts on medications. They are the most accessible member of today's health care team, and often are the first source of assistance and advice on many common ailments and health care matters.

EDUCATION

There is currently one professional degree in pharmacy: the doctorate (PharmD). The PharmD curriculum usually requires 6 academic years to complete the degree requirements. Pharmacists who hold the baccalaureate in pharmacy degree (BSPharm or BPharm) may be admitted to a doctor of pharmacy program, in which instance the combined period of study may be longer than 6 academic years. There are 87 colleges and schools of pharmacy in the United States (see www.aacp.org).

In 1992, the American Association of Colleges of Pharmacy (AACP) house of delegates voted "to support a single entry-level educational program at the doctoral level (PharmD)." The vote of the deans and faculty delegates affirmed their support of an entry-level program of at least 6 years. Perhaps even more importantly, the Accreditation Council for Pharmaceutical Education (ACPE), the national organization that accredits professional degree programs in pharmacy, has adopted that position as well. The transition from a two-degree approach (BSPharm and PharmD) to the current sole degree is now complete.

GENERAL EDUCATION—Courses in the social sciences, humanities, arts, history, and literature provide the broad general education required of a professional in today's society.

PREREQUISITE COURSES—Mathematics and the physical and biological sciences teach the principles, the application of which find their way into many of the upper-level professional pharmacy courses.

PROFESSIONAL COURSES—Basic to most pharmacy curricula are courses in pharmacology, medicinal chemistry, pharmaceutics, biopharmaceutics, and the clinical-pharmacy externships. Courses in social and administrative pharmacy as well as pharmacy law also are found in this sequence.

Opportunities for students to specialize or minor in certain professional areas have become more available and increasingly popular. Most prominent are hospital/institutional pharmacy, nuclear pharmacy, management, and various research specialties.

LICENSURE REQUIREMENTS

The practice of pharmacy in any given state is regulated by that state and the Board of Pharmacy within that state. The law in all states, including the District of Columbia and Puerto Rico, requires applicants for licensure to be of good moral character; have graduated from an Accreditation Council for Pharmaceutical Education (ACPE) accredited first professional degree program; have passed an examination given by the Board of Pharmacy; and be 21 years of age.

All states require that candidates for licensure have a record of practical experience or internship training acquired under the supervision and instruction of a licensed practitioner. Some jurisdictions grant licensure by licensure transfer, known colloquially as reciprocity. Requirements vary from state to state.

The vast majority of jurisdictions have established continuing education/competency requirements for relicensure. The types of programs that are recognized and the prescribed range of acceptable content matter are fairly uniform. The ACPE also has responsibility for accrediting providers of professional continuing education programming.

A list of the governmental agencies that license pharmacists in the various states is available from the National Association of Boards of Pharmacy, 700 Busse Highway, Park Ridge, IL 60068-2402 (see www.nabp.org).

CAREERS

Job opportunities for pharmacists are expected to grow about as fast as the average for all occupations, mainly due to the increased pharmaceutical needs of a larger and older population. Other factors likely to increase demand for pharmacists include the likelihood of scientific advances that will provide more drug products for the prevention, diagnosis, and treatment of dis-

ease; new developments in administering medication; and increasingly well-informed consumers who are sophisticated about health care and eager for more detailed information about drugs and their effects.

Community pharmacy is a hybrid requiring well-developed professional skills and, in many cases, management abilities. In addition to dispensing pharmaceuticals, pharmacists in community pharmacies answer questions about prescription and over-the-counter (OTC) drugs and give advice about home health care supplies and durable medical equipment. Of an estimated 200,000 pharmacists now in practice, the majority are in community pharmacy practice (see Chapter 4).

Health-systems pharmacy is the practice of pharmacy in private and government-owned hospitals, health maintenance organizations (HMOs), clinics, walk-in health centers, and nursing homes. This has become a significant setting for pharmacy practice over the past 50 years or so. In these settings, pharmacists dispense medication, prepare sterile solutions, advise other professionals and patients on the use of drugs, monitor drug regimens, and evaluate drug use. They advise other professionals on the selection and effects of drugs and, in some cases, make patient rounds with them or provide direct patient care (see Chapters 123, 127, and 129).

Nuclear pharmacy applies the principles and practices of pharmacy and nuclear chemistry to produce radioactive drugs used for diagnosis and therapy (see Chapters 29 and 106).

Industrial pharmacy offers opportunities to pharmacists of all educational levels. The largest number of pharmacists are involved in marketing and administration. Some pharmaceutical manufacturers employ pharmacists as their professional service representatives, to educate physicians and pharmacists about the manufacturer's products. This can be a rewarding career for persons with the right personality and motivation, and it is often a stepping-stone to supervisory positions in sales and a path toward integration into the administrative and sales structure of a pharmaceutical firm. Pharmacists with master's degrees in business or additional degrees in law find additional opportunities in the pharmaceutical industry in the marketing, sales, and legal departments. Pharmacists can also serve the industry as professional communications managers and clinical research scientists; research and development personnel often have advanced degrees, although this is not always the case. Production and quality-control (or quality-assurance) supervisory positions often are held by pharmacists (see Chapters 5 and 10).

Government service offers opportunities to pharmacists in various capacities. They may serve as noncommissioned or commissioned officers in the Army, Navy, Air Force, and Coast Guard. They also serve as commissioned officers in the United States Public Health Service, which furnishes pharmacists for the Food and Drug Administration, Bureau of Prisons, and the Indian Health Service. Appointments are available for pharmacists in the Drug Enforcement Administration of the Department of Justice, and in the National Institutes of Health, the Center for Medicare and Medicaid Services, the Health Resources and Services Administration, and various other agencies (see Chapter 6).

Pharmaceutical education offers opportunities to pharmacists with advanced degrees in any of the professional specialties. Expanding enrollments and changes in the curricula at colleges to meet the employment needs of the future result in an increased need for college-level instructors. Potentially higher salaries, more freedom for research and writing, independence of action, and the cultural surroundings in pharmaceutical education make teaching attractive.

Pharmaceutical journalism offers rewarding experiences for a limited number of pharmacists with writing and editing skills.

Organizational management careers are available for those with pharmacy education who wish to serve in national and state associations and on boards of pharmacy. The increasing number of pharmacists and the interface of pharmacy with insurance carriers and health and welfare agencies mean the responsibilities of associations and boards must expand accordingly, and be complicated by the greater involvement of state and federal governments in health care. Thus, pharmacists who have organizational interests and talents will be in great demand and will play important roles in the future of pharmacy in the United States.

GRADUATE EDUCATION

Areas of graduate study include pharmaceutics, industrial pharmacy, pharmacology, pharmaceutical/medicinal chemistry, pharmacognosy, and social and administrative pharmacy. A master's or PhD degree in pharmacy or a related field usually is required for research positions (Chapter 10), and a PharmD, MS, or PhD degree is necessary for administrative or faculty positions.

Although a number of graduates pursue advanced degrees in pharmacy, some enter a 1- or 2-year residency program or fellowship. A pharmacy residency is an organized, directed, postgraduate training program in a defined area of pharmacy practice.

ORGANIZATIONS

AMERICAN PHARMACISTS ASSOCIATION (APhA)—The APhA is the national professional organization of pharmacists representing pharmacy practitioners, and pharmaceutical scientists and students. Since its founding in 1852, APhA has been a leader in the professional and scientific advancement of pharmacy. Membership in one of the three academies of the APhA—the Academy of Pharmacy Practice and Management (APPM), the Academy of Pharmaceutical Research and Science (APRS), and the Academy of Students of Pharmacy (ASP)—offers members specialized benefits and the opportunity to influence their practice areas.

AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS (ASHP)—The ASHP is the professional association of pharmacists who practice in organized health care settings. The ASHP endeavors to create an environment in which pharmacists can focus the full potential of their knowledge and expertise on patient care. The mission of ASHP is to represent its more than 25,000 members, providing leadership that will enable pharmacists in organized health-care settings to provide high-quality pharmaceutical services that foster the efficacy, safety, and cost-effectiveness of drug use; contribute to programs and services that emphasize the health needs of the public and the prevention of disease; and promote pharmacy as an essential component of the health care team.

AMERICAN SOCIETY OF CONSULTANT PHARMACISTS (ASCP)—The ASCP promotes the development and advancement of pharmaceutical care activities directed at patients in long-term care institutions.

NATIONAL COMMUNITY PHARMACISTS ASSOCIATION (NCPA)—Membership in NCPA, formerly known as the National Association of Retail Druggists (NARD), is open to independent community pharmacy owners, managers, and employees, as well as pharmacy students and corporations. NCPA is dedicated to the continuing growth and prosperity of the independent community pharmacy in the United States.

AMERICAN ASSOCIATION OF PHARMACEUTICAL SCIENTISTS (AAPS)—The AAPS serves an advocacy role for the pharmaceutical sciences, promotes the economic viability of the pharmaceutical sciences and its scientists, and represents scientific interests within academia, industry, government, and other research institutions. AAPS members are eligible for membership in one of several disciplinary sections: Analysis and Pharmaceutical Quality; Biotechnology; Clinical Sciences; Economic, Marketing, and Management Sciences; Medicinal and Natural Products Chemistry; Pharmaceutical Technology; Pharmaceutics and Drug Delivery; Pharmacokinetics, Pharmacodynamics, and Drug Metabolism; and Regulatory Affairs.

PHARMACY PROFESSIONAL DEGREE PROGRAMS

The following colleges and schools offering professional degree programs in pharmacy hold membership in the AACP.

Alabama	Auburn University, Harrison School of Pharmacy, Auburn University, AL 36849
	Samford University, McWhorter School of Pharmacy, Birmingham, AL 35229
Arizona	Midwestern University, College of Pharmacy-Glendale, Glendale, AZ 85308
	University of Arizona, College of Pharmacy, Tucson, AZ 85721
Arkansas	University of Arkansas for Medical Sciences, College of Pharmacy, Little Rock, AR 72205
California	University of California, San Francisco, School of Pharmacy, San Francisco, CA 94143
	University of the Pacific, Thomas J. Long School of Pharmacy and Health Sciences, Stockton, CA 95211
	University of Southern California, School of Pharmacy, Los Angeles, CA 90089
	Western University of the Health Sciences, College of Pharmacy, Pomona, CA 91766
	Loma Linda University, School of Pharmacy, Loma Linda, CA 92350
	University of California, San Diego, School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA 92093
Colorado	University of Colorado, Health Sciences Center, School of Pharmacy, Denver, CO 80262
Connecticut	University of Connecticut, School of Pharmacy, Storrs, CT 06269
District of Columbia	Howard University, College of Pharmacy, Nursing and Allied Health Sciences, Washington, DC 20059
Florida	Florida Agricultural and Mechanical University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307
	Nova Southeastern University, College of Pharmacy, Fort Lauderdale, FL 33328
	Palm Beach Atlantic University, School of Pharmacy, West Palm Beach, FL 33416
	University of Florida, College of Pharmacy, Gainesville, FL 32610
Georgia	Mercer University, Southern School of Pharmacy, Atlanta, GA 30341
	University of Georgia, College of Pharmacy, Athens, GA 30602
Idaho	Idaho State University, College of Pharmacy, Pocatello, ID 83209
Illinois	Midwestern University, Chicago College of Pharmacy, Downers Grove, IL 60515
	University of Illinois at Chicago, College of Pharmacy, Chicago, IL 60612
Indiana	Butler University, College of Pharmacy and Health Sciences, Indianapolis, IN 46208
	Purdue University School of Pharmacy and Pharmacal Sciences, West Lafayette, IN 47907
Iowa	Drake University, College of Pharmacy and Health Sciences, Des Moines, IA 50311
	University of Iowa, College of Pharmacy, Iowa City, IA 52242
Kansas	University of Kansas, School of Pharmacy, Lawrence, KS 66045
Kentucky	University of Kentucky, College of Pharmacy, Lexington, KY 40536
Louisiana	University of Louisiana at Monroe, School of Pharmacy, Monroe, LA 71209
	Xavier University of Louisiana, College of Pharmacy, New Orleans, LA 70125
Maryland	University of Maryland, School of Pharmacy, Baltimore, MD 21201
Massachusetts	Massachusetts College of Pharmacy and Health Sciences-Boston Campus, Boston, MA 02115
	Massachusetts College of Pharmacy and Health Sciences-Worcester Campus, Worcester, MA 01610
	Northeastern University, School of Pharmacy, Boston, MA 02115
Michigan	Ferris State University, College of Pharmacy, Big Rapids, MI 49307
	University of Michigan, College of Pharmacy, Ann Arbor, MI 48109
	Wayne State University, Eugene Applebaum College of Pharmacy and Health Sciences, Detroit, MI 48202
Minnesota	University of Minnesota, College of Pharmacy, Minneapolis, MN 55455
Mississippi	University of Mississippi, School of Pharmacy, University, MS 38655
Missouri	St Louis College of Pharmacy, St Louis, MO 63110
	University of Missouri-Kansas City, School of Pharmacy, Kansas City, MO 64110
Montana	University of Montana, School of Pharmacy and Allied Health Sciences, Missoula, MT 59812
Nebraska	Creighton University, School of Pharmacy and Health Professions, Omaha, NE 68178
	University of Nebraska Medical Center, College of Pharmacy, Omaha, NE 68198
Nevada	University of Southern Nevada, Henderson, NV 89014
New Jersey	Rutgers, the State University of New Jersey, Ernest Mario College of Pharmacy, Piscataway, NJ 08854
New Mexico	University of New Mexico, College of Pharmacy, Albuquerque, NM 87131
New York	Union University, Albany College of Pharmacy, Albany, NY 12208
	Long Island University, Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Brooklyn, NY 11201
	St John's University, College of Pharmacy and Allied Health Professions, Jamaica, NY 11439
	State University of New York at Buffalo, School of Pharmacy and Pharmaceutical Sciences, Amherst, NY 14260
North Carolina	Campbell University, School of Pharmacy, Buies Creek, NC 27506
	University of North Carolina at Chapel Hill, School of Pharmacy, Chapel Hill, NC 27599
North Dakota	North Dakota State University, College of Pharmacy, Fargo, ND 58105
Ohio	Ohio Northern University, R.H. Raabe College of Pharmacy, Ada, OH 45810
	The Ohio State University, College of Pharmacy, Columbus, OH 43210
	University of Cincinnati, College of Pharmacy, Cincinnati, OH 45267
	University of Toledo, College of Pharmacy, Toledo, OH 43606
Oklahoma	Southwestern Oklahoma State University, School of Pharmacy, Weatherford, OK 73096
	University of Oklahoma, College of Pharmacy, Oklahoma City, OK 73190
Oregon	Oregon State University, College of Pharmacy, Corvallis, OR 97331
Pennsylvania	Duquesne University, Mylan School of Pharmacy, Pittsburgh, PA 15282
	Lake Erie College of Osteopathic Medicine, School of Pharmacy, Erie, PA 16509
	Temple University, School of Pharmacy, Philadelphia, PA 19140
	University of Pittsburgh, School of Pharmacy, Pittsburgh, PA 15261
	University of the Sciences in Philadelphia, Philadelphia College of Pharmacy, Philadelphia, PA 19104
	Wilkes University, Nesbitt School of Pharmacy, Wilkes-Barre, PA 18766
Puerto Rico	University of Puerto Rico, School of Pharmacy, San Juan, PR 00936

Rhode Island	University of Rhode Island, College of Pharmacy, Kingston, RI 02881
South Carolina	Medical University of South Carolina, College of Pharmacy, Charleston, SC 29425
	University of South Carolina, College of Pharmacy, Columbia, SC 29208
South Dakota	South Dakota State University, College of Pharmacy, Brookings, SD 57007
Tennessee	University of Tennessee, Memphis, College of Pharmacy, Memphis, TN 38163
Texas	Texas Southern University, College of Pharmacy and Health Sciences, Houston, TX 77004
	Texas Tech University Health Sciences Center, School of Pharmacy, Amarillo, TX 79106
	University of Houston, College of Pharmacy, Houston, TX 77204
	The University of Texas at Austin, College of Pharmacy, Austin, TX 78712
Utah	University of Utah, College of Pharmacy, Salt Lake City, UT 84112
Virginia	Hampton University, School of Pharmacy, Hampton, VA 23668
	Shenandoah University, Bernard J Dunn School of Pharmacy, Winchester, VA 22601
	Virginia Commonwealth University, School of Pharmacy, Richmond, VA 23298
Washington	University of Washington, School of Pharmacy, Seattle, WA 98195
	Washington State University, College of Pharmacy, Pullman, WA 99164
West Virginia	West Virginia University, School of Pharmacy, Morgantown, WV 26506
Wisconsin	University of Wisconsin-Madison, School of Pharmacy, Madison, WI 53705
Wyoming	University of Wyoming, School of Pharmacy, Laramie, WY 82071

CHAPTER 2

Evolution of Pharmacy

Gregory J Higby, PhD

THE DRUG-TAKING ANIMAL

Among the several characteristics unique to *Homo sapiens* is our propensity to treat ailments, physical and mental, with medicines. From archeological evidence, this urge to soothe the burdens of disease is as old as humanity's search for other tools. Like the nodules of flint used to make knives and axes, medicines rarely occur in nature in their most useful (or palatable) form. First, the active ingredients or *drugs* must be collected, processed, and prepared for incorporation into medicaments. This activity, done since the dawn of humanity, is still the central focus of the practice of *pharmacy*. Put another way, pharmacy is, and has been, the art (and later science) of fashioning one of our most important tools—medicines.

For today's pharmacists it is imperative that this deep-seated role of medicines in human history is understood. As with other tools, drugs have been used to gain increased control over our lives, to make them better and longer. Over the millennia the understanding of how drugs work has changed dramatically, in part influencing how they are used (and abused). As is often the case with knowledge, however, common wisdom about medicines is a mixture of myth and science, folklore, and demonstrated fact. Old ideas meld with new concepts to produce a faulty jumble that can lead patients into trouble.

A basic introduction to the development of ideas concerning drugs, as well as the evolution of the profession, increases the ability of pharmacists to adjust to the challenges presented as our professional roles expand. As the dispensers of medicine, we have much to gain from a basic appreciation of the complex role that drugs and medicines have played in the past and of pharmacy's part in this development.

A complete world history of how increased drug knowledge, medical progress, commerce, technology, and professional development came together to produce modern pharmacy would fill this entire volume. Instead, this short chapter will tell two parallel stories: how the concept of *drug* evolved over time and how a separate profession arose to prepare drugs into medicines in the West.

Throughout history, drugs have held a special fascination. Beyond the sensational stories of the part drugs have played in exploration, commerce, political intrigue, scientific discovery, and the arts, they have directly influenced the lives of millions. Drugs such as insulin have kept thousands alive, and antibiotics and chemotherapeutic agents have saved thousands more. The simple fact that all medicines become useful through pharmacy bears repeating, and the safe and effective use of such medicines has developed recently into a primary concern for this relatively young profession. Although pharmacy as a skill is perhaps as old as the making of stone implements, the practice of this singular art by a recognized specialist is only about 1000 years old. For this specialization to occur a need had to arise—but that is getting a bit ahead of the story.

PREHISTORIC PHARMACY

Since humanity's earliest past, pharmacy has been a part of everyday life. Excavations of some of mankind's oldest settlements, such as Shanidar (*ca* 30,000 BCE), support the contention that prehistoric peoples gathered plants for medicinal purposes. By trial and error, the folk knowledge of the healing properties of certain natural substances grew. Although tribal healers or *shamans* often guarded this healing knowledge closely, the recognition of medicinal plants, which were sometimes used as food, spices, or charms, apparently was so widespread that it hindered any necessity for a special class of drug gatherers and keepers. The arts of primitive pharmacy probably were mastered by all who practiced the domestic medicine of the household.

When healers at Shanidar or other prehistoric settlements approached disease, they placed it within the context of their general understanding of the world around them, which was alive with good and evil spirits. Early peoples explained illness in supernatural terms, as they did the other changes and disasters surrounding them. Treatments followed suit, in that beneficial medicines worked through supernatural means. The spells of sorcerers, sometimes cast with the aid of magical substances, could be combated with the same remedies.

The magical potions for curing were part of the duty of the shaman. Usually in charge of all or most things supernatural in a tribe, the shaman diagnosed and treated most serious or chronic illness. He or she compounded the remedies needed to stave off the influences of evil spells or spirits. This basic pattern, common among ancient peoples, held sway over nearly all of the span of human existence. The substances of healing potions, connected for thousands of years with the supernatural world, continue to hold a special place, a fascination for all. Thus, out of these origins a dual heritage has been derived: drugs as both simple tools and special substances with nearly supernatural powers.

The discovery that certain natural substances could ease the suffering of human existence, however, should not be trivialized. Even though early peoples discovered only a small number of effective drugs, the very concept of influencing bodily functions via an outside force must be considered one of humanity's greatest advances. The further development of this concept required the environment of civilization. To flourish, rational medical therapy needed the tools provided by settled cultures—writing, systems of exchange, and weights and measures. Contemporary

tribal peoples such as the Tasaday demonstrate that, without the more advanced tools, pharmaceutical practices fail to progress.

ANTIQUITY

When organized settlements arose in the great fertile valleys of the Nile, the Tigris and Euphrates, the Yellow and Yangtze, and the Indus Rivers, changes occurred that gradually influenced the concepts of disease and healing. As men and women learned how to control aspects of nature through farming, permanent shelter, and large-scale building projects, the powers of the gods in day-to-day life started to decline. These changes are evident among the remains of the great civilizations of Mesopotamia and Egypt of the second millennium BCE, whose clay tablets and papyri document the beginnings of rational drug use in the West.

An examination of these ancient records reveals a gradual separation of empirical healing (based on experience) from the purely spiritual. For the Babylonians, medical care was provided by two classes of practitioners: the *asipu* (magical healer) and the *asu* (empirical healer). The *asipu* relied more heavily on spells and used magical stones far more than plant materials; the *asu* drew upon a large collection of drugs and manipulated them into several dosage forms that are still basic today, such as suppositories, pills, washes, enemas, and ointments. The *asipu* and the *asu* were not in direct competition and sometimes cooperated on difficult cases. Apparently the ill often went back and forth between the two types of healers looking for a cure.

The extensive records that survive of Egyptian medical practices demonstrate even greater pharmaceutical sophistication, with more dosage forms compounded from more detailed formulas. The Egyptian medical texts, like those from Babylon, show a close connection between supernatural and empirical healing. Suggested recipes usually began with a prayer or incantation. Plant drugs, of which laxatives and enemas were the most prominent, were the main vehicle of healing power. As was the case with healing practices in Mesopotamia, certain individuals specialized in the preparation and sale of drugs. Were these early medicine makers the forebears of today's pharmacists? No, because physicians and other healers again took on the duties of medicine preparation as these two great river civilizations declined. A fully separate pharmaceutical calling would be centuries away.

During the millennium that followed, the roots of the modern medical profession in the West arose out of the flowering of Greek civilization in the basin of the Aegean Sea. In the earliest records of ancient Greece, one finds a similar mixed concept of drug or *pharmakon,* a word that meant magic spell, remedy, or poison. In the *Odyssey,* Homer (*ca* 800 BCE) refers to the esteemed medical wisdom of Egypt, thus illustrating the ebb and flow of ancient knowledge long before the printed word. The early Greek physicians described by Homer, the *demiourgoi,* had advanced to where they diagnosed *natural* causes for illness, while still not rejecting the use of supernatural healing in conjunction with empirical remedies. Some people beset with persistent afflictions traveled to a temple of the god Asklepios, where they would sleep with the hope of being visited during the night by the god or his daughter Hygeia, who carried a magical serpent and a bowl of healing medicine.

The rational tradition within Greek medicine that was evident in Homer's work was refined and codified in the body of literature connected with the name of Hippocrates of Cos (*ca* 425 BCE). Building on the foundations laid by previous natural philosophers such as Thales (*ca* 590 BCE), Anaximander (*ca* 550 BCE), Parmenides (*ca* 470 BCE), and Empedocles (*ca* 450 BCE), the Hippocratic writers constructed a rational explanation of illness. They accomplished this by forging a conceptual link between the environment and humanity by connecting the four elements of earth, air, fire, and water to four governing humors of the body: black bile, blood, yellow bile, and phlegm. The trained Greek physician (*iatros*) who followed the Hippocratic method favored dietary and life-style adjustments over drug use. If these conservative methods failed, the Greek physician prepared his own medicines or left prescriptions behind for family members to compound and administer.

Most Greek medicines were prepared from plants, and the first great study of plants in the West was accomplished by Theophrastus (*ca* 370–285 BCE), a student of Aristotle. His example of combining information from scholars, midwives, root diggers, and traveling physicians was emulated 300 years later by Dioscorides (*ca* 65 AD). The latter Greek physician's summary of the drug lore of his times, the *Materia Medica,* became, in its various forms, the standard encyclopedia of drugs for hundreds of years to follow.

Through the teachings and writings of Galen, a Greek physician who practiced in Rome in the 2nd century AD, the humoral system of medicine gained ascendancy for the next 1500 years. Setting aside the conservative drug use of the orthodox Hippocratists, Galen devised an elaborate system that attempted to balance the humors of an ill individual by using drugs of a supposedly contrary nature. For example, to treat an external inflammation, a follower of Galen might apply cucumber, a cool and wet drug. The same Galenist also might have tried bleeding, a favorite treatment to remove the apparent excess of blood that caused the illness. In addition to the questionable practice of bleeding, Galen advocated the use of polypharmaceutical preparations (what would be termed "shotgun prescriptions" today). He argued that the patient's body would pull out of a complex prescription the substances that it needed to restore its humoral balance.

Medicine in classic antiquity reached its pinnacle with Galen, and the writers who followed tended to be compilers and commentators on his work, not original thinkers. Galen's influence was so pervasive among medical practitioners that the basics of his healing approach—the balance of the body's four humors through contrary drugs—mixed with folklore and superstition to guide common people in their own treatment of ailments. In the Western half of the Roman Empire, such medical knowledge became especially valuable as civilization crumbled in the years following 400 AD.

THE MIDDLE AGES

Traditionally, the Middle Ages are defined as the period from the first fall of Rome (*ca* 400 AD) to the fall of Constantinople (1453). The first half of this millennium was once referred to as the "Dark Ages" by historians because of the political and social chaos that existed in the lands that had once been part of the western half of the Roman Empire. Modern historians have revealed, however, that many advances were made during the centuries between 400 and 900 AD, including a new, independent calling that emerged out of the flourishing Islamic civilization—pharmacy.

The story of how Greco-Roman philosophy, science, and art returned to western Europe and sparked the creative period known as the Renaissance is one of the most fascinating of human history. It began with the crumbling of civil authority in the western half of the Roman Empire during the 4th and 5th centuries. Greco-Roman culture survived in the Eastern (Byzantine) half of the empire, but with considerably less creative energy. With Roman authority gone in the West, the Church became the stabilizing cultural force, and local feudalism arose to replace centralized government.

The use of drugs to treat illness underwent another shift, as pagan temples, some of which had operated in conjunction with Greco-Roman healing methods, were closed. Rational drug therapy declined in the West, to be replaced by the Church's teaching that sin and disease were related intimately. The cult surrounding the healing saints of Cosmas and Damian exemplifies this attitude. Monasteries became centers for healing, both spiritual and corporal, because the two were not viewed as

essentially separate. Cast to their own devices, monks put together their own short versions of classical medical texts (epitomes) and planted gardens to grow the medicinal herbs that were no longer available after the collapse of trade and commerce. Strong in their faith, these amateur healers tended to ascribe their cures to the will of God, rather than to their meager medical resources.

As Western Europe struggled, a new civilization arose among those who followed the teachings of Mohammed (570–632). The formerly nomadic peoples who united into the nations of Islam conquered huge areas of the Middle East and Africa, eventually expanding into Spain, Sicily, and Eastern Europe. Because their faith taught them to respect the written word and those who studied it, they tolerated the scholarship of the Christian sectarians who had fled persecution in the Eastern Roman Empire; the Nestorians, for example, established a famous school in Gondeshapur in the 6th century.

Among the Islamic nations, Greek writings, including those dealing with medicine, were translated into Arabic. At first the Arabs accepted the authority of Greek medical writings totally, especially those of Galen and Dioscorides. But as their sophistication grew, Islamic medical men like Rhazes (860–932) and Avicenna (980–1063) added to the writings of the Greeks. The far-flung trading outposts of the conquering Arabs also brought new drugs and spices to the centers of learning. Moreover, Arab physicians rejected the old idea that foul-tasting medicines worked best. Instead, they devoted a great deal of effort to making their dosage forms elegant and palatable, through the silvering and gilding of pills and the use of syrups.

The new, more sophisticated medicines required elaborate preparation. In the cosmopolitan city of Baghdad of the 9th century, this work was taken over by specialists, the occupational ancestors of today's pharmacists. In places such as Spain and southern Italy where the Islamic world interacted most with recovering western Europe, several of the institutions and developments of the more highly developed Arabic culture—such as the separation of pharmacy and medicine—passed over to the West.

By the mid-13th century, when Frederick II, the ruler of the Kingdom of the Two Sicilies, codified the separate practice of pharmacy for the first time in Europe, public pharmacies had become relatively common in southern Europe. Practitioners of pharmacy had joined together within guilds, which sometimes included dealers in similar goods, such as spicers or grocers, or physicians.

Arabic culture had returned classical scientific and medical knowledge to Europe. At centers such as Toledo and Salerno, the writings of the Greeks, which had been translated into Arabic centuries before on the fringes of the old eastern half of the Roman Empire, were translated into Latin for the use of European scholars. Thus, at the emerging universities of Europe such as Paris (1150), Oxford (1167), and Salerno (1180), scholars discussed the works of the great medical authorities such as Dioscorides, Galen, and Avicenna.

However, the debates on medicine among European academics were based on speculation, not observation. Theirs was a philosophical pursuit, with no great impact on medical practice. For significant change to occur in the use of drugs, the scholastic approach had to be set aside and a more skeptical, observational methodology adopted. This new, experimental age we now call the Renaissance.

THE RENAISSANCE AND EARLY MODERN EUROPE

The Renaissance, simply put, was the beginning of the modern period. Changes that had begun during the European Middle Ages, and were stimulated further by contacts with other cultures, gained momentum. The burst of creative energy that would result in our present shared culture of the West stemmed not from a single episode, but from a series of events.

In 1453 Constantinople (Istanbul) fell to the conquering Turks, and the remnants of the Greek scholarly community there fled west, carrying their books and knowledge with them. About that same time, Johann Gutenberg began printing with movable type, starting an information revolution. Within a half century, Columbus discovered the New World, Vasco da Gama found the sea route to India that Columbus had sought, commerce based on money and banking was established, and syphilis raged through Europe. It was a time for new ideas through reinterpretation of the old classical themes, and through exploration on the high sea and in the laboratory.

The time was ripe for casting off the old concepts of diseases and drugs of Galen. The new drugs that were arriving from far-off lands were unknown to the ancients. Printers, after fulfilling the demand for religious books such as bibles and hymnals, turned to producing medical and pharmaceutical works, especially those that could benefit from profuse and detailed illustrations. On the medical side, for example, this trend is exemplified in the anatomical masterworks of Andres Vesalius (1514–1564).

For pharmacy, printing had a profound effect on the study of plant drugs, because illustrations of the plants could be reproduced easily. Medical botanists such as Otto Brunfels (1500–1534), Leonhart Fuchs (1501–1566), and John Gerard (1545–1612) illustrated their works with realistic renditions of plants, allowing readers to do serious field work or find the drugs needed for their practices. Among the most gifted of these investigators was Valerius Cordus (1515–1544), who also wrote a work in another popular genre—formula books. His *Dispensatorium* (1546) became the official standard for the preparation of medicines in the city of Nuremberg and generally is considered the first pharmacopeia.

Although they were critical to the advancement of medical science, the nearly modern, precise works of Fuchs and Vesalius did not influence the treatment of disease as much as the speculative, mystically tinged writings of an itinerant Swiss surgeon who dubbed himself "Paracelsus." Born Philippus Aureolus Theophrastus Bombastus von Hohenheim in 1493, the year Columbus went on his second trip, this medical rebel represents well the combined attitudes of the common man, the scholarly physician, the practical surgeon, and the alchemist. The battles of Paracelsus against the static ideas of Galen, Avicenna, and other traditional authorities opened a window into the complicated mind of the Renaissance. As Erwin Ackerknecht observed in *A Short History of Medicine,*

> "Paracelsus is one of the most contradictory figures of a contradictory age. He was more modern than most of his contemporaries in his relentless and uncompromising drive for the new and in his opposition to blind obedience to authoritarianism and books. On the other hand, he was more medieval than most of his contemporaries in his all-pervading mystic religiosity. His writings are a strange mixture of intelligent observation and mystical nonsense, of humble sincerity and boasting megalomania."

Paracelsus was the most important advocate of chemically prepared drugs from crude plant and mineral substances, yet he believed firmly that the collection of those substances should be determined by astrology. He stated, again and again, his total faith in observation while at the same time preaching the "doctrine of signature," a belief that God had placed a sign on healing substances indicating their use against disease (eg, liverwort resembles a liver, so it must be good for liver ailments).

An outspoken enemy of university-educated physicians, Paracelsus denigrated their scholasticism and wrote his own works in his native language rather than in the traditional Latin. He harshly criticized pharmacy practitioners as well, even though his advocacy of chemically prepared medicines was to spark the growth of the modern pharmaceutical sciences. Chemical processes, especially distillation, empowered the follower of Paracelsus to isolate the healing principles of a drug, its *quintessence*. Eventually, as the efficacy of some of these drugs became known, they entered professional medical

practice and appeared in books on medicines. Thus, a great leap in the history of pharmacy, the preparation of medicines, emerged when a tool of science, chemistry, was adopted to make one of humanity's most ancient of tools, drugs.

Paracelsus and his followers, who chastised practitioners of pharmacy, soon took a position on the forefront of chemistry during the 16th century. The apothecary Johann Hartmann (1568–1631), for example, was the first professor of chemistry at a European university. This trend continued through the 17th, 18th, and into the beginning of the 19th century as chemistry emerged as a separate profession. For a period of about 300 years, a small minority of practicing pharmacists made significant investigations into the chemistry of drugs, and along the way isolated many drugs that are still used today and contributed much to general chemical knowledge. During that same period, when men and their ships sailed the seas looking for new lands, and returned with new drugs, practitioners of pharmacy explored a much smaller, but equally exciting, world in their laboratories.

Much of the stimulation for the early research came out of the discovery of drugs in recently explored lands. Just as Galen did not know all the diseases in the world, Dioscorides and his Arab elaborators did not know all the drugs in the world. Tobacco, guaiac, cascara sagrada, ipecac, and cinchona bark were among the scores of new plant drugs from the New World.

Cinchona bark, from which quinine was extracted in 1820, first came to Europe around 1640, at which point it created a crisis within scholastic medicine. Galen's elaborate system of balancing humors by using drugs of opposite qualities could not explain cinchona bark's efficacy against malaria. Not only did the bark cure malarial fevers, but also it had little effect on other fevers. Here was something Galen said could *not* exist, but Paracelsus insisted *must* exist—a specific remedy for a disease. This conceptual crisis, plus the efforts of those advocating chemical medicines, displaced the therapeutic agreement of Galenism, which had lasted nearly 1500 years. The following period, about 250 years, was a time of therapeutic chaos that lasted until the present era of modern pharmacology.

During the time of turmoil for therapeutics while the followers of Paracelsus and Galen argued, the calling of pharmacy established the legal and scientific foundations of the modern profession. Out of the medieval complex of guilds on the European continent grew organizations that represented pharmacy.

As the occupational division from medicine spread north, pharmacy practitioners joined together or aligned themselves with similar groups, such as the sellers of spices or physicians and surgeons. The guilds of the late Middle Ages and early Renaissance wielded considerable power, setting up training requirements, examinations, and restrictions on the number and locations of shops. Conflicts within guilds that held pharmacists and near competitors often led to government intervention and new laws that clarified the professional role of pharmacy. Eventually, however, interprofessional friction would lead to the separation of pharmacists into their own organizations, often under governmental authority (eg, the French Collége de Pharmacie in 1777).

The cooperation between pharmaceutical guilds and governmental bodies also led to the standardization of medicines through the publication of books called *pharmacopeias.* Because of greater pharmaceutical sophistication, the increased number of herbals and distillation books, and the availability of new drugs, physicians wanted assurance that their prescriptions would be prepared uniformly within their city or state. To this end, in 1499 the guild of physicians and pharmacists of Florence sanctioned the *Nuovo receptario* as their book of standards. Historians, however, generally credit the *Dispensatorium* of Valerius Cordus as the first pharmacopeia, which was adopted by the government of Nuremberg, Germany, in 1546.

It is a bit ironic that from the mid-1600s to the mid-1800s, when controversy raged within medicine regarding the proper use of drugs, pharmacy made its greatest contribution to science as well as becoming firmly established as a profession on the European continent. As chemical medicines became more prevalent in medical practice, pharmacists were forced to learn the new methods of preparation and manipulation. To do so they turned to the most popular textbooks on chemistry, which were composed by pharmacists such as Nicaise LeFebvre (*Traité de chymie,* 1660) and Nicolas Lemery (*Cours de chymie,* 1675).

The volume of chemical discoveries made by pharmacists would fill a chapter twice this size. Carl Wilhelm Scheele (1742–1786), for example, discovered oxygen in 1773, a year before Priestley, as well as chlorine, glycerin, and several inorganic acids. Martin Klaproth (1743–1817) was a pharmacist who pioneered the field of analytical chemistry. Like Scheele, he made his discoveries using the equipment of the pharmacy in which he worked. Other pharmacists, such as Andreas Marggraf (1709–1782), became such proficient chemists that they pursued chemical work full-time. Along the way pharmacists contributed much to the development of chemical apparatus, especially analytical chemists such as Klaproth, Marggraf, Antoine Baumé (1728–1804), Carl Freidrich Mohr (1806–1879), and Henri Moissan (1852–1907). Moissan, a French pharmacist, received the Nobel prize in chemistry in 1906 for his isolation of fluorine.

Since most drugs before 1900 were derived from the plant kingdom, it is not surprising that pharmacists dominated the investigation of botanical drugs during the 1700s and 1800s. In collaboration with interested physicians, pharmacists documented the sources of plant drugs around the globe, making significant contributions to the nascent science of botany. Combining this proficiency with their skills in manipulative chemistry, pharmacists continued the search begun by the Paracelsians to find pure healing principles within medicinal plants.

Approaching pharmacy with a more modern viewpoint, these men sought to isolate pure, crystalline chemicals that could be measured accurately and identified chemically. Medicinal preparations of crude drugs, no matter how carefully made, fluctuated considerably in potency because of the natural variation of active constituents in botanicals. Thus, the pursuit of active principles was no easy task, and it fascinated pharmaceutical investigators for nearly 300 years. To search, separate, characterize, and identify the scores of chemicals contained in the simplest plant drug was a challenge as great as any exploration.

Discoveries came gradually through hit and miss research until the late 1700s, when Scheele, for example, extracted several plant acids including citric acid (1784). The single, most important breakthrough occurred during the first decade of the 19th century when the pharmacist Friedrich Sertürner extracted morphine from crude opium. The announcement of his method opened up the era of alkaloidal chemistry, which resulted in the isolation of several pure drugs from crude preparations. The French pharmacists Joseph Pelletier and Joseph Caventou isolated several alkaloids, notably quinine in 1820. Not only were these new, pure drugs rapidly adopted by physicians because their potency was assured, but their existence allowed physiologists to administer drugs accurately during their research, which became the wellspring for modern pharmacology.

Much later, after 1850 or so, the scientific disciplines of pharmacy began to become more professionalized in colleges and manufacturing concerns with a subsequent decline in *drug shop science.* Pharmacists interested in research left the shop behind for the institutional laboratory.

Despite the impressive achievements of a few pharmacy practitioners, most pharmacists of the early modern period viewed science as secondary to professional and financial success. European pharmacists achieved these goals through strict internal controls on the profession and relatively cordial relations with physicians. In some states on the European continent, the number and location of pharmacies were limited by law, as were the requirements for education and licensure. Lists of standard prices softened competition. By the 19th

century, the combination of the fame generated by scientific contributions and solid upper-middle-class credentials had elevated pharmacists throughout much of Europe to a social position similar to that of physicians.

Such conditions did not hold for Britain, however, where the position of the pharmaceutical profession within the hierarchy of healing did not become established firmly until the mid-19th century. The original class of pharmacy practitioners, the apothecaries, had evolved during the 1600s and 1700s into a second group of medical practitioners, servicing those who could not afford the high fees demanded by the small cadre of university-educated physicians.

As apothecaries became more and more like general practitioners of medicine, *chemists* and *druggists* (ie, those who manufactured and sold drugs and medicines for the apothecaries) rose up to take over the open pharmaceutical niche. Conflicts and court cases erupted during these years, and the boundaries between the physicians, apothecaries, chemists, and druggists shifted accordingly. It was during this period of confusion within the British health community that the British settled what would become the United States of America, a situation that contributed to the development of the unique American profession of pharmacy.

AMERICAN PHARMACY

The exceptional character of American pharmacy* arises out of its remarkable history. When settlers came to the shores of North America, there was little to attract trained or established medical personnel. Unlike the lands of Central and South America, there were no treasures to confiscate or spices to export. This was a land for toil, not spoils. As the frontier was pushed back slowly, most of the populace relied on domestic or "kitchen" medicine guided by home medical books (if the settler could read). When this failed, the colonist often turned to a nearby figure of authority such as a clergyman or government official to provide medical advice or guidance.

As the colonies grew more prosperous during the early 18th century, they attracted ambitious businessmen from England, including apothecaries. In the New World, British apothecaries continued to combine pharmaceutical and medical practice, serving the large segment of the public who could not afford university-trained physicians. In North America, the boundaries between medicine and pharmacy were even cloudier, with most physicians having some sort of shop practice. Most apothecary shops were run either by an attending physician or his apprentice, or by an apothecary hired by the owner-physician. In other words, most men who practiced medicine for their livelihood also practiced their own pharmacy, either out of their homes or in *doctor shops*.

A few 18th-century chemists and druggists—practitioners who limited themselves to drug-selling and medicinal preparation—did practice in the larger cities on the Atlantic coast. These forerunners of today's pharmacists had two main areas of sales. As *druggists* they served as wholesalers of the drugs and medicines used by apothecaries, surgeons, midwives, and physicians. They also undersold the apothecaries in the marketing of patent medicines (secret remedies of unknown composition), which became increasingly popular up through the Revolutionary War. There were very few laws that directly involved Anglo-American pharmacy during the colonial period, and no effective laws restricted the practice of American pharmacy until the 1870s. Anyone with luck, pluck, and sufficient capital could open up an apothecary or druggist shop.

The hardships imposed by the Revolutionary War proved to be critical in the development of a separate pharmaceutical occupation in America. Britain had been the source of almost all of the drugs dispensed by physicians and apothecaries. In order to meet the demand, American druggists, the wholesale distributors of drugs, had to learn how to manufacture their own chemically based drugs and how to make common preparations of the crude drugs previously obtained from Britain. In addition, these druggists had to learn how to imitate the popular British patent medicines that were so much in demand by the public. To meet war needs druggists, such as the Marshalls in Philadelphia, greatly expanded their production capabilities. Out of the war came a network for the production, packaging, and distribution of drugs and medicines.

But a profession of pharmacy, at least as we know it, was not spawned during the period of the Revolutionary War. Pharmacy—the compounding of medicines—still was done almost completely by physicians in their own shops or offices (continuing to practice according to the model of the British apothecary) or by their apprentices. Aside from those wholesale druggists who also had an *out front* business—that is, a retail store that sold their products and filled occasional prescriptions—nonmedical practitioners of pharmacy were rare and without any sort of group identity. Many of those who did practice pharmacy solely were either immigrants from the European continent or former employees in doctor shops who bought businesses from their old physician-employers.

To succeed, of course, these chemists needed prescriptions to dispense. Back in the 1760s, in his famous *Discourse* on medical education, Dr John Morgan, a pioneer in American medical education, had advocated the separation of medicine and pharmacy with physicians writing prescriptions. A few physicians did follow Morgan's lead, but the practice did not become common until well into the 19th century. Morgan himself returned to operating a shop to make ends meet.

The years surrounding the War of 1812 brought significant changes in American business and health care that strongly influenced pharmacy's professional development. It was not until the early years of the 19th century that American physicians began to view the special service of an apothecary as distinct and essential. The first hospitals of the young republic, for instance, employed medical apprentices as staff apothecaries. As described in the *Brief Account of the New-York Hospital* (1804), a "house Surgeon and Apothecary constantly reside in the Hospital—these offices are filled by the students of the Physicians and Surgeons belonging to the Hospital, which affords an excellent school for the young men appointed to those places." The staff apothecary practiced both pharmacy and medicine in a manner analogous to the British apothecary of the 18th century, going on rounds and treating patients.

By 1811, however, the position of apothecary at the New-York Hospital had changed. The person chosen was a full-time pharmaceutical practitioner who was tested, before hiring, on his prowess as a compounder of medicines. Instead of being obligated to go on rounds, he was required to stay in his *shop* at all times. By 1819 the services of the New-York Hospital apothecary were so critical that he was required to put up a $250 bond to guarantee that he would not leave his position with less than a 2-month notice.

The war with England cut off trade with the largest suppliers of drugs and medicines to the US. In contrast with the stopgap measures used during the Revolutionary War to meet military and domestic demands, during the War of 1812 the American drug trade developed its own resources for the production of basic pharmaceuticals, including patent medicines. When peace returned, some American firms faltered under English pressure, but others continued and formed the basis for the future American drug industry.

The years following the War of 1812 were transitional. More and more physicians gained their clinical experience in hospitals and dispensaries instead of with preceptors, learning to write prescriptions, rather than compound them. After graduation some of these young physicians continued to write out prescriptions, thereby stimulating the growth of pharmacy. As physicians began writing prescriptions for apothecaries to

*The discussion on American pharmacy is based in part on data from "Professionalism and the Nineteenth-Century American Pharmacist," *Pharm Hist* 1986; 28: 115.

dispense, concern arose over the consistency with which these medicines were being compounded. In 1808 the Massachusetts Medical Society published a state guide to drug standards, with a national convention of physicians approving a *Pharmacopoeia of the United States of America* (USP) in 1820. Although the USP was not recognized as official by the federal government for years to come, it rapidly became accepted nationally as the primary guide to drugs.

The appearance of these books reflected both the growing amount of prescription writing and the medical profession's increasing reliance on pharmacists. The number of pharmacy practitioners in urban areas reached the critical mass necessary for the establishment of local pharmaceutical societies such as the Philadelphia College of Pharmacy (1821) and the Massachusetts College of Pharmacy (1823). These *colleges* (the term being used in the sense of associated colleagues) established night schools for the instruction of apprentices and discussion groups on scientific pharmacy. The small class of retail apothecaries and wholesale druggists presented no particular threat to urban physicians in the first decades of the 19th century, and the situation provided them with several conveniences.

ANTEBELLUM AMERICA: PHARMACY FINDS ITS NICHE

The years prior to the American Civil War were to be the most critical for American practitioners of pharmacy; the boundaries of practice between physicians and pharmacists that were drawn during this period still exist relatively unchanged today. During the 1820s and 1830s, East Coast apothecary shops became more standardized in their appearance and in the stock they carried. Pharmacy followed the trend of specialty retailing and concentrated on drugs, medicines, surgical supplies, artificial teeth and limbs, dyestuffs, essences, and chemicals. Grocers took over the selling of exotic dietary items such as figs, raisins, and citrus fruits. Drugstores in small cities and towns, however, tended to keep in stock more general articles such as glass, paints, varnishes, and oils. Above all, apothecary shops became the main distributors of patent medicines, one of the most profitable lines of merchandise in the history of American business.

The educated elite of Atlantic coast physicians fostered the development of a well-trained, yet subservient, pharmaceutical profession. They welcomed the early pharmaceutical associations and served as faculty for the first American pharmacy schools. Physicians voiced support for the growth of an independent profession of pharmacy as a "necessity for a division of labor" to meet the "growing demands" of their communities. As the quality of drugs imported from Europe declined, physicians began to rely on the expertise of pharmacy practitioners to detect adulterated or low-potency drugs.

The relationship between the physician and the druggist began to sour in the 1840s. Feeling more confident of their social standing, apothecaries began shifting their efforts from pleasing physicians to attending the ills of customers. Consequently, American apothecaries took to refilling prescriptions without physician authorization or directly treating customers, a practice called *counter-prescribing*. In the large cities, doctor's shops were back on the rise after a decline of two decades. Medical schools continued to turn out graduates by the hundreds, most of whom sought their fortunes in urban areas, where they would *open shop*.

As the 1850s progressed, the growth of American pharmacy accelerated. The US Census figures for druggists and apothecaries in 1850 and 1860 illustrate the dramatic growth in the profession, especially when compared with physicians. In 1850 and 1860, respectively, the *per capita* number of physicians did not change significantly (1:572 to 1:576), while the number of druggists grew by nearly 25% (from 1:3778 to 1:2850). This trend continued, at a slightly lower rate, through the rest of the 19th century.

American pharmacy was caught up both in developments within the health-care sector and in the larger changes occurring in American commerce. As mass-manufacturers began producing drug preparations in the late 1850s, less-skilled men entered the ranks of pharmacy. With large firms doing much of the complicated work, these *mere shopkeepers* flooded the marketplace. Physicians had supported the growth of the pharmaceutical profession largely because it served their own interests, releasing them from the drudgery of compounding medicines and stocking a shop. Moreover, physicians came to depend upon the expertise of the best druggists and apothecaries. With the development of the pharmaceutical industry, however, this relationship changed. As one physician put it in 1860, "It is an admitted and lamentable fact that many of those now practicing pharmacy are totally incompetent to fulfill the responsibilities of the true apothecary. They know nothing of the science of preparing medicines."

By the late 1850s, while the general economy was in crisis and secession strife was imminent, physicians and pharmacists indulged in a great deal of finger-pointing in both the professional and popular arenas. Both groups blamed each other for the continued popularity of patent medicines. Moreover, competition had reached such a high level that it threatened the integrity of the boundaries that had developed to separate the two professions. Pharmacists were convinced that dispensing physicians and doctor's shops were the cause of much of their difficulties, while physicians complained about *counter-prescribing*. With no legal restrictions on medical or pharmaceutical practice, the lines of separation between medicine and pharmacy were growing hazy. The onset of the Civil War ended much of the bickering between apothecaries and physicians. After the War, the boundaries between the professions were drawn more clearly, aided in part by new approaches to professionalization.

THE SEARCH FOR PROFESSIONALISM

In part to raise the stature of their rapidly growing calling, a small group of elite druggists and apothecaries met in Philadelphia in 1852 to found the American Pharmaceutical Association (APhA). They saw the gains made by pharmacy in the 1830s and 1840s being swept away by a rising tide of destructive competition. For American pharmacists of the mid-19th century, organizations like the Philadelphia College of Pharmacy or the APhA held the promise of increasing their professional stature by fostering individual improvement, not by winning the favor of physicians or government bureaucrats.

The crux of this independent achievement was the mastery of prescription compounding. The growth of large-scale pharmaceutical manufacturing during the Civil War years struck fear in the hearts of pharmacy leaders. As William Procter Jr stated (1869),

> "Pharmacy may be defined to be the art of preparing and dispensing medicines, and embodies the knowledge and skill requisite to carry them out in practice. But if the preparation of medicines is taken from the apothecary and he becomes merely the dispenser of them his business is shorn of half its dignity and importance, and he relapses into a simple shopkeeper."

Most American pharmacists, undereducated and underskilled, took advantage of the growing number of ready-made preparations offered by large firms. This was in spite of the arguments put forth by the leaders of pharmacy since the 1830s that the special ability to produce official preparations successfully in-house was what made the individual pharmacist more than a mere merchant. Moreover, this expertise only could be learned through experience, under the watchful eye of a preceptor. As fewer basic ingredients for compounding were made in the shop, however, apprentices would become preceptors and pass along their ignorance.

Pharmacists, at the conclusion of the Civil War, initially rejected the notion that formal educational requirements would solve the problem. They had no interest in any measures that interfered with their freedom to practice. Moreover, some

immigrants from the Continent, where states often restricted pharmaceutical practice, expressed opposition to the legal control of pharmacies. Many had come to North America to open their own shops, rather than wait years in their native lands for permission.

In the late 1860s the academic model of professionalism being worked out by other so-called "new professions" such as engineering attracted the attention of some pharmaceutical leaders. Using university degrees, plus state licensing or institutional certification, these new professions set themselves apart from other occupations as "communities of the competent." They sought to avoid the ordeals of the marketplace by putting a cognitive gap between their work and the public's understanding. Theoretically, by controlling admissions to professional schools and raising examination standards, destructive competition could be reduced or even eliminated.

LEGISLATION

The APhA responded to the movement of the late 1860s toward increased public protection and occupational security through law by publishing a model pharmacy act. Physicians and others concerned with the safe use of poisons and potent drugs had petitioned state legislatures for laws governing pharmacy. Initially, pharmacists took a negative view, reacting to the idea that physicians or bureaucrats would gain authority over pharmacy practice via state inspectors or licensing boards. To ensure that the profession's best interests would be protected, the APhA empowered a committee to draw up a model law. Reflecting the ambivalent attitude of many pharmacists toward legal regulation, the APhA published and distributed their model law without endorsement. As small businessmen, pharmacists did not want outside restriction on their trade.

During the 1870s state legislatures began considering in earnest pharmacy bills sponsored by nonpharmacists. Reacting to this trend, pharmacists organized statewide associations to coordinate support for their own bills, which were often versions of the APhA model. Although not enthusiastic at first about regulation of their businesses, pharmacists wanted a voice in the process. The eventual success of their efforts in the 1870s, 1880s, and 1890s evinced a changing attitude toward the pursuit of professionalism from the 1860s.

The boundary between masters of the pharmaceutical art and mere store clerks, which had always been flimsy, was disintegrating. Pharmacists sought new ways to demonstrate their competence and to separate themselves from ignorant drug sellers and quacks. The evidence for this expertise, however, shifted away from individual achievement in the marketplace toward group identification and institutional certification.

TRANSITION TO A MODERN PROFESSION

The period between 1870 and 1920 was transitional for both pharmacy and pharmaceutical education. Before the Civil War perhaps only 1 in 20 American pharmacists had finished formal schooling in pharmacy, which had consisted of night courses to supplement apprenticeship training. With the passage of state laws requiring the examination and registration of pharmacists from the 1870s on, pharmacy became part of the wave of professionalization sweeping across American society. The new professionals based their claims of status on their diplomas and licenses, not their products.

Pharmacy got caught up in this trend, and even though state laws did not require a pharmacy school diploma for licensure until the early 20th century, the prestige attached to the sheepskin attracted students to the burgeoning number of schools, as public expectations increased and "professional" became a coveted title.

Pharmaceutical education around the turn of the century was related closely to practice as pharmacist-educators such as Joseph Remington replaced the physicians and other nonpharmacy practitioners who had dominated the earlier schools. Students also had a wide range of possible educational experiences.

- Short-term cram schools were available for those who just wanted to pass a state board exam.
- Small, local schools sprang up in medium size cities offering basic instruction and large diplomas for display.
- The old-line schools, affiliated with local pharmaceutical organizations, provided students with excellent practical education, plus an opportunity to explore specialty areas, depending on the college's faculty.
- Starting with the University of Michigan in 1868, schools of pharmacy affiliated themselves with state colleges and universities, a trend that altered the direction of American pharmaceutical education.

As part of larger university communities, these pharmacy schools aspired to the high standards of scholarship exhibited by established disciplines and other professions. The leaders of the university faculties helped transform pharmaceutical education from a vocational to a scientific orientation through pharmacy programs that emphasized full-time coursework and laboratory study.

During this period pharmacy's part in health care solidified, as the dispensing of medicines by physicians declined. However, the rise of the cut-rate drugstore and, more importantly, the chain drugstore, also occurred during these 50 years, which further increased economic pressure on the profession.

Still, most pharmacists worked in their own *corner drugstore,* which became a fixture in American life with its shelves of patent medicines for all ills and a soda fountain for delightful beverages; the proprietor, often called *doc,* attended to the minor aches and pains of customers or made chocolate sodas with equal skill. Although the pharmacist relied on prescription compounding for his professional identity, this provided only a small fraction of his income. To protect this independent and uniquely American style of practice from the incursion of larger retailers, the National Association of Retail Druggists (NARD) was founded in 1898. At first the APhA welcomed and cooperated with the new national organization, but the split that eventually developed between the APhA, which was oriented to scientific and professional advancement, and NARD, which concentrated on the individual commercial success of owners, weakened the profession's voice in national affairs in the years to come.

It was an exciting time in medicine, with therapeutics undergoing a transformation. The germ theory of disease, championed by laboratory scientists such as Louis Pasteur and Robert Koch, resulted in significant immunological advances in the 1880s and 1890s. Pasteur's rabies vaccine and Emil von Behring's diphtheria antitoxin demonstrated that cures for infectious diseases could arise from the laboratory. Paul Ehrlich transcended the biological efforts of his predecessors when he introduced Salvarsan in 1910, the first chemotherapeutic agent. Although it fell short of Ehrlich's ideal of a *magic bullet,* which could destroy microorganisms selectively without damaging the patient, Salvarsan did inspire others to search for drugs with chemotherapeutic potential. Aside from the biologicals, however, few of the drugs discovered during the late 19th and early 20th centuries had a significant impact on the prevention or cure of disease.

Industrial research on drugs produced several new agents, such as the analgesic and antipyretic aspirin or the sedative chloral hydrate, that reduced the pain and suffering associated with illness. Even though pharmacies served as important outlets for sera, antitoxins, and vaccines, most of the medicines compounded or sold by pharmacists around the turn of the century eased symptoms, rather than treated root illnesses.

As scientific pharmacology explained how drugs worked on a cellular and organ system level, the concept of drugs and their actions held by professionals and laypeople diverged. The public clung to outdated ideas of humoralism augmented by a modicum of germ theory. Such beliefs made consumers susceptible to patent medicine advertising, which misled them into equating the effects of strong laxatives and analgesics with the

cure of disease. With far greater understanding of the nature of disease, health professionals joined together with muckraking journalists and politicians of the Progressive Era to attack patent medicine *cure-alls*. The 1906 Food and Drugs Act, passed mainly in response to poor food-production methods, also addressed problems in the drug trade. Even though it proved ineffectual against patent medicine fakery, the 1906 act did establish the *United States Pharmacopeia* as well as the *National Formulary* of the APhA as official compendia, providing the US with truly national drug standards for the first time.

It was during these years that pharmacists finally abandoned the in-shop manufacturing of the ingredients of their prescriptions. The pharmaceutical industry had progressed to the point where they could produce basic preparations of crude drugs more cheaply and reliably than could the individual practitioner. Moreover, industry was the source for the new synthetic drugs such as antipyrine and aspirin that resulted from developments in organic chemistry. As compounding, not the making of stock preparations, always had been the crux of pharmacy practice, this change was lamented only by a few of the profession's old guard. The hands of pharmacists still fashioned the essential tools of medicine.

Pharmacy education adapted gradually to the change. Coursework shifted away from the identification of crude plant drugs and their various preparations to a greater emphasis on the chemical compatibility of the ingredients within each prescription. The professional credentials of American pharmacists were strengthened in 1932 when a 4-year BSc degree became standard for licensure. For the next three decades pharmacy schools graduated pharmacists who could claim to be *chemists on the corner*. Yet at the same time that the profession achieved the goal of a scientifically trained workforce fully capable of carrying out all the steps involved in the making of medicines, the technology of the pharmaceutical industry assumed that responsibility.

THE ERA OF COUNT AND POUR

The middle third of the 20th century was a time of dramatic change for all of medical care including pharmacy. In therapeutics, many of the great scourges of humanity were conquered through the introduction of antibiotics. Although the phenomenon of antibiosis had been observed by Pasteur in the 1870s, the first significant antibiotic substance was not discovered until Alexander Fleming noticed the effects of a colony of *penicillium* mold on a misplaced petri dish in 1928. Development of penicillin did not occur, however, until a decade later when the threat of war in Europe inspired a British team to pursue the scaled-up production of the drug. Other antibiotics followed shortly, as did new classes of therapeutic agents, such as the corticosteroids, tranquilizers, antidepressants, antihypertensives, radioactive isotopes, and oral contraceptives. The pharmacy, which had served as an outpost for the relief of suffering and the treatment of minor ailments, came to hold preventives and cures for serious disease.

Following World War II American pharmaceutical firms applied high technology to the production of medicines and rapidly became one of the most advanced industries in the world. New drugs, new dosage forms, and new marketing methods reinforced a trend evident from the early 1900s of physicians shifting away from prescribing complex mixtures of ingredients toward ready-made, single-entity medicines mass-manufactured by large companies. In the 1930s about 75% of prescriptions required some compounding by a pharmacist; by 1950 that figure had dropped to about 25%. The movement away from prescriptions "tailor-made" for each individual patient accelerated so that by 1960 only about 1 in 25 prescriptions needed the compounding skills of a pharmacist, with the trend leveling out around 1970 at about 1 in 100.

Pharmacists, however, were not at a loss for work. The number of prescriptions grew even faster as new, effective drugs came onto the market. In community pharmacies the income from the sale of prescription drugs increased faster than *out-front* sales of over-the-counter medicines, cosmetics, and other traditional *drugstore* goods. Chain stores and other large retailers rushed into the drug business, displacing the independent corner drugstore as the typical purveyor of pharmaceutical services, especially in urban areas.

Modifications in pharmaceutical legislation and education reflected these dramatic changes in therapeutics and practice, to varying degrees. Federal laws regulating the production of drugs and pharmacy practice were modernized in 1938, 1952, and 1962, the last set of amendments requiring that medicines be judged both safe and effective to be on the market. Laws regulating drugs of high abuse potential were updated through the Drug Abuse Act of 1970, which was subsequently enforced through the Drug Enforcement Agency. In contrast to the law, educational reform came more slowly.

Proposals for 6-year Doctor of Pharmacy degrees to raise the professional standing of pharmacy gained interest in a few places, with the first such program initiated at the University of Southern California in 1950. But, as a whole, pharmaceutical educators compromised and selected a 5-year bachelor of science in pharmacy as the standard degree beginning in 1960. The pharmacy curriculum continued to emphasize the physical sciences that underlie the making of medicines, however, ignoring the fact that compounding was disappearing from American pharmacy practice.

Because of the large growth of prescribing, community pharmacists of the 1950s and 1960s stepped back from soda fountains and cigar counters to practice pharmacy nearly full time. Yet, for all of their education, they did little more than routinely fill prescriptions—placing a small number of dosage units from a large bottle into a smaller, properly labeled one. Despite the added responsibility of distributing the hundreds of new and potent medicines coming on the market, pharmacists had little opportunity to use their 4, 5, or 6 years of higher education. The restricted role of the pharmacist is exemplified by the following statement from the Code of Ethics of the APhA, which was in effect from its adoption in 1952 until its revision in 1969:

> "The pharmacist does not discuss the therapeutic effects or composition of a prescription with a patient. When such questions are asked, he suggests that the qualified practitioner (ie, physician or dentist) is the proper person with whom such matters should be discussed."

In 1969 the APhA revamped its Code of Ethics in the face of the large changes occurring in pharmacy. Instead of deferring to physicians, the APhA advanced this statement as the first section of its Code: "A pharmacist should hold the health and safety of patients to be of first consideration; he should render to each patient the full measure of his ability as an essential health practitioner." This dramatic reversal resulted from a new idea that swept through pharmacy during the mid- to late-1960s called clinical pharmacy.

THE EMERGENCE OF CLINICAL PHARMACY

The concept of *clinical pharmacy* sprang from a combination of factors, including the development of the subdiscipline of hospital pharmacy since the 1920s, the growth of clinical pharmacology since the 1940s, innovative teaching programs, and the decline of pharmacology instruction in medical schools. To some extent, pharmacy took over an aspect of medical care that had been partially abandoned by physicians. Overburdened by patient loads and the explosion of new drugs, physicians turned to pharmacists more and more for drug information, especially within institutional settings.

Viewed historically, however, the expansion of pharmacy's role to include patient instruction on proper drug use seems a logical extension of the pharmacist's role as toolmaker. More-

over, clinical pharmacy practice bridged the gap between professional and lay understanding of drug action. During the past century medical science far surpassed the public's comprehension of physiology and disease. The concept of how the tool of medicine works, once shared by both doctor and patient, had been lost. The public's trust in medical practitioners subsequently has declined. Pharmacists, by sharing insights into the workings of medicines, have become trusted professionals in American society.

Aside from recent innovations in the relationship between pharmacist and patient, several other notable changes have occurred within American pharmacy that have gone relatively unnoticed by the public. Outwardly, the practice of pharmacy today differs little in appearance from that of 60 years ago. An individual hands over a small slip of paper received from a physician to a pharmacist who then retreats into a work area and appears later with a container of medicine. But on closer examination, the changes seem revolutionary. For example, women, who made up only 4% of the profession in 1950, entered the field rapidly starting in the 1970s. By the year 2000 they were approximately 40% of the pharmaceutical workforce and will be the majority in the near future.

Pharmacists, traditionally conservative in the face of technological innovation, adapted computer technology to their work as quickly as any other profession of the late 20th century. Institutional practice, once viewed as the lowest rung on the profession's ladder, became the work area of choice for graduates during the 1970s and 1980s, a period of unprecedented hospital growth. Just as the division of labor opened up a niche for pharmacists in the early 1800s, pharmaceutical specialties such as radiopharmacy, clinical pharmacotherapy, and nutritional support practice have demonstrated the maturity of the American pharmaceutical profession. Once relegated to counting and pouring, pharmacists headed institutional reviews of drug utilization and served as consultants to all types of health-care facilities. A comparison of Part I of this current edition of this text with previous editions will reveal the unprecedented expansion of opportunities for pharmacists in recent times.

THE CONFLICTING PARADIGMS OF PHARMACEUTICAL CARE AND MANAGED CARE

The 1990s in American pharmacy begin with a clarion call for a paradigm shift to Pharmaceutical Care, a practice model described by Charles D. Hepler and Linda Strand as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." The diverse organizations of American pharmacy rallied to this expanded vision of practice. Established schools of pharmacy shifted in earnest to all-PharmD programs to better prepare graduates for the expected challenges. Governmental regulations, such as those connected with the Omnibus Budget Reconciliation Act of 1990 (OBRA 90), pushed pharmacy in the direction of greater responsibility. OBRA 90 requires pharmacists to provide counseling to Medicaid patients and to participate in prospective and retrospective drug use review (DUR) programs. Eventually, states added rules calling for more pharmacy services. This new path to a greater professional role for pharmacist seemed assured.

As the 1990s moved ahead, it soon became clear that the supposed decade of pharmaceutical care was turning into a decade of confusion, conflict, and controversy. The Clinton Administration tackled the difficult task of reforming the complex American health care system. This effort failed, but it did inspire a raft of consolidations throughout the pharmaceutical enterprise, which resulted in a leaner and meaner industry. Third-parties turned to the principles of managed care to cut costs. Important new classes of drugs appeared, which when combined with an aging population, led to a rapid rise in prescription volume. Prescribing further increased under the pressure of direct-to-consumer advertising, which was given relatively free rein by the late 1990s. The emergence of Internet pharmacies, building on the established mail-order business of earlier years, added to the turmoil of the pharmaceutical marketplace. Independently owned drugstores closed across the nation, replaced in many localities by pharmacies tucked inside mass merchandisers or grocery stores. As the decade ended with the distractions of the Y2K non-event, far more pharmacists found themselves acting as arbiters of managed care squabbles than as advanced care providers.

THE FUTURE

It is too soon for historians to judge the long-term influence of the pharmaceutical care concept. Two full generations of pharmacists have been educated and trained after the general adoption of the aims of clinical pharmacy. Present day-to-day practice reflects this important shift from the product orientation of previous decades to an orientation concerned with patients receiving necessary drug information. In the midst of a harsh economic and regulatory climate, only time will tell if the often divided and divisive pharmaceutical profession will unite and continue its progress toward greater societal responsibility for the ancient tool we call medicines.

HISTORY AS A DISCIPLINE

Like the other fields of pharmacy described in this textbook, the history of pharmacy is a distinct discipline that produces a body of research. The following bibliography and chronology, updated from the previous editions by Glenn Sonnedecker, is provided for those interested in pursuing some specific aspect of pharmaceutical history. Readers interested in learning more about important figures in the history of American pharmacy should consult *RPS-13,* page 20. Additional guidance can be obtained from the American Institute of the History of Pharmacy, University of Wisconsin at Madison, 777 Highland Avenue, Madison, WI 53705. Links to useful websites pertinent to the field are found at www.aihp.org.

BIBLIOGRAPHIC NOTES

Besides giving recognition to sources on which the above historical essay is based, these references suggest further readings and reference materials. English-language publications are cited unless there is no approximate counterpart of a foreign-language publication. For those with deeper historical interests, bibliographies in some of the publications mentioned will lead to more specialized and often more meaningful literature.

The book with the most comprehensive scope in English is *Kremers and Urdang's History of Pharmacy,* revised by Glenn Sonnedecker (Philadelphia: Lippincott, 1976; AIHP reprint, 1986); see the glossary, Appendix 6, as well as the notes and references for bibliographic material. Hermann Schelenz, *Geschichte der Pharmazie* (Berlin: J. Springer, 1904; republished Hildesheim: Gg Olms, 1965) is a monumental reference work; although it is now outdated in many details, it richly documents the earlier literature. Erwin H Ackerknecht, *Therapeutics from the Primitives to the 20th Century* (New York: Hafner [1973]; German edition, 1970) is a general overview. Another overview is Ronald D Mann, *Modern Drug Use: An Enquiry on Historical Principles* (Lancaster; Boston: MTP Press, 1984). See also GJ Higby and EC Stroud, editors, *The Inside Story of Medicines: A Symposium* (Madison, WI: American Institute of the History of Pharmacy, 1997). A valuable short synthesis is John Parascandola, "A Brief History of Drug Use," in *Perspectives on Medicines in Society,* Albert I Wertheimer and P Bush, editors (Drug Intell, 1977). For illustrations, see partic-

ularly W-H Hein and DA Wittop Koning, *Bildkatalog zur Geschichte der Pharmazie* (ns Bd 33), *Veroffentlichungen der Internationalen Gesellschaft fur Geschichte der Pharmazie* (Stuttgart, 1969). For an excellent survey with scores of fine historical images, see DL Cowen and WH Helfand, *Pharmacy: An Illustrated History* (New York: Abrams, 1990).

A few general guides to the historical literature are GJ Higby and EC Stroud, editors, *The History of Pharmacy: A Selected, Annotated Bibliography* (New York: Garland, 1995); Glenn Sonnedecker, JH Hoch, and Wolfgang Schneider, *Some Pharmaco-Historical Guidelines to the Literature* (Madison, WI: American Institute of the History of Pharmacy, 1959; reprinted from *Am J Pharm Educ* 1959; 23: 143); *Index-Catalogue of the Library of the Surgeon-General's Office* (Washington, DC: US Army, 4 series, 1880–1936); E-H Guitard, *Manuel d'histoire de la littérature pharmaceutique* (Paris, 1942); *Bibliography of the History of Medicine* (Bethesda, MD: National Library of Medicine, USPHS, No. 1, 1965, et seq.; annual that includes pharmacy); *Current Work in the History of Medicine*, a quarterly from The Wellcome Historical Medical Library, London, since 1954 (includes pharmacy internationally), most recently collated in 1986; "Bibliography of the History of Medicine of the United States and Canada," published annually, 1939–1966, in the *Bulletin of the History of Medicine,* which includes a pharmacy section; E-H Guitard, *Index des travaux d'histoire de la pharmacie de 1913 à 1963* (Paris: Société d'Histoire de la Pharmacie [1968]); "Pharmazie Geschichtliche Rundschau," GE Dann, editor, vol 1 (1954–1957, et seq) is historical abstracts, a periodic supplement to the *Pharmazeutische Zeitung*; Glenn Sonnedecker and Alex Berman, *Some Bibliographic Aids for Historical Writers in Pharmacy* (Madison, WI: American Institute of the History of Pharmacy, 1958); and David L Cowen, *America's Pre-Pharmacopeial Literature* (Madison, WI: American Institute of the History of Pharmacy, 1961). Nydia M King's *A Selection of Primary Sources for the History of Pharmacy in the United States* (Madison, WI: American Institute of the History of Pharmacy, 1987) describes in detail 89 key works that document American pharmacy from 1720 to 1940 (microform or photoduplicated copies of 85 of the 89 works are available from University Microfilms International of Ann Arbor, MI.) For the scientific aspects of pharmacy see the *ISIS Cumulative Bibliography* (London: Mansell, 1971) and its continuations, which includes pharmacy. Useful World Wide Web resources include HISTLINE from the National Library of Medicine (http://igm.nlm.nih.gov/) and the Pharmaziehistorischen Biblographie or PhB (http://www.ubka.uni-karlsruhe.de/pharm/phb.html). Some general information about the history of pharmacy can be obtained from the website of the American Institute of the History of Pharmacy (http:// www. aihp.org).

On Antiquity: The most definitive paper of general scope on Egypt is by Frans Jonckheere, *Le 'Préparateur de Remédes' dans l'organisation de la pharmacie égyptienne* (Veroffentlichung Nr 29; Berlin: Deutsche Akademie der Wissenschaften zu Berlin, Institut fur Orientforschung, 1955; Sonderdruck aus "Aegyptologische Studien . . ."). CD Leake, *The Old Egyptian Medical Papyri* (Lawrence: University of Kansas Press, 1952) gives an overview of the documents; for a first-hand impression of the papyrus most important pharmaceutically, see Bendix Ebbell's translation, *The Papyrus Ebers: The Greatest Egyptian Medical Document* (Copenhagen: Levin & Munksgaard; London: H. Milford, Oxford University Press, 1937). Henry Sigerist, *A History of Medicine, Vol 1: Primitive and Archaic Medicine* (New York: Oxford University Press, 1951–1961) is the best general survey. See also J. Worth Estes, *The Medical Skills of Ancient Egypt* (Canton, MA: Science History/USA, 1989), and Lise Manniche, *An Ancient Egyptian Herbal* (Austin: University of Texas Press, 1989). On Mesopotamia, an excellent book of breadth, relevant to pharmacy, is Martin Levey's, *Chemistry and Chemical Technology in Ancient Mesopotamia* (Amsterdam; New York: Elsevier, 1959); on Assyria, see monographs by Reginald C Thompson. The best sociohistorical review in English is Henry E Sigerist, *A History of Medicine, Vol II: Early Greek, Hindu and Persian Medicine* (New York: Oxford University Press, 1961); works more specifically on pharmacy are J Berendes, *Die Pharmacie bei den alten Culturvolkern,* 2 vols (Halle aS, 1891), and Alfred Schmidt, *Drogen und Drogenhandel im Altertum* (Leipzig: JA Barth, 1924). The Hippocratic treatises have been translated into English by WHS Jones and ET Withington, *Hippocrates,* 4 vols (London, 1923–1931); a compilation on Hippocratic drugs was published by Johann H Dierbach, *Die Arzneimittel des Hippokrates . . .* (Heidelberg, 1824). For modern scholarship, from a different viewpoint, see Jerry Stannard, "Hippocratic Pharmacology" (*Bull Hist Med* 1961; 35: 497); see also his article "Materia Medica and Philosophical Theory in Aretaeus" (*Sudhoffs Arch Gesch Med Naturw* 1964; 48: 27). The foundation of western drug lore, the Materia Medica of Dioscorides, is reinterpreted by John Riddle in *Dioscorides on Pharmacy and Medicine* (Austin: University of Texas Press, 1985). Those interested in texts from the ancient period should check "Texts and Sources in Ancient Pharmacy," by John Scarborough (*Pharm Hist* 1987; 29: 81, 133). Common dealers in drugs are discussed by Vivian Nutton, "The Drug Trade in Antiquity" (*J Roy Soc Med* 1985; 78: 138). On Greek temple medicine, see Ch Kerenyi, *Le Medecin divin* (Basle, 1948), and EJ Edelstein and L Edelstein, *Asclepius, A Collection and Interpretation of the Testimonies,* 2 vols (Baltimore, 1945; reprinted New York: Arno Press, 1975). The first volume of a projected series by the late Rudolf Schmitz, *Geschichte der Pharmazie* (Eschborn: Govi-Verlag, 1998), covers the ancient period up to the start of the Middle Ages.

On the Middle Ages: For a general survey of *medieval Islam* and its influence, see Lucien Leclerc, *Histoire de la médecine Arabe,* 2 vols (Paris: E Leroux, 1876); also see Donald Campbell, *Arabian Medicine and Its Influence on the Middle Ages,* 2 vols (London: K. Paul, Trench, Trubner, 1926), and Cyril Elgood, *A Medical History of Persia and the Eastern Caliphate from the Earliest Times until the Year A.D. 1932* (Cambridge, England: Cambridge University Press, 1951). Much has been translated or written about Arabic materia medica and drug therapy, to which the principal key is Sami K Hamarneh's *Bibliography on Medicine and Pharmacy in Medieval Islam* (Stuttgart: Wissenschaftliche Verlagsgesellschaft, 1964), a part of the Internationale Gesellschaft für Geschichte der Pharmazie series. Among Hamarneh's other publications, see especially *Origins of Pharmacy and Therapy in the Near East* (Tokyo: Naito Foundation, 1973); also of much general interest is "The Rise of Professional Pharmacy in Islam" (*Med Hist*1962; 6: 59). For a detailed view into 10th-century Spain (with a useful bibliography), see SK Hamarneh and G Sonnedecker, *A Pharmaceutical View of Abulcasis al-Zahrawi in Moorish Spain* (Leiden: EJ Brill, 1963). Important works by Max Meyerhof include several on materia medica, such as his monograph *The Abridged Version of "The Book of Simple Drugs" of Ahmad ibn Muhammad al-Ghâfiqî* (Publication no 4, Cairo: The Egyptian University Faculty of Medicine/Government Press, 1932), on al-Beruni in *Studien zur Geschichte des Naturwissenschaften und der Medizin*, vol 3 (Berlin, 1943, pp 159–208); and his four articles in the Ciba Symposia (vol 6, Nos 5 and 6, 1944). See likewise the writings of Martin Levey, such as *The Medical Formulary, or Agrabadhin of al-Kindi* (Madison: University of Wisconsin Press, 1966).

On Medieval Europe: A volume still not superseded (although outdated in details) is George F Fort, *Medical Economy During the Middle Ages* (New York, 1883; reprinted New York: AM Kelley, 1970); see also David Riesman, *The Story of Medicine in the Middle Ages* (New York: PB Hoeber, 1935). A valuable guide and commentary is Henry E Sigerist's, "The Latin Medical Literature of the Early Middle Ages" (*J Hist Med* 1958; 13: 127). Four papers contained in the *Symposium on Byzantine Medicine* (Washington, DC: Dumbarton Oaks Research Library and Collection, 1985), edited by John Scarborough, relate to the history of pharmacy. Works of more specifically pharmaceutical interest must include the definitive study on the renowned pharmacomedical edicts in the Kingdom of the Two Sicilies by Wolfgang-Hagen Hein and Kurt Sappert, *Die*

Medizinalordnung Friedrichs II. Eine pharmaziehistorische Studie (Eutin: Internationale Gesellschaft für Geschichte der Pharmazie, 1957). In the periodical literature, note particularly the writings of Alfons Lutz, such as "Der verschollene frühsalernitanische Antidotarius magnus . . ." and its rich bibliography (new series, vol 16; Stuttgart: Veröffentlichungen der Internationalen Gesellschaft für Geschichte der Pharmazie, 1960, pp 97–133); also see the works of Rudolf Schmitz, such as ". . . Apothekerstandes im Hoch und Spät-Mittelalter" (vol 13; Stuttgart: Veröffentlichungen der Internationalen Gesellschaft für Geschichte der Pharmazie, 1958, pp 157–165) and "Ueber deutsche mittelalterliche Quellen zur Geschichte von Pharmazie und Medizin" (*Deut Apotheker-Ztg* 1960; 100: 980). English language studies of unusual value and clarity include articles by GE Trease, such as "The Spicers and Apothecaries of the Royal Household in the Reigns of Henry III, Edward I and Edward II" (*Nottingham Mediaeval Studies* 1959; 3: 19; abridged in *Pharm J*, 4 April 1949, pp 246–248). A uniquely useful work is Sister Mary Francis Xavier [Welhoefer], "Statutes of the Guild of Physicians, Apothecaries and Merchants in Florence (1313–1316): A Brief Commentary, with an Introduction and Translation," (unpublished PhD dissertation, University of Wisconsin, 1935), even though it is dated as to many details. On medieval European materia medica, see Henry E Sigerist, "Materia Medica in the Middle Ages" (*Bull Hist Med* 1939; 7: 417), and his "Studien und Texte zur frühmittelalterlichen Rezeptliteratur" (vol 13; Leipzig: Studien zur Geschichte der Medizin, 1923, pp 187ff). Probably the earliest pharmacist's textbook and manual has been translated into German by Leo Zimmermann, *Saladini de Asculo . . . Compendium aromatariorum* (Leipzig, 1919); for a Hebrew translation, see Suessmann Muntner, editor, *Sefer ha-rokhim* (Tel-Aviv: np, 1953).

On Modern Europe: For a reliable and concise medical overview, see Erwin Ackerknecht, *A Short History of Medicine* (New York: Ronald Press, 1955); for detailed references, supplement it with Fielding H Garrison, *An Introduction to the History of Medicine,* 4th ed (Philadelphia; London: WB Saunders, 1929; republished 1960), noting especially the bibliographic essays of Appendix III. Some international survey volumes on pharmacy, with particular reference to the modern period, are listed in Sonnedecker and Berman's *Some Bibliographic Aids for Historical Writers in Pharmacy* (Madison, WI: American Institute of the History of Pharmacy, 1958). A gap has been closed, meanwhile, by Leslie G Matthews, *History of Pharmacy in Britain* (Edinburgh and London: E & S Livingstone, 1962) and Cecil Wall, HC Cameron, and EA Underwood, *A History of the Worshipful Society of Apothecaries of London, Vol I: 1617–1815* (London: Oxford University Press, 1963). For those contemplating research in British archives, see L Richmond, J Stevenson & A Turton, eds., *The Pharmaceutical Industry: A Guide to Historical Records* (Burlington, VT: Ashgate, 2003). There is not yet a comprehensive, up-to-date history that deals with European pharmacy; bibliographies, such as those cited in the earlier section on general literature guides, will yield books and monographs from particular topical and national viewpoints. For an example of a specialized topic, see Richard Palmer, "Pharmacy in the Republic of Venice," in *The Medical Renaissance of the Sixteenth Century,* A Wear, editor (New York: Cambridge University Press, 1985); see also R Pötzsch, editor, *The Pharmacy: Windows on History* (Roche, 1996). A specialized book of note is M. S. Conroy, *In Health and Sickness: Pharmacy, Pharmacists, and the Pharmaceutical Industry in Late Imperial, Early Soviet Russia* (New York, Columbia University Press, 1994). Especially rich in European history are the publications, 1927 to the present, of the International Society for the History of Pharmacy; a partial key has been published by Herbert Hugel, Die "Veroffentlichungen der Internationalen Gesellschaft fur Geschichte der Pharmazie 1953–1965: Eine Bibliographie" (new series Bd 29; Stuttgart: Veröffentlichungen der Internationalen Gesellschaft für Geschichte der Pharmazie, 1967).

On the US: The standard volume in English, *Kremers and Urdang's History of Pharmacy*, revised by Glenn Sonnedecker (Philadelphia: Lippincott, 1976), devotes approximately two-thirds of the main text to the United States, and its bibliographies open up a wide range of other American literature. Noteworthy are the anniversary issues of *Druggists Circular* (vol 51, January 1907) and *Pharmaceutical Era* (vol 16, no 27, 31 December 1896). See also Glenn Sonnedecker, "Structure and Stress of American Pharmacy" (*Pharm J*, 14 April 1956, pp 3–8). A series of 18 historical articles on American pharmacy were published in *J APhA* during 2000, 2001, and 2002. Four papers covering a wide variety of American topics are contained in GJ Higby & EC Stroud, eds., *Apothecaries and the Drug Trade* (Madison: American Institute of the History of Pharmacy, 2001). The story of American pharmacy's umbrella organization is told by George Griffenhagen, *150 Years of Caring: A Pictorial History of the American Pharmaceutical Association* (Washington, DC: APhA, 2002). Pharmaceutical education is explored in depth by Robert A. Buerki, "In Search of Excellence: The First Century of the American Association of Colleges of Pharmacy," *Am J Pharm Ed* 63 (Fall Supplement 1999): 1–210. A useful look at certain aspects of colonial American pharmacy can be found in Renate Wilson, *Pious Traders in Medicine: a German Pharmaceutical Network in Eighteenth-Century North America* (University Park, PA: Pennsylvania State University Press, 2000). Several different aspects of 19th-century practice are considered by Gregory Higby, *In Service to American Pharmacy: The Professional Life of William Procter, Jr* (Tuscaloosa: University of Alabama Press, 1992). A solid biography of a 20th-century American pharmacist is James Madison, *Eli Lilly: A Life, 1885–1977* (Indianapolis: Indiana Historical Society, 1989). Other valuable biographies include Michael A Flannery, *John Uri Lloyd: The Great American Eclectic* (Carbondale: Southern Illinois University Press, 1998) and Sabine Knoll-Schütze, *Friedrich Hoffmann (1832–1904) and the 'Pharmaceutische Rundschau'* (New York: Peter Lang, 2003). Changes in the use and production of drugs are explored by John Harley Warner, *The Therapeutic Perspective: Medical Practice, Knowledge, and Identity in America, 1820–1885* (Cambridge: Harvard University Press, 1986) and John P Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1988). See also John Parascandola, *The Development of American Pharmacology: John J. Abel and the Shaping of a Discipline* (Baltimore: Johns Hopkins University Press, 1992) and Harry M Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (Cambridge, UK; New York: Cambridge University Press, 1997). Short histories of individual drugs are provided by Walter Sneader, *Drug Prototypes and Their Exploitation* (New York: John Wiley, 1996). For a contemporary use of historical arguments in policy analysis, see a series of articles written by RW Holland & CM Nimmo on "Transitions in Pharmacy Practice," that appear in the *Amer J Health-System Pharm* 56 (1999): 1758–64, 1981–7, 2234–41, 2458–62, 57 (2000): 64–72. A useful bibliography that is still in print is by George Griffenhagen, *Bibliography of Papers Published by the American Pharmaceutical Association that were presented before the Association's Section on Historical Pharmacy, 1904–1967* (Madison, WI: American Institute of the History of Pharmacy, nd), which includes subject and author indexes; although it emphasizes American history, it is by no means restricted to it. The "Pharmacy" section of the annual bibliography in the *Bulletin of the History of Medicine* at one time offered an important key to the literature, which was cumulated in *Bibliography of the History of Medicine of the United States and Canada, 1939–1960,* Genevieve Miller, editor (Baltimore: Johns Hopkins University Press, 1964). See also other bibliographies listed earlier in the section on general literature guides. Also noteworthy is the "Bookshelf" section of *Pharmacy in History*, a quarterly of the American Institute of the History of Pharmacy (Madison, WI); and the sections on "History and Ethics," "Sociology and Economics," and "Literature" in the ongoing *International Pharmaceutical Abstracts* (Washington, DC: American Society of Hospital Pharmacists).

A CHRONOLOGY FOR PHARMACISTS

The dating of events often involves uncertainties, approximations, and questions of meaning that are not apparent in a concise table such as that below. Particularly, dates before the 18th century often are unverifiable or estimated.

BCE

2000? **Earliest formulary** known in history (Sumerian).
1500 **Ebers Papyrus**, Egyptian manuscript pertaining to pharmacy and therapy.
460 **Hippocrates**, famous Greek physician, is born.
350 **Diocles** writes an important treatise on materia medica.
372 **Theophrastus** (372–285), the "father of botany," is born.

AD

50 **Dioscorides** writes an important book on materia medica.
130 **Galen**, a Roman physician who experimented with compounded drugs, is born.
303 **Cosmas and Damian**, patron saints of pharmacy and medicine, are martyred.
857 **Johann Mesue Senior** (777–857), Arabian physician, dies.
925 **Rhazes** (865–925), Persian physician, dies.
1035 **Avicenna** (980–1035), physician and philosopher, dies.
1178 **Pharmacists are mentioned in French records.**
1180 **Guild of Pepperers** is already active in London.
1225 **Apothecary shop** is established at Cologne.
1297 **Guild of Pharmacists** is organized in Bruges (Flanders).
1345 **Apothecary shops** have been established in London.
1348 **The Black Death** (bubonic plague) strikes Europe.
1480 **Poison law** is enacted by James I of Scotland.
1499 **Guild pharmacopoeia** is published in Florence, Italy.
1529 **Paracelsus** (1493–1541) publishes his first treatise.
1546 **The Nuremberg Pharmacopoeia** (Dispensatory of Valerius Cordus) is perhaps the first to become "official."
1589 **Galileo Galilei** demonstrates the law of falling bodies.
1604 **Louis Hébert** becomes first pharmacist to settle in North America.
1617 **Society of Apothecaries** in London is organized.
1618 **First London pharmacopoeia** is published.
1620 **Pilgrims** settle at Plymouth, Massachusetts.
1628 **William Harvey** publishes his book on the **circulation of the blood**.
1646 **William Davis** operates an apothecary shop, possibly one of the first in America (Boston).
1665 **Sir Isaac Newton** describes the law of gravitation.
1680 **Antonie van Leeuwenhoek** discovers **yeast** plants.
1703 **English apothecaries are authorized to prescribe** as well as dispense.
1715 **Bartram's Botanical Gardens** established at Philadelphia.
1718 **E-Fr Geoffroy,** French pharmacist, establishes the first tabulation of relationships between chemical substances.
1736 **First law related to pharmacy** in America is enacted in Virginia.
1752 **First hospital pharmacy** in America is established at Pennsylvania Hospital in Philadelphia; Jonathan Roberts is the apothecary.
1762 **Antoine Baumé** publishes his *Élémens de pharmacie* in France.
1765 **John Morgan,** American medical education pioneer, advocates **prescription writing** in US.
1773 **Karl Wilhelm Scheele isolates oxygen** about 1773; **Joseph Priestley** independently isolates oxygen by 1774.
1774 **Scheele** discovers **chlorine.**
1776 **Declaration of Independence** is written, and the position of Apothecary General is created for the Continental Army.
Christopher Marshall, famous American pharmacist, makes medicines for wounded soldiers.
1777 **Collége de Pharmacie** is established in Paris.
1783 **Pilâtre de Rozier,** a pharmacist, makes **first human flight** in a balloon accompanied by the Marquis d'Arlandes.
1785 **William Withering** publishes his treatise on **digitalis**.
Thomas Fowler introduces **Fowler's Solution** (potassium arsenite solution).
1787 **Ergot** introduced in obstetrics by **Paullitzsky**.
1790 **First US patent law passed**. Elisha Perkins takes out first medical patent in 1796.
1793 **Yellow fever epidemic** strikes Philadelphia.
Trommsdorff's *Journal der pharmacie* is founded, the first professional-scientific journal devoted to pharmacy.
1798 **Edward Jenner** publishes his work on **vaccination**.
1805 German pharmacist **Friedrich Sertürner** reports isolation of **morphine**.
1809 ***Journal de pharmacie et de chimie*** founded; first published as *Bulletin de pharmacie.*
1811 **Bernard Courtois**, a French pharmacist, discovers **iodine**.
1818 French pharmacist-chemists **Joseph Caventou** and **Pierre Pelletier** isolate **strychnine**.
1820 **Pelletier** and **Caventou** isolate **quinine**.
First edition of *United States Pharmacopoeia* is published.
1821 **Philadelphia College of Pharmacy** is founded as the first local association and school of pharmacy in the United States.
1823 **Massachusetts College of Pharmacy** founded.
1825 **First American professional journal of pharmacy published**, the *American Journal of Pharmacy.*
1826 **Antoine Balard,** French pharmacist, discovers **bromine**.
Hennel synthesizes **ethyl alcohol**.
1828 **Friedrich Wöhler** synthesizes **urea**, thus bridging gulf between organic and inorganic chemistry.
1829 **New York College of Pharmacy** is founded.
1831 **Chloroform** is prepared independently by **Justus von Liebig** and by **Eugene Soubeiran**.
1832 **Pierre Robiquet,** French pharmacist, isolates **codeine**.
1834 **Friedlieb Ferdinand Runge,** German pharmacist, prepares **carbolic acid** and **aniline**.
1842 **Crawford Long** performs the first **operation using ether anesthesia**.
1843 **Oliver Wendell Holmes** points out that puerperal fever is contagious.
1848 **First American code of pharmaceutical ethics** prepared by Philadelphia College of Pharmacy.
First drug import law enacted by Congress to curb adulterations.
1852 **American Pharmaceutical Association**is founded as the first national organization.
Charles Darwin publishes his *Origin of Species.*
1865 **First international pharmaceutical conference** is held in Brunswick, Germany.
1868 **University of Michigan** opens pharmacy course that will have far-reaching influence in modernizing American pharmaceutical education.
1883 **First National Retail Druggists Association** founded.
1888 **First National Formulary** issued by American Pharmaceutical Association.
1890 **Emil von Behring** and **Shibasaburo Kitasato** introduce **serum therapy**.
1893 **Felix Hoffmann** and **Arthur Eichengrün** discover **aspirin**.
1895 **Wilhelm Roentgen** discovers **x-rays**.
1898 **Marie** and **Pierre Curie** discover **radium**.

National Association of Retail Druggists is founded in the US.

1899 **Walter Reed** proves mosquitoes carry **yellow fever**.

1900 **American Association of Colleges of Pharmacy** is founded.

1902 **First International Pharmacopeial Conference** held at Brussels, Belgium.

First American PhD supervised in pharmacy granted at University of Wisconsin.

1906 **Federal Food and Drugs Act** passed in the US.

1910 **Paul Ehrlich** and **Sahachiro Hata** introduce **arsphenamine** (also known as Salvarsan or "606") in widespread clinical trial for the treatment of syphilis.

1912 **First** Assembly of **International Pharmaceutical Federation** (The Hague, Netherlands).

1922 **Sir Frederick Banting** and **Charles Best** isolate **insulin**.

1928 **Sir Alexander Fleming** discovers **penicillin**, the first antibiotic.

1935 **Gerhard Domagk** introduces **prontosil**, the first sulfa drug.

1937 ***American Journal of Pharmaceutical Education*** is founded, the first periodical devoted to **pharmaceutical education**.

1938 **League of Nations Commission on International Pharmacopeial Standards** holds conferences.

Important revision of Federal Pure Food and Drugs Act (US).

1940 **Howard Florey** and **Ernst Chain** hold the first **clinical trials of penicillin**.

1942 **American Society of Hospital Pharmacists** is founded.

1944 Antibiotic activity of **streptomycin** is announced.

1945 **Atomic energy** released for use in warfare and medicine.

1947 **Medical Service Corps** created in US Army, with pharmacy represented by special group of commissioned officers.

1948 **First Pan-American Congress of Pharmacy and Biochemistry**.

1949 **Cortisone** and **ACTH** are introduced for rheumatic arthritis.

Influence for change initiated by analysis and suggested reforms from **Pharmaceutical Survey** (US).

1951 **First International Pharmacopoeia** of the World Health Organization.

1952 **Chlorpromazine** is introduced into psychiatry, thus opening the field of psychopharmacology.

1955 **Salk poliomyelitis vaccine** is released for general use.

1959 **Synthetic modifications of natural penicillin** introduced.

American Society of Pharmacognosy founded.

1962 Important amendments of the **US Food, Drug, and Cosmetic Act**.

1969 American Society of **Consultant Pharmacists** (ASCP) established.

1973 US Supreme Court decision (No 72-1176) holds that states may require that licensed pharmacists have **ownership-control of pharmacies**.

Congress enacts **Health Maintenance Organization** Act.

1975 Official **drug standardization program** is unified by US Pharmacopeia absorbing National Formulary.

Report by Study Commission on Pharmacy (AACP) gives impetus to trend toward drug information and **counseling role** of pharmacists.

1977 Clinical trials of **adenine arabinoside** against herpes raise prospect of **controlling viral diseases**.

1979 **American College of Clinical Pharmacy** is founded.

1982 **Specialty certification** begins in American pharmacy with the board certification of 63 pharmacists in the field of nuclear pharmacy.

1984 Drug Price Competition and Patent Term Restoration Act encourages **growth of generics**.

1986 **American Association of Pharmaceutical Scientists** is founded.

1989 **American Council on Pharmaceutical Education** (ACPE) announces intent to develop accreditation standards for **Doctor of Pharmacy** programs only.

1990 Omnibus Budget Reconcilation Act (OBRA) requires that **pharmacists counsel Medicaid patients** (effective 1993).

1995 **Pharmacy Technician** Certification Board formed.

1996 National Association of Retail Druggists (f. 1898) **changes name** to National Community Pharmacists Association.

1997 **National Association of Boards of Pharmacy** (NABP) proposes **regular competency tests** for pharmacists.

2003 After 150 years, the APhA changes its name to the **American Pharmacists Association**.

CHAPTER 3

Ethics and Professionalism

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Robert L McCarthy, PhD

The quest to construct systematically an ethical framework for Western civilization was begun over 2000 years ago by Socrates. He approached ethics as a science, as being "governed by principles of universal validity, so that what was good for one was good for all, and what was my neighbor's duty was my duty also."[1] However, acceptance of the Socratic approach has proved burdensome. After 2000 years of effort, humankind universally adheres to not even one ethical principle.

No set of ethical principles, no matter how carefully thought out or how well constructed, can provide the individual professional with guidance for each decision about clients, peers, or society. There are people who believe that because each situation is different, each decision requires separate analysis of possible outcomes from different actions and the weighing of right and wrong. Regardless of one's stance or approach, however, the health professional in today's society needs continual self-examination of professional duties and ethical principles to be prepared for the conflicts and dilemmas they will face.

BEING PROFESSIONAL

In this discussion, professional ethics is used only to denote "the profession's interpretation of the will of society for the conduct of the members of that profession augmented by the special knowledge that only the members of the profession possess."[2] In other contexts, the term might be used to denote those ethical principles to which society believes any individual claiming professional status should subscribe. What is to be gained by development of a set of ethical principles, or a code of ethics (Fig 3-1), by a profession to which it expects its members to abide?

First, a code of ethics makes the decision-making process more efficient. In opposition to situational ethicists, Veatch claims:

> "Yet if those who must resolve the ever-increasing ethical dilemmas in medicine—including patients, family members, physicians, nurses, hospital administrators, and public policy-makers—treat every case as something entirely fresh, entirely novel, they will have lost perhaps the best way of reaching solutions: to understand the general principles of ethics and face each new situation from a systematic ethical stance."[3]

Clinical practice predisposes pharmacists to a situationalist approach to ethics through its emphasis on individual differences in response to therapeutic regimens. Some guidelines, however, exist for adjusting drug therapy in patients with compromised renal or hepatic function, electrolyte or hormonal imbalance, and other pathological abnormalities. Therapeutic guidelines give us a place to begin solving a clinical problem. Rules of morality serve the same purpose:

> "They may at least act as rules-of-thumb for handling easy cases. They may at least summarize ethical reasoning that has gone before by others who have found themselves in somewhat similar situations. They may at least serve as guidelines for formulating thinking about the problem at hand."[4]

Second, individual professionals occasionally may need guidelines for directing their professional behavior. Each decision made by a professional requires calling upon a store of technological information as well as the individual's own sense of right and wrong. Almost assuredly, all professionals will be confronted with situations that they have never considered in great detail. Where one can find no apparent theological or personal ethical principles to apply, one might turn to professional ethics for guidance.

Finally, professional ethics establish a pattern of behavior that clients come to expect from members of the profession. Once a consistent pattern of behavior is discerned by clients, they expect that behavior to remain constant, and their expectations become part of the relationship they establish with the professional. To better understand the role of and necessity for ethics in professions, one must first look at the characteristics of professions.

PROFESSIONAL CHARACTERISTICS

The first characteristic of a professional is possession of a specialized body of knowledge; using this body of knowledge enables the practitioner to perform a highly useful social function. All lawful occupations provide some positive benefit to society and are based on specialized knowledge. The professions generally are more socially useful than many other occupations, but social utility alone does not make an occupation a profession.

An applied body of knowledge may be composed of knowledge of a manual skill or intellectual knowledge. The latter is of primary significance as a criterion for professions. The pharmacist is not considered a professional because of good typing skills. Rather, he or she possesses the relevant professional knowledge about drugs and patients that permits the pharmacist to advise patients and prescribers concerning drug therapy, detect drug interactions, select appropriate product sources, and exercise professional judgment.

The exercise of proper judgment is a key element in this first professional characteristic. Professional services traditionally are rendered to an individual rather than to a group. Using the specialized body of knowledge of the profession and the intellectual abilities of the professional, the practitioner makes a judgment as to the best course of treatment for each individual.

Code of Ethics

American Pharmacists Association

Preamble

Pharmacists are health professionals who assist individuals in making the best use of medications. This Code, prepared and supported by pharmacists, is intended to state publicly the principles that form the fundamental basis of the roles and responsibilities of pharmacists. These principles, based on moral obligations and virtues, are established to guide pharmacists in relationships with patients, health professionals, and society.

I. A pharmacist respects the covenantal relationship between the patient and pharmacist.

Considering the patient-pharmacist relationship as a covenant means that a pharmacist has moral obligations in response to the gift of trust received from society. In return for this gift, a pharmacist promises to help individuals achieve optimum benefit from their medications, to be committed to their welfare, and to maintain their trust.

II. A pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner.

A pharmacist places concern for the well-being of the patient at the center of professional practice. In doing so, a pharmacist considers needs stated by the patient as well as those defined by health science. A pharmacist is dedicated to protecting the dignity of the patient. With a caring attitude and a compassionate spirit, a pharmacist focuses on serving the patient in a private and confidential manner.

III. A pharmacist respects the autonomy and dignity of each patient.

A pharmacist promotes the right of self-determination and recognizes individual self-worth by encouraging patients to participate in decisions about their health. A pharmacist communicates with patients in terms that are understandable. In all cases, a pharmacist respects personal and cultural differences among patients.

IV. A pharmacist acts with honesty and integrity in professional relationships.

A pharmacist has a duty to tell the truth and to act with conviction of conscience. A pharmacist avoids discriminatory practices, behavior or work conditions that impair professional judgment, and actions that compromise dedication to the best interests of patients.

V. A pharmacist maintains professional competence.

A pharmacist has a duty to maintain knowledge and abilities as new medications, devices, and technologies become available and as health information advances.

VI. A pharmacist respects the values and abilities of colleagues and other health professionals.

When appropriate, a pharmacist asks for the consultation of colleagues or other health professionals or refers the patient. A pharmacist acknowledges that colleagues and other health professionals may differ in the beliefs and values they apply to the care of the patient.

VII. A pharmacist serves individual, community, and societal needs.

The primary obligation of a pharmacist is to individual patients. However, the obligations of a pharmacist may at times extend beyond the individual to the community and society. In these situations, the pharmacist recognizes the responsibilities that accompany these obligations and acts accordingly.

VIII. A pharmacist seeks justice in the distribution of health resources.

When health resources are allocated, a pharmacist is fair and equitable, balancing the needs of patients and society.

Figure 3-1. Code of ethic (Originally published in "Code of Ethics for Pharmacists." *Am J Health-Syst Pharm* 1995; 52: 2131. © 1995, American Society of Health-System Pharmacists, Inc. All rights reserved. Reprinted wiith permission.)

The second characteristic of a professional is a set of specific attitudes that influence professional behavior. The basic component of this set of attitudes is altruism, an unselfish concern for the welfare of others:

> "The professional man, it has been said, does not work in order to be paid: he is paid in order that he may work. Every decision he makes in the course of his career is based on his sense of what is right, not on his estimate of what is profitable."[5]

Professionals are concerned with matters that are vital to the health or well-being of their clients. The practitioner employs highly specialized technical knowledge, which the patient or client does not possess. Both the client's lack of knowledge and the vital nature of professional services provide the professional with an opportunity to exploit the client. The consequences of such exploitation are severe. The smooth functioning of the professions requires that the practitioner must consider the needs of the patient as paramount, relegating his or her own material needs to an inferior position.

Social sanction, the third characteristic of a professional, is a resultant effect of the two characteristics already discussed. Whether an occupation is considered to be a profession depends, to a large degree, on whether society views it as such. One measure of social sanction is the granting of exclusive rights of practice through the licensing power of the state.

Licensing not only attempts to protect the public from incompetent practitioners, but also frequently creates a relationship of trust between society and the professionals, because within the sphere of professional activities, the professional exercises an authoritative power over patients. As explained by Greenwood,

> "[T]he professional dictates what is good or evil for the client, who has no choice but to accede to professional judgment. Here the premise is that, because he [or she] lacks the requisite theoretical background, the client cannot diagnose his [or her] own needs or discriminate among the range of possibilities for meeting them."[6]

The extent of the public's trust is a measure of the degree of social sanction, and this is evident in society's permitting the exercise of sovereign power over professional matters. Given the legal monopoly inherent in professional licensing, the failure of society to impose further controls on the profession is sanctioning, by implication, the profession's performance and self-regulation. Thus, professions have evolved as occupations connected with high status. The functional relationship of professions to

Oath of a Pharmacist

American Association of Colleges of Pharmacy

At this time, I vow to devote my professional life to the service of all humankind through the profession of pharmacy. I will consider the welfare of humanity and relief of human suffering my primary concerns. I will apply my knowledge, experience, and skills to the best of my ability to assure optimal drug therapy outcomes for the patients I serve.

I will do my best to keep abreast of developments and maintain professional competency in my profession of pharmacy. I will maintain the highest principles of moral, ethical, and legal conduct. I will embrace and advocate change in the profession of pharmacy that improves patient care. I take these vows voluntarily with the full realization of the responsibility with which I am entrusted by the public.

Figure 3-2. Oath of a pharmacist. (From http://www. aacp.org/site/ tertiary.asp? TRACKID 5 & VID 5 2 & CID 5 686 & DID 5 4339. Accessed May 14, 2004.)

society reinforces their status position, and the status itself acts as a motivating factor in the drive of any occupation to gain recognition as a profession.

Several studies have attempted to identify which occupations qualify as professions. The most prominent study was done by Carr-Saunders and Wilson in 1933.[7] Primarily because of the commercial elements inherent in modern pharmacy practice, the study reached no definitive conclusion as to pharmacy's professional status. More recent studies have produced similar results. Montague,[8] Smith,[9] Smith and Knapp,[10] and Denzin and Mettlin[11] consistently found pharmacy to fall short of full professional status. The key issues include a lack of autonomy (eg, pharmacists follow orders, fill prescriptions, decided by others, the prescriber) and potential or real conflicts regarding professional compensation based more so on products than on services (eg, pharmacists counsel patients on nonprescription products without charging a fee, but compensation comes through the sale of that product).

All professions, however, can be found to fall short of being a complete profession in at least a few respects. Pharmacy has a legitimate claim to a theoretical body of knowledge, to a growing degree of socially sanctioned decision-making authority, and to a commitment of service functions as articulated by a code of ethics and an oath (Fig 3-2) that is sworn by individuals entering the profession.

ETHICAL DECISIONMAKING

Pharmacy ethics has received a great deal of recent attention, but the study of ethics, ethical questions, and codes of ethics has been an integral component of pharmacy and medical practice for centuries. The first code of ethics for medicine was credited to Hippocrates in the 4th century BC. In many ways, the Hippocratic code is timeless. For example, his direction that no physician should "give a deadly drug to anybody if asked for it, nor . . . make a suggestion to this effect"[12] provides one moral perspective on the contemporary issue of assisted suicide.

Over the past decade or so, the attention given to pharmacy ethics in the professional and scientific literature, and in schools and colleges of pharmacy, has changed a great deal. Only 2 of the 52 schools that responded to a 1980 survey required a formal, separate course in ethics; 32 schools offered no course, required or elective, of which ethics was an explicit part.[13] Today, however, most pharmacy schools require some instruction in ethics. A 1991 survey of ethics instruction at pharmacy schools found that, "while the quantity of ethics instruction has not increased, there are encouraging signs that the quality and depth of ethics education is improving."[14]

Several factors appear responsible for the heightened attention given to the study of ethics in pharmacy, including the explosion of biotechnology and the rapidly rising cost of health care in the US, of which drugs are an important component.

Macro Ethical Issues versus Micro Ethical Situations

Ethical situations in pharmacy can be divided into two broad categories: macro and micro.

Macro ethical issues are issues that are not specific to a given pharmacist, but rather are those that must be addressed by all pharmacists and by society in general. These include abortion, assisted suicide, genetic engineering, rationing of and access to health care, organ transplantation, and *in vitro* fertilization.

Micro situations are those issues that may confront individual pharmacists in the course of their daily practice. They include the use of placebos, patient confidentiality (eg, revealing information about a patient's medications to members of the family), and informed consent (eg, what and how much information about a medication should be disclosed to a patient).

Sometimes, *macro* issues are manifested in *micro* situations. This is especially true with socially controversial issues. For example, a pharmacist may receive a prescription for a drug and know that it is intended for use in an assisted suicide. Not only must the pharmacist deal with the legal issues involved, but also with the ethical responsibility as a health care professional. A further complication in such situations is the influence of the pharmacist's personal beliefs in choosing the course of action.

Competence, Trustworthiness, and Caring

Any examination of pharmacy ethics must begin with a discussion of the basic moral responsibilities that all health care practitioners have toward their patients. Berger[15] has attempted to describe the characteristics that a pharmacist should possess:

1. Pharmacists must be competent. They must possess a knowledge base that at least minimally allows them to carry out their functions as reliable therapeutic experts.
2. Pharmacists must be trustworthy. Patients must know that they can seek the confidential advice and assistance of their pharmacist and that their wishes will be carried out.
3. Pharmacists must care for and about their patients. As the 1995 American Pharmaceutical (now Pharmacists) Association (APhA) Code of Ethics directs, "A pharmacist places concern for the well-being of the patient at the center of professional practice."[16]

Pharmacists, unfortunately, do not always effectively communicate their concern for the welfare of their patients. All too often patients perceive just the opposite. Busy practitioners who fail to spend adequate time interacting with their patients do little to alter this perception. Conversely, pharmacists who do spend time with their patients and attempt to understand their concerns are much more likely to be viewed as caring.

Health Professional–Patient Relationship: Consumerism Versus Paternalism

It was not long ago that when a patient was instructed by their physician or pharmacist to take a medication, they did so with-

out question. Medical paternalism—the belief that the health care professional knew best—was accepted as standard practice by most health care professionals and their patients. The medical rights of patients were not as widely recognized as other rights they held, such as suffrage or due process. Today, patients have become true consumers of medical care. Patients wish, and have a right, to be informed and asked for their consent. For a health care professional to do otherwise would not only be unprofessional and unethical, but also have potential legal ramifications.

Patients also expect a certain level of service. As with sellers of other goods and services, health professionals who fail to meet the demands of medical consumers for care will quickly find themselves without customers and, sometimes, with legal problems.[17]

Moral Rights Versus Legal Rights to Health Care

Any discussion of pharmacy ethics must be clear about what is meant by the term *right*. In this society, one frequently refers to the legal rights of individuals. *Legal rights* are either guaranteed fundamentally in the US Constitution (eg, the rights of free speech and assembly) or are provided by laws and regulations promulgated at the federal, state, or local level. We sometimes confuse what are really legal rights with our moral obligations.

Moral rights are quite different from legal rights. Granted, these rights may be reinforced by laws, but their basis lies not in law but in ethical principles. Such rights might include the right to live without fear of harm and the right to food and adequate shelter. More recently, Americans have grappled with the question of health care as a moral right.

As one might expect, moral rights and legal rights may conflict. There is disagreement, for example, over whether issues such as abortion involve moral rights or legal rights.

Patient's Rights

When a patient seeks the care of a pharmacist, what rights do they have? What can they reasonably expect from pharmacists? Patients can expect that pharmacists will employ their knowledge and experience in caring for them. They can expect that, as autonomous individuals, pharmacists will respond to their wishes about their treatment.

The American health care system seems fundamentally based upon ensuring the rights of patients. Patients generally choose their own physician, pharmacy, and hospital. Patients are allowed to choose from multiple options of treatment when they exist. Patients must give their approval, through the process of informed consent, prior to the initiation of care. All of the preceding presupposes that treatment is available and that the patient has the economic wherewithal to pay for that treatment. For patients who are uninsured or lack the ability to pay, the right to choose the nature of their health care is meaningless.

Patients also have a right to treatment that is both safe and effective within given parameters. The fundamental question that must be posed prior to considering any medical or surgical treatment for a patient is, Is the treatment safe and effective? Such a legal standard for drugs has been in effect since the passage of federal legislation in the early part of the 20th century.[18] Not only must a drug be shown to be effective—that is, able to produce the effect for which it was administered—it must work with a certain degree of safety.

Medical Practitioners' Duty to Their Patients

What is the responsibility of medical practitioners? Some might argue that health care providers have a Hippocratic responsibility to their patients, and that this responsibility focuses solely on what is best for the patient, irrespective of the consequences to others. This view is supported by the Code of Ethics of the APhA (American Pharmaceutical Association, now called the American Pharmacists Association), which states in part that "a pharmacist promotes the good of every patient in a caring, compassionate, and confidential manner."[16]

The Code appears to suggest that pharmacists have a moral obligation to do whatever they deem necessary in the interest of their patients. But the Code goes on to state that "a pharmacist serves individual, community and societal needs."[16] What then is the extent of the pharmacist's duty to his or her patients? Is it the pharmacist's moral obligation to care for them without exception?

Legal Responsibility Versus Moral Obligation

Rem Edwards provides an example of a radical interpretation of the Hippocratic oath insofar as he asserts that medical professionals have an obligation to do whatever is necessary to relieve the pain and suffering of their patients.[19] Edward's contention, however laudatory, has serious flaws when applied to pharmacists. All pharmacists practice under the practical constraints of law that may limit their doing *whatever is necessary*. Consequently, although they have a moral obligation to care for their patients, this obligation is constrained by law.

Thus, patient rights and practitioner responsibility may sometimes be in conflict, not on ethical grounds but on legal ones. Directing a pharmacist to assume an individualistic approach and take an illegal, yet ethical, action for a patient despite legal consequences is asking the pharmacist to subjugate his or her own interests to that of the patient.

ETHICAL RESPONSIBILITY

In traditional pharmacy practice, both the legal and ethical obligations of pharmacists centered around ensuring that the proper medication as ordered by the prescriber was delivered to the patient. Physicians, not pharmacists, were the health care professionals who held ultimate responsibility for monitoring the progress of a patient and ensuring that the desired outcome was achieved.

The concept of "pharmaceutical care," however, directs that this responsibility is to be a shared obligation between the prescriber and the pharmacist.[17] According to the Commission to Implement Change in Pharmaceutical Care, the mission of pharmacy practice is to render pharmaceutical care. Pharmaceutical care focuses pharmacists' attitudes, behaviors, commitments, concerns, ethics, functions, knowledge, responsibilities, and skills on the provision of drug therapy with the goal of achieving definite outcomes toward the improvement of the quality of life of the patient.[20] Pharmaceutical care forces pharmacy practitioners to change their focus, broaden their professional responsibility.

VEATCH'S FRAMEWORK FOR ETHICAL ANALYSIS

Robert Veatch[21] has suggested a framework for ethical analysis that can be used by pharmacists to determine the ethical course of action to follow in a given situation. His four-step approach involves (1) ensuring adequate knowledge of all the pertinent facts involved in a given situation, and the application of (2) moral rules, (3) ethical principles, and (4) ethical theories.

Veatch contends that some ethical situations can be solved without the application of moral rules, ethical principles, or ethical theories. Sometimes an ethical dilemma can be solved by simply ensuring all the facts are known about a case (step 1). For example, a question of whether to break patient confiden-

tiality might be moot if the patient has already agreed to allow the health professional to divulge such information.

If step 1 does not provide an answer, the professional may proceed to step 2, the application of moral rules. The rules of confidentiality and/or consent (informed consent) may offer some guidance. If a dilemma still exists, ethical principles may be employed (step 3). These include autonomy, beneficence, nonmaleficence, veracity, fidelity, and justice. Ethical theories, Veatch suggests, are the ultimate arbiter of ethical dilemmas (step 4).

ETHICAL THEORIES

Although many approaches to ethics (such as virtue-based and feminist theories) have applicability to the biomedical field, the majority of contemporary biomedical texts focus on two prominent types: teleological (consequentialist) theories and deontological (nonconsequentialist) theories.

Teleological theories, such as utilitarianism, state that the rightness or wrongness of an action depends on the consequences produced. As Beauchamp and Childress suggest, "Consequentialism is the moral theory that actions are right or wrong according to their consequences rather than any intrinsic features they may have, such as truthfulness or fidelity."[22] Utilitarianism, as a consequentialist theory, directs that the most appropriate course of action is that which will produce the *greatest good for the greatest number* when the consequences of all action alternatives in a given situation are weighed.

Conversely, deontological theories, such as Kantian ethical theory, argue that the rightness or wrongness of an action is independent of the actions produced. As Beauchamp and Childress point out, "Deontologists maintain that the concepts of obligation and right are independent of the concept of good and the right actions are not determined exclusively by the production of good consequences."[23] Deontologists maintain that factors such as integrity and truth must be included when determining the ethical acceptability of a given action.

ETHICAL PRINCIPLES AND MORAL RULES

Pharmacists have an ethical obligation to care for their patients. Moral rules and ethical principles, rather than ethical theories, are more likely to be the *tools* used by pharmacists on a daily basis as they face ethical situations. Ethical principles and moral rules provide guidance for practitioners about what the commitments of patient care entail.

Autonomy

The principle of autonomy states that an individual's liberty of choice, action, and thought is not to be interfered with. As Beauchamp and Childress have noted, "Autonomy has . . . been used to refer to a set of diverse notions including self-governance, liberty rights, privacy, individual choice, liberty to follow one's will, causing one's own behavior, and being one's own person."[24]

In health care, we think of autonomy as the right of individuals to make decisions about what will happen to their bodies, what choices will be made among competing options, and what they choose to take, or not take, into their bodies. We also allude to questions of autonomy when we refer to choice among health care providers, and the choice of refusing medical treatment.[25] There are two ethically justifiable exceptions to the principle of autonomy: weak paternalism and the harm principle.

The concept of medical paternalism is in direct conflict with the principle of autonomy. Medical paternalism suggests that pharmacists and other health care professionals—because of their education and training—know what is best for their patients. As a result, health care professionals believe they are justified in overriding the autonomy of a patient. Medical paternalism dominated Western medical practice until the last several decades, when the primacy of patient rights and the concept of medical consumerism became recognized.

A form of medical paternalism, weak paternalism, still allows the autonomy of an individual to be violated if that individual is not or does not appear to be autonomous, or if minimal intervention is necessary to determine whether the patient is autonomous. Some have argued that weak paternalism isn't paternalism: if one lacks the ability to make an autonomous decision, then how can his or her autonomy be overridden? Weak paternalism has remained generally accepted as a justifiable exception to the principle of autonomy.

Strong paternalism—the violation of the autonomy of another person because you believe they are either making the wrong decision or a decision that will cause harm to themselves—is not considered an ethically justifiable reason to override a patient's autonomy. However, under the harm principle, one is justified in overriding the autonomy of another if, in the exercise of that autonomy, harm may come to others.

Informed Consent

The principle of autonomy is a vital component of informed consent. For example, when one provides informed consent to an individual contemplating participation in a clinical research trial, one respects the right of that individual to make an autonomous decision. The rule of informed consent directs that patients must be fully *informed* about the *benefits* and *risks* of their participation in a clinical trial, taking a medication, or electing to have surgery, and this disclosure must be followed by their autonomous consent.

For legal and ethical reasons, informed consent is always obtained formally in situations such as clinical research and surgery through an informed consent form. In the case of clinical research, these documents are usually drafted by the investigator or pharmaceutical manufacturer and subsequently are approved by the institutional review board (IRB) where the research will take place. The role of the IRB will be discussed later in this chapter.

Informed consent is also obtained informally in some instances. For example, whenever a pharmacist counsels a patient and dispenses a medication to a patient, a type of informal informed consent occurs. The patient is informed about the benefits and any risks of the drug, and then decides whether to take it. Informed consent is composed of five elements: disclosure, understanding, voluntariness, competence, and consent.[25]

Disclosure directs that all the pertinent information that is necessary for an informed decision must be made available to the patient. *Understanding* requires that patients fully understand what they are consenting to, including any benefits or hazards. *Voluntariness* instructs that patients who choose to enroll in a research endeavor or be compliant in taking medication must be free from coercion. *Competence* requires that patients be autonomous individuals, who have the functioning ability to make decisions for themselves. *Consent* provides the patient with a point of decision, and is the final legal and moral criterion to be met in ensuring that informed consent has been obtained.

Confidentiality

The rule of *confidentiality,* like informed consent, is an application of the principle of patient autonomy. When pharmacists keep information private from others, unless the patient gives permission to release it, they respect the autonomous decision of the individual. Medical confidentiality need not be requested explicitly by patients; all medical information, by nature, is generally considered to be confidential, unless the patient

grants approval for its release. Confidentiality and privacy have received a great deal of attention recently with the passage and implementation of the Health Insurance Portability and Accountability (HIPAA) Act.

Though often used interchangeably, the terms *confidentiality* and *privacy* do differ. A violation of privacy occurs in situations where personal information is obtained/revealed by an individual who has not been granted access to such information. A computer hacker would be an example. Conversely, a violation of confidentiality results from the inappropriate release of personal information to others by a person, such as a health care professional, who has been granted access to such information.

In health care, it is sometimes unclear which members of the health care team may have access to confidential medical records without the express consent of the patient. Should a pharmacist or physical therapist caring for a patient have the same access to medical records that is afforded the patient's physician or hospital nurse? Another difficult ethical situation involves a patient who explicitly expresses a desire not to have information divulged to a member of the health care team. For example, a patient may tell a pharmacist of her decision to alter her prescribed therapeutic regimen, but request that the pharmacist not disclose this information to her physician.

Confidentiality has the same two ethically justifiable exceptions as does the principle of autonomy, the harm principle, and weak paternalism. As with autonomy, a pharmacist may be ethically justified in violating the confidentiality of a patient when keeping information private may harm others (harm principle) or when the patient lacks autonomy (weak paternalism).

Beneficence/Nonmaleficence

Beneficence and nonmaleficence are ethical principles that are, in a sense, complimentary to one another. Beneficence indicates that you act in a manner to *do good*. Nonmaleficence refers to *taking due care or avoiding harm*. Beauchamp and Childress compare these related principles:

> The word nonmaleficence is sometimes used more broadly to include the prevention of harm and the removal of harmful conditions. However, because prevention and removal require positive acts to assist others, we include them under beneficence along with the provision of benefit. Nonmaleficence is restricted . . . to the noninfliction of harm.[26]

Fidelity

Fidelity requires that pharmacists act in such a way as to demonstrate loyalty to their patients. A type of bond or promise is established between the practitioner and the patient. This professional relationship places on the pharmacist the burden of acting in the best interest of the patient. Pharmacists have an obligation of fidelity to all their patients, regardless of the length of the professional relationship. In community pharmacy, for example, practitioners have the same obligation to show fidelity to an occasional patient as they have for a *regular* customer.[17]

The depth of the fidelity relationship between the pharmacist and patient is a topic of ongoing discussion among pharmacy ethicists. Two forms of fidelity are frequently alluded to: covenantal and contractual. Covenantal fidelity is often described as an intimate and spiritual commitment between individuals. Examples would include the fidelity of marriage and the fidelity between a member of the clergy and his or her congregation. Conversely, contractual fidelity does not involve a level of commitment beyond that owed another as the result of a binding agreement. An example of this form of fidelity would be the relationship one might have with a contractor such as a plumber or electrician. What remains in dispute is where the pharmacist–patient relationship lies along the continuum between covenant and contract.

Veracity

Veracity is the ethical principle that instructs pharmacists to be honest in their dealings with patients. There may be times when the violation of veracity may be ethically justifiable (as with the use of placebos), but the violation of this principle for non-patient-centered reasons would appear to be unethical. In a professional relationship based upon professional fidelity, patients have a right to expect that their pharmacist will be forthright in dealings with them.[17]

Distributive Justice

Distributive justice refers to the equal distribution of the benefits and burdens of society among all members of this society. We often think of distributive justice in terms of our health care delivery system. This principle is frequently used as a justification for providing health care as a right to all Americans.

Even though justice instructs that pharmacists demonstrate an equivalent amount of care, pharmacists do not always provide care with equal fervor to all patients. Sadly, issues such as the patient's socioeconomic status often impact the level and intensity of care provided by health care professionals. Medicaid patients are sometimes provided a much lower quality of care than a patient who is a cash-paying customer or who has a full-coverage drug benefits plan. All too often, the care provided by a health care professional is viewed in terms of the personal reward for the professional, such as the level of reimbursement the care is likely to reap. Justice demands that the focus be on patients and their medical needs, not on the financial impact on the health care professional.[17]

ETHICAL CODES

Ethical principles and rules that apply to medical practice and research, such as autonomy, beneficence, and justice, have long served as the basis for a system or code of ethical conduct. Western medical ethics is primarily based on the Hippocratic code attributed to the Greek philosopher Hippocrates, 5th century BC Medicine (American Medical Association) and pharmacy (Philadelphia College of Pharmacy) developed codes of conduct for their respective practitioners in 1848. As Montagne notes, "the guiding principles of these codes were a respect for human life and service to humanity."[27] The Holocaust during World War II, and the subsequent Nuremberg trials, would prompt the first major development of a code dealing specifically with experimentation on human subjects.

Subsequent to Nuremberg, several other codes of medical ethics were established. In 1949, the World Medical Association drafted the Geneva Convention Code of Medical Ethics, a contemporary version of the Hippocratic oath. In the 1960s, the same organization established an ethical code on clinical research. In 1964, the Declaration of Helsinki was adopted based upon the Nuremberg principles, and it was further revised in 1975. In 1972, the American Hospital Association issued a *Statement on a Patient's Bill of Rights*. In 1977, the Declaration of Hawaii provided ethical guidelines for clinical research in psychiatry.[27]

Ethical codes provide health care professionals with ethical principles and standards by which to guide their practice. However, ethical principles and codes cannot hope to provide health care professionals with answers to every moral question that may arise in the course of their practice. Ethical questions in health care involve decision-making that is usually situation-specific. The purpose of such principles and codes is not to provide practitioners with right and wrong answers, but to offer them a framework to use when faced with ethical questions. As

Montagne points out, "the formulation of an oath or ethical code does not remove the moral choices and the need to carefully consider in each situation and the alternative actions or decisions that can be made."[28]

APhA Code of Ethics

The Code of Ethics of the APhA is the only code of ethics that specifically guides the practice of pharmacy. A careful examination of the evolution of the Code since its inception in 1852 shows both a greater degree of responsibility to the patient expected of the pharmacist and a greater respect for the autonomy of patients.

The first APhA Code in 1852 seemed to reflect the wide acceptance of medical paternalism, the attitude that the *physician knows best.* Amazingly, the code seems to suggest that errors by physicians or pharmacists, unless done with malice, need not—in fact should not—be revealed to patients!

The 1952 version of the Code clearly outlined the duties of a pharmacist, and these were quite in conflict with what is accepted practice today. The 1952 Code instructs, seemingly in direct conflict with what we see as pharmaceutical care today, that "the pharmacist does not discuss the therapeutic effects or composition of a prescription with a patient."[29]

The 1994 Code (see Fig 3-1), much less prescriptive than earlier versions, speaks to the "covenantal relationship between the patient and the pharmacist" and the obligation of pharmacists to promote "the good of every patient in a caring . . . manner."[16] The elements of pharmaceutical care appear throughout, and the Code is consistent with the new mission of pharmacy.

ETHICAL CONFLICTS AND ISSUES IN HEALTH CARE

The conflict between the personal interests of the professional and the duty to subordinate these interests to the benefit of the patient presents one of the major unresolved problems of the professions. In addition, changing patterns in pharmacy and health care delivery present additional ethical conflicts.

The traditional focus of professional service has been on the individual. Professional services have not been mass-produced, but rather each rendering of a service is specifically tailored to the individual needs of a specific patient. In general, the ethics of professions have evolved on the basis of primacy of the individual.

Within the health professions, the impairment of physical or mental functioning as a result of drug use or other factors has become a very important issue. While some studies have indicated that the level of social/recreational drug use among physicians and pharmacists does not differ much from that of general society, the extent of drug-use problems in the health professions is great enough to warrant the development of prevention programs and referral groups.[30] Regardless of the appropriateness or inappropriateness of such drug-taking in general, the professional ethics of the pharmacist should dictate that any degree of impairment while practicing pharmacy is unacceptable. The impact of such impairment on the ability to perform one's professional duties, especially the delivery of patient care, is considerable. Such cases affect the image of pharmacy, the trust of the patient, and impact many other ethical and interpersonal aspects of professional practice.

Innovative uses for old and new drug products have created a number of ethical dilemmas.[31–33] Conflicts continue to occur for many pharmacists when they find themselves faced with dispensing placebogenic agents, oral contraceptives, drugs for lethal injections, and drugs for controlling certain types of behavior (see the bibliography for some representative references in this area). The whole process of modern drug development probably will continue to generate a wide variety of ethical concerns. In a way, these activities might represent the most important type of emerging conflicts for society and for pharmacy, which is viewed as the profession responsible for monitoring and controlling drug use.

Law and Ethics

Many of the laws, regulations, and other rules that govern our daily life are an outgrowth of our morality and ethics. Those laws that prevent homicide, robbery, and other offenses are simply a codification of the values we share as members of society. Unfortunately, laws and regulations cannot be promulgated to cover every eventuality, nuance, condition, or situation. They are created in such a way as to provide legal guidelines for the *usual* or *most common* situation. What should be done, therefore, when such a situation (eg, committing homicide in self-defense) arises, especially if the legal course of action is inconsistent with the ethical course of action?

Conflicts can and will emerge with changes in the laws relating to the practice of pharmacy, in the evolution of new problems and developments in both the profession and the population it serves, and in the roles and functions of drug use in our society. The conflict often might be between a certain law or regulation and an ethical principle held by the profession. Many pharmacists have faced dispensing decisions in which the act of providing the drug would be in the best interests of the patient, but it also would violate a specific law or regulation related to the practice of pharmacy, or it would be contrary to his or her own beliefs and ethical stances.

These conflicts occur fairly routinely in pharmacy. For example, what should a pharmacist do when a patient's prescription for heart medicine has been depleted, no refills remain, and the prescriber is unavailable? Clearly, most pharmacists would do the ethical thing and provide such patients with a few doses to hold them over until a new prescription can be obtained, even though this course of action is illegal. To follow the example a bit farther, what if the medication is a controlled substance used for pain control in a terminally ill patient? The potential for legal action from drug enforcement authorities might make a pharmacist reluctant to dispense extra doses, even though the patient might be in just as much need.

Rationing of Health Care Services

As the cost of providing health care services continues to grow, some have suggested and even attempted to implement a system that would ration the availability of health care. American health care policy makers have tried to avoid this approach because it represents a contradiction with a long-standing implicit belief that all that can be done for each patient ought to be done. Medical insurance, both publicly and privately funded, has attempted to support this ideal. But, in the absence of cost-containment, rising insurance rates have resulted, thereby driving individuals out of the health insurance system and threatening the viability of governmental programs.

The consequence of this policy is seen in both increasing numbers of individuals who are unable to afford health insurance and increasing restrictions on who qualifies for public programs. Therefore, fewer people have access to health care, or at the very least many have decreased choices of where they can receive health care (eg, municipal hospitals, free clinics). As McDermott points out,

> "Approximately 15% of our people [Americans] have no health insurance coverage at any one time, and at least 57 million nonelderly Americans lack health insurance for some part of the year. This does not even include the underinsured and those on Medicaid whose coverage cannot begin to provide them with access that is consistent with good health care."[34]

For at least the present, most American health care planners have determined that rationing of care, in any manner, is not a

viable alternative for dealing with our present crisis, current facts not withstanding.[35–37] At the same time, there is a shared determination by the government and the public at large that reform is essential and, further, that whatever changes are made, they must ensure universal access to health care while controlling costs and reducing fraud.[38,39] As Friedman notes, "high health care costs breed medical indigence; if one is to be fixed, so must the other."[40]

Assisted Suicide

Although medical euthanasia (*mercy killing*) has long been an ethical issue, it has only been in recent years that the question of assisted suicide has been examined. The activities of assisted suicide advocate Dr Jack Kevorkian spurred a great deal of public and professional discussion of this issue.[41–44] Several states have considered the legality of assisted suicide; some have rejected it, while others have accepted it within strict guidelines.[45] The US Supreme Court decided that there is no constitutionally guaranteed right to assisted suicide. This decision has not ended the legal debate, but rather has shifted it to the states, who must decide the legality of assisted suicide on their own.

From an ethical perspective, the key issue remains whether assisted suicide violates the Hippocratic responsibilities of health care practitioners to *do no harm*. Those who advocate its availability to patients suggest that allowing a patient to continue to experience unrelenting pain is doing harm.[46,47] They suggest that patients have the right to make an autonomous decision to end their life; their opponents worry that legal assisted suicide would be abused.

Human Drug Experimentation

Several ethical codes deal with research on human subjects, including the testing of drugs.[48–50] Two important ethical aspects of human drug experimentation are the role of the institutional review board (IRB) and the use of placebos.

The IRB is the body responsible for overseeing all clinical research conducted within a given institution.[51] Traditionally, most clinical drug research was conducted in hospital settings; however, with the shift in the locus of health care delivery from the inpatient to the ambulatory setting, IRBs are now found in managed-care organizations and other ambulatory facilities.

The IRB has two primary responsibilities. The first is to ensure the integrity and scientific rigor of the proposed research study. The risk versus benefit ratio for the study's participants is evaluated. Should the risks outweigh the benefits, the IRB would likely reject the research. The board acts as somewhat of a *subject advocate,* making sure that the rights and welfare of the patient-subject are protected.[52] The IRB's second major responsibility is to evaluate and approve informed consent forms used in conjunction with the research. Such forms should be drafted consistent with the elements of informed consent discussed previously.

IRBs vary in their size and representation. Their membership may include physicians, nurses, other allied health professionals (including pharmacists), institutional administrators, attorneys, clergy, medical ethicists, and community members.[25]

Placebos have generally had two roles in medicine: (1) in clinical drug research, as part of the research methodology; and (2) as a means for providing a therapeutic response in selected patient situations.[53–55] The use of placebos has long been an integral component of clinical drug research. Whether the drug being tested is a new drug compound or an existing drug under study for a new indication, placebos have served as a point of comparison for determining therapeutic efficacy. Although the use of placebos in some instances has been shown to provide therapeutic usefulness (eg, pain control), placebos, by definition, are agents devoid of pharmacologic activity.

Patient-subjects who receive placebos as a component of their participation in a clinical drug study generally cannot hope to derive any benefit (beneficence) from these substances. This raises the question of whether the use of placebos in drug research, despite the obvious scientific advantages, is ethical. The question is further complicated by the expectation that placebos will be employed in clinical research. An FDA regulator has stated, "it is desirable to include some placebo controlled studies unless it is considered unethical to do so."[56] This suggests that the use of placebos is ethical in certain instances, but unethical in others.[25]

The use of placebos to address genuine or perceived therapeutic outcomes is even more ethically problematic. The belief that the health care practitioner *knows best* and, therefore, is justified in practicing medical paternalism has been a long-standing component of the so-called *medical authority* model of practice. Under this model, the perceptions/desires of the patient are subjugated to the judgment of the health care professional. It would be used, for example, as justification for a practitioner to place a patient on a placebo without the knowledge of the patient. In current medical ethic, however, this use of placebos in the absence of the patient's knowledge and consent might be judged to be unethical—a direct violation of patient autonomy and informed consent.

Drug Formularies

Drug formularies are a list of drugs that are approved for use either within an institution or for reimbursement by a third-party payer. Their purpose is to eliminate therapeutic duplication and provide patients with the best drug at the lowest cost.

In the early days of formularies, they were used by hospitals to control drug inventories and provide prescribers with a list of *drugs of choice* for various conditions. However, the absence of a drug from the formulary was not usually a great barrier to a prescriber obtaining it for the patient. A special request could be made by the prescriber to a member of the pharmacy and therapeutics committee of the hospital, and usually the drug would be obtained.

When managed-care organizations (MCOs) and pharmacy benefit management companies (PBMs) began to employ formularies, circumventing them became much more difficult. This restrictive use of formularies has led to a number of important ethical questions. For example, does the use of generic and/or therapeutic substitution violate the autonomy of the patient and/or prescriber? Is the use of such substitution a violation of informed consent? Does the use of formularies violate the ethical principles of beneficence (*do good*) and nonmaleficence (*avoid harm*)?[57]

CONCLUSION

The ethics of pharmacy in the US has experienced a continuous evolution as the profession itself has changed. Pharmacy practice is far different today than it was when APhA issued its first code of ethics in 1852. The current changes that pharmacy (and indeed all of health care) is experiencing makes the existence of an ethical framework and personal ethic even more vital today than it was in the past. The pharmacists of the mid-19th century could not imagine the medical innovations and technological wonders that have occurred, and the financial questions that have been raised and debated in the last quarter of the 20th century.

As the concept of pharmaceutical care expands to an ever-growing number of practice sites, pharmacists must be schooled not only in their expanding ethical responsibilities as independent practitioners, but also in their traditional moral obligations to patients. The APhA Code of Ethics and the profession at large must remain responsive to an ever-changing environment.

In spite of the deficiencies of self-regulation, there remains much that can be done within pharmacy to increase the service contribution of pharmacists through ethics. The situation was summarized by Dean LaWall when, 85 years ago, he described pharmacy as "[a] highly specialized calling, which may rise to the dignity of a true profession or sink to the level of the lowest commercialism, according to the ideals, the ability, and the training of the one who practices it."[58]

REFERENCES

1. Tomlin EWF. *The Western Philosophers: An Introduction*. New York: Harper & Row, 1963, p 26.
2. Smith MC. In Wertheimer AI, Smith MC, eds. *Pharmacy Practice: Social and Behavioral Aspects,* 2nd ed. Baltimore: University Park Press, 1981, p 305.
3. Veatch RM. *Case Studies in Medical Ethics*. Cambridge: Harvard University Press, 1977, p 1.
4. Veatch RM. *A Theory of Medical Ethics*. New York: Basic Books, 1981.
5. Marshall TH. *Can J Econ Political Sci* 1939; 5:325.
6. Greenwood E. In Noscow S, Form WH, eds. *Man, Work and Society*. New York: Basic Books, 1962, p 210.
7. Carr-Saunders AM, Wilson PA. *The Professions*. New York: Oxford University Press, 1933, p 141.
8. Montague JB. *J APhA* 1968; NS8:228.
9. Smith MC. *Am J Pharm Educ* 1970; 34:16.
10. Smith MC, Knapp DA. *Pharmacy, Drugs and Medical Care,* 4th ed. Baltimore: Williams & Wilkins, 1987.
11. Denzin NR, Mettlin CJ. *Soc Forces* 1968; 46:357.
12. Edelstein L. In Temkin O, Temkin CL, eds. *Ancient Medicine: Selected Papers of Ludwig Edelstein*. Baltimore: Johns Hopkins University Press, 1967, p 6.
13. Smith MC, Smith MD. *Am J Pharm Educ* 1981; 45:14.
14. Haddad M et al. *Am J Pharm Educ* 1993; 57:34S.
15. Berger BA. *Am J Hosp Pharm* 1993; 50:2399.
16. "Code of Ethics for Pharmacists." *Am J Health-Sys Pharm* 1995; 52:2131.
17. McCarthy RL. In Haddad AM, Buerki, RA, eds. *Ethical Dimensions of Pharmaceutical Care*. Binghamton, NY: Pharmaceutical Products Press, 1996.
18. Musto DF. *The American Disease: Origins of Narcotic Control.* New York: Oxford University Press, 1987.
19. Edwards RB. *Soc Sci Med* 1984; 18:515.
20. American Association of Colleges of Pharmacy. *What is the Mission of Pharmaceutical Education?* Background Paper I, Commission to Implement Change in Pharmaceutical Education, 1991.
21. Veatch RM. *Am J Hosp Pharm* 1989; 46:109.
22. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics,* 3rd ed. New York: Oxford University Press, 1989, p 25.
23. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics,* 3rd ed. New York: Oxford University Press, 1989, p 26.
24. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics,* 3rd ed. New York: Oxford University Press, 1989, pp 67–68.
25. McCarthy RL. In Bleidt B, Montagne M, eds. *Clinical Research in Pharmaceutical Development*. New York: Dekker, 1996.
26. Beauchamp TL, Childress JF. *Principles of Biomedical Ethics,* 3rd ed. New York: Oxford University Press, 1989, p 194.
27. Montagne M. In Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, vol 5. New York: Dekker, 1992, p 303.
28. Montagne M. In Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*, vol 5. New York: Dekker, 1992, p 304.
29. "Code of Ethics of the American Pharmaceutical Association." *J APhA* 1952; 13:721.
30. McAuliffe WE, et al. *Am J Hosp Pharm* 1987; 44:311.
31. Montagne M, ed. *J Drug Issues* 1988; 18:139.
32. Montagne M, ed. *J Drug Issues* 1992; 22:195.
33. McCarthy RL, Montagne M. *Am J Hosp Pharm* 1993; 50:992.
34. McDermott J. *JAMA* 1994; 271:782.
35. Butler J. *The Ethics of Healthcare Rationing*. Herndon, VA: Cassell Academic, 2000.
36. Hunter DJ. *Desperately Seeking Solutions: Rationing Health Care*. Reading, MA: Addison-Wesley, 1998.
37. Ubel PA. *Pricing Life: Why It's Time for Health Care Rationing*. Cambridge, MA: MIT Press, 1999.
38. Hall MA. *Making Medical Spending Decisions: The Law, Ethics, and Economics of Rationing Mechanisms*. New York: Oxford University Press, 1997.
39. Strosberg MA, Wiener JM, Baker R, et al, eds. *Rationing America's Medical Care: The Oregon Plan and Beyond*. Washington DC: The Brookings Institution, 1992.
40. Friedman E. *JAMA* 1993; 269:2437.
41. Dworkin G, Frey RG, Bok S. *Euthanasia and Physician-Assisted Suicide*. New York: Cambridge University Press, 1998.
42. Battin MP, Rhodes R, Silvers A, eds. *Physician Assisted Suicide: Expanding the Debate*. London: Routledge, 1998.
43. Snyder L, Caplan AL. *Assisted Suicide: Finding Common Ground*. Bloomington, IN: Indiana University Press, 2001.
44. Torr J, ed. *Euthanasia: Opposing Viewpoints*. San Diego, CA: Greenhaven Press, 2000.
45. Haley K, Lee M, eds. *The Oregon Death with Dignity Act: A Guidebook for Health Care Providers*. Portland, OR: Center for Ethics in Health Care, 1988.
46. Humphry D. *Final Exit: The Practicalities of Self-Deliverance and Assisted Suicide for the Dying,* 3rd ed. Reno, NV: Delta, 2002.
47. Palmer LI. *Endings and Beginnings: Law, Medicine, and Society in Assisted Life and Death*. New York: Praeger, 2000.
48. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects: Facing the 21st Century*. Frederick, MD: University Publishing Group, 1996.
49. Shamoo AE, Resnik DB. *Responsible Conduct of Research*. New York: Oxford University Press, 2003.
50. Brody BA. *Ethical Issues in Drug Testing, Approval, and Pricing: The Clot-Dissolving Drugs*. New York: Oxford University Press, 1995.
51. Amdur RJ. *Institutional Review Board Member Handbook*. Sudbury, MA: Jones & Bartlett, 2002.
52. Gallelli JF, Hiranaka PK, Grimes GJ Jr. In Brown TR, Smith MC, eds. *Handbook of Institutional Pharmacy Practice,* 2nd ed. Baltimore: Williams & Wilkins, 1986.
53. Harrington A, ed. *The Placebo Effect: An Interdisciplinary Exploration*. Cambridge, MA: Harvard University Press, 1999.
54. Shapiro AK, Shapiro E. *The Powerful Placebo: From Ancient Priest to Modern Physician*. Baltimore: Johns Hopkins University Press, 2001.
55. Moerman DE. *Meaning, Medicine and the Placebo Effect*. New York: Cambridge University Press, 2002.
56. Freedman B. *IRB* 1990; 12:1.
57. McCarthy RL. *J Managed Care Pharm* 1996; 2(2):76.
58. LaWall CH. *Four Thousand Years of Pharmacy*. Philadelphia: Lippincott, 1920: p v.
59. http://www.aacp.org/site/tertiary.asp? TRACKID = &VID = 2&CID = 686 & DID = 4339. Accessed May 14, 2004.

BIBLIOGRAPHY

Asbury CH. *Orphan Drugs: Medical Versus Market Value*. Lexington, MA: Lexington Books, 1985.

Bakalar JB, Grinspoon L. *Drug Control in a Free Society*. London: Cambridge University Press, 1984.

Basara LR, Montagne M. *Searching for Magic Bullets: Orphan Drugs, Consumer Activism, and Pharmaceutical Development*. New York: Haworth, 1994.

Bezold C. *The Future of Pharmaceuticals*. New York: Wiley, 1981.

Boyce E, et al. *DICP Ann Pharmacother* 1989; 23:590.

Brody H. *Placebos and Philosophy of Medicine: Clinical, Conceptual, and Ethical Issues.* Chicago: University of Chicago Press, 1977.

Buerki RA, Vottero LD. *Ethical Responsibility in Pharmacy Practice.* Madison, WI: American Institute of the History of Pharmacy, 1994.

Cook RJ, Dickens BM, Fathalla MF. *Reproductive Health and Human Rights: Integrating Medicine, Ethics, and Law*. New York: Oxford University Press, 2003.

Coombs RH. *Drug-Impaired Professionals.* Cambridge: Harvard University Press, 1997.

Goodman KW. *Ethics and Evidence-Based Medicine: Fallibility and Responsibility in Clinical Science*. New York: Cambridge University Press, 2003.

Haddad A. *Teaching and Learning Strategies in Pharmacy Ethics*. New York: Pharmaceutical Products Press, 1997.

Heifetz MD. *Easier Said Than Done: Moral Decisions in Medical Uncertainty*. Buffalo, NY: Prometheus Books, 1992.

Humber JM, Almeder RF, eds. *Mental Illness and Public Health Care*. Totowa, NJ: Humana Press, 2002.

Jonsen AR, Siegler M, Winslade WJ. *Clinical Ethics: A Practical Approach to Ethical Decisions in Clinical Medicine*. New York: McGraw-Hill, 1998.

Lennard HL. *Mystification and Drug Misuse*. San Francisco: Jossey-Bass, 1971.

Lock S, Wells F, Farthing M, eds. *Fraud and Misconduct in Biomedical Research,* 3rd ed. London: BMJ Books, 2001.
Montagne M, Pugh CB, Fink JL. *Am J Hosp Pharm* 1988; 45:1509.
Murray TH, Gaylin W, Macklin R, eds. *Feeling Good and Doing Better: Ethics and Nontherapeutic Drug Use*. Clifton, NJ: Humana Press, 1984.
Salek S, Edgar A, eds. *Pharmaceutical Ethics*. New York: J Wiley, 2002.
Sechzer JA, ed. *The Role of Animals in Biomedical Research*. New York: New York Academy of Science, 1983.
Silverman M, Lee PR, Lydecker M. *Prescriptions for Death: The Drugging of the Third World*. Berkeley: University of California Press, 1982.
Smith MC, et al. *Pharmacy Ethics*. New York: Pharmaceutical Products Press, 1991.
Smith T. *Ethics in Medical Research: A Handbook of Good Practice*. New York: Cambridge University Press, 1999.
Temin P. *Taking Your Medicine: Drug Regulation in the United States*. Cambridge: Harvard University Press, 1980.
Veatch RM. *J Drug Issues* 1977; 7:253.
Veatch RM, Haddad A. *Case Studies in Pharmacy Ethics*. New York: Oxford University Press, 1999.
Weinstein B. *Ethical Issues in Pharmacy*. Vancouver, WA: Applied Therapeutics, 1996.

CHAPTER 4

The Practice of Community Pharmacy

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Community Pharmacy Practice: The Context of the System

While few may take the time to look back to past editions of *Remington*, if you were to do so what you would find is an ongoing pilgrimage of change for community pharmacists. The direction clearly has been, and continues to be, a path toward increasing a patient care focus. The scenery and contextual landscape have changed dramatically. Polemics formerly surrounding the commercialization of community practice—the separation of professional and business functions—continue; however, the accretion of US health care in general from professionalism and autonomy toward a business structure has tended to mitigate the view of pharmacists as the singular 'sore thumbs' entrenched in an obvious commercial backdrop, as compared to other players in the diverse health care arena.

As this pilgrimage continues toward asserting a role in optimizing the medication use process (ie, pharmaceutical care), community pharmacy is not yet there in its nascent measure of success. Progress has been made in cognitive service remuneration and some score carding based upon improvement in economic, clinical, and humanistic patient outcomes; however, the customary success metrics for community pharmacy remain focused upon the processing of Rxs rather than the outcome associated with appropriate medication management by pharmacists. Continuing in the classical metric tradition, in 2002 the 54,000 community pharmacies processed, on average, 56,550 Rxs per pharmacy at an average price of $54.[1] For the first time in recent history, the 2002 Rx market sagged compared to previous years. While a decade earlier Rx volume (both number of Rxs and revenue from Rxs) rose unabated at 8% to 10% per year, 2002 was flat with 2001.

The community pharmacy workforce continues to gain in sophistication. In spite of the uptake of the PharmD degree, which entices practitioners to an array of non-community pharmacy based clinical opportunities, the surge of certified pharmacy technicians and technology has enabled community pharmacy to dispense these 3.1 billion Rxs. These same workforce enhancers have also provided community pharmacists with time to initiative various patient care services that have started to demonstrate the value of pharmaceutical care in the community setting. The leading of these studies were the Asheville Project and Project ImPACT.

The Asheville Project (12 pharmacies, 85 patients with diabetes) found that patients with pharmaceutical care interventions faired better than a comparison group. The Asheville Project started in March 1997. The services performed by pharmacists include patient education and training, clinical assessment, monitoring, follow-up, and referral. Participating patients had lower overall health costs, missed fewer days of work or school, and required less intensive health care interventions.[2,3,4]

Project ImPACT focus on community pharmacists' interventions (26 pharmacies) with patients suffering dyslipidemias (397 patients). With this pre-post comparison group design, rates of persistence, compliance, and attainment of clinical goals was demonstrated using pharmaceutical care.[5]

Distribution and Control of Medications

The classical paradigm in community pharmacy was that the community pharmacist must assess all of the following:

- Appropriateness of dose for this patient
- Patient allergy to the medication or similar medication
- Potential interactions with other prescribed and non-prescription medications
- Contraindications of the medication with other known diseases the patient may have
- Appropriate dose scheduling to maximize effect and minimize adverse events
- Appropriateness of this medication for this patient for this health condition

The pharmacist also is, and has been, required to:

- Assure accuracy of dispensing and labeling
- Provide the patient with information on proper storage of the medication
- Advise the patient on potential risks and benefits
- Advise the patient on how to deal with missed doses and adverse events and
- Assess the patient's understanding of the prescription instructions to maximize compliance and adherence to the instructions.

The contemporary thrust includes an expansion of responsibility to:

- Consider the appropriateness of the entire pharmacotherapy care plan
- Consider the inherited parameters that may affect medication transport, receptor activity, and metabolism (eg, pharmacogenomics)
- Monitor the results of the pharmacotherapy care plan (eg, pertinent clinical endpoints and quality of life outcomes secondary to the medication regimen)

Preparation of Compounded Pharmaceuticals

The vast majority of prescriptions dispensed are for dosage forms manufactured by the Food and Drug Administration (FDA)-approved manufacturers. These standardized dosages meet the

needs for most patients and are produced under the Good Manufacturing Practices established by the FDA. Many patients, however, need custom-made dosages to solve specific problems. For these unique needs many community pharmacists offer specialized compounding services. Patients may need extremely small doses for pediatric or geriatric use. They may also need preservative-free products, liquids with special flavors or delivery systems that are not commercially available. Additionally some medications may not have sufficient shelf life to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. For all of these reasons, compounding of finished dosage forms is a valuable service offered in thousands of community pharmacies across the nation.

Compounding has always been the art and science unique to pharmacists and continues to be a part of contemporary pharmacy practice. Those community pharmacists who continue to offer these services do so under *Good Compounding Practices* established by the United States Pharmacopoeia.[6] The array of dosage forms possible through compounding is far wider than those available from manufacturers. It is more economical to compound specialized prescriptions since the market demand for each product is not sufficient to justify creation of a manufactured product.

Forces of Change in Community Pharmacy Practice

There are a number of external forces at work encouraging change in pharmacy practice. The five most definitive forces are (1) the demand for prescription drugs, (2) pharmaceutical innovation, (3) health care cost containment initiatives, (4) the need for improved medication safety, and (5) the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Demand for prescription drugs has increased through two modes. The evolution of third-party payment cards has removed some of the economic barriers to drug therapy. The conversion of many indemnity and major medical plans to direct insurance coverage has increased prescription volume 20% to 35% among those patients. With financial barriers removed, many prescriptions are now dispensed that previously were not. Additionally the number of people over 65 years old is significantly increasing in the US population. This age group uses 33% of prescription drugs and 40% of non-prescription drugs while they represent only 12% of the population.[7] By the year 2020 the number of people over the age of 65 will double. These two factors alone will contribute to a 35% increase in prescriptions dispensed. Legislative proposals to include coverage of prescription drug within the Medicare benefit may increase this pressure as well.

Pharmaceutical innovation has further accelerated the growth in the prescription drug market. The continued introduction of new, more powerful, more potent, more useful and more toxic drug entities continues to increase the number of patients for whom drug treatment replaces surgery, hospitalization, or other treatment modes. Dramatic new entries that do not replace existing drugs but do replace other treatment modes drive an expanding market for prescription medications and pharmacy services. The combination of these two forces has given rise to the third trend, which are health care cost containment initiatives.

The health financing system in the US has experienced cost increases in excess of the Consumer Price Index (CPI) for more than two decades. As a result insurers and employers who pay the insurance bills have demanded that controls be applied to these rising costs.[8] Insurers, pharmacy benefit managers (PBMs), and governmental agencies have applied various strategies to prescription drug benefit plans in an effort to control costs. Many now use generic incentive policies, prior authorization programs, therapeutic formularies, and competitive bidding procedures to reduce the total cost of prescription drugs. Community pharmacists now spend a significant amount of time administering these cost-controlling strategies for insurers. It is estimated that 20% of the time spent by pharmacists in the fulfillment of these tasks can be delegated to non-licensed personnel.[9] These three forces drive community pharmacy practice in new directions creating a need for continued automation, a need for more technical support, and opportunities for alternate pharmacist roles.

The pace of pharmaceutical innovation combined with the increasing use of medications has exposed a major public health problem—the need for improved medication safety. Medications are only effective when taken properly, yet medication compliance is very poor in the US[10–12] This failure to take drugs as prescribed results in drug misadventuring or increased drug-related problems. Drug-related problems can also be caused by issues other than compliance as described below[13]

- Indication issues (eg, untreated indication, unnecessary drug therapy)
- Effectiveness issues (eg, wrong drug, dosage too low)
- Safety issues (eg, adverse drug reactions, dosage too high)
- Adherence issues (eg, inappropriate compliance)

Clearly, these issues warrant a need for more assessment and monitoring of medication use.[10,13] This need is magnified as one investigates those increases in unnecessary morbidity and mortality associated with drug misadventuring.

The literature provides significant evidence that drug misadventuring, whether intentional or unintentional, is associated with increased costs and negative patient outcomes. Johnson and Bootman published one of the most alarming studies in 1995.[14] The study results suggest that drug-related morbidity and mortality in the US ambulatory care population was estimated to cost $76.6 billion in 1994. These costs are attributed mainly to an increased number of hospital admissions, long-term care admissions, physician visits, and prescription drug use, as shown below:

- Hospitalizations: 8.7 million admissions at a cost of $47 billion
- Long-term care facilities: 3.15 million admissions at a cost of $14.4 billion
- Physician visits: 115 million visits at a cost of $7.5 billion
- Prescriptions to resolve treatment failures and new medical problems: $1.93 billion

As evidenced by this study, drug-related morbidity and mortality represent a serious public health problem. The problem is becoming more visible as public policy makers, employers, and managed care administrators attempt to understand health care resource utilization. They are illuminating the magnitude of the drug-related morbidity and mortality problem and affirming the need for improvement in medication management. Furthermore, they are emphasizing disease prevention and patient education as ways to reduce overall medical and prescription costs.

Community pharmacists are in a position to fulfill this societal need and provide pharmaceuticals and pharmaceutical services with the intention of improving patient health outcomes. They have the education and ability to manage drug therapy and provide prevention and education services to patients. Moreover, pharmacists are the most accessible and trusted health care professionals. The 1995 Report of the Pew Health Professions Commission supports pharmacists fulfilling these alternate roles and recommends that pharmacists, in particular, engage in activities related to comprehensive drug therapy management such as selecting appropriate drug therapies, educating and monitoring patients, and continually assessing therapy outcomes.[15]

The Health Insurance Portability and Accountability Act of 1996 went into effect in April 2003. It is a far-reaching piece of legislation. Its intent is to secure patient records containing individually identifiable health information so that they are not readily available to those who do not need them. All community pharmacies manage personal health information (PHI) as a routine part of doing business. Pharmacies are required to train

all personnel who may handle PHI in how to maintain PHI security and document employee competency. Systems for maintaining the security of PHI must be in place as well. Patient consultation areas need to be designed to insure complete confidentiality of the conversation between patient and pharmacist. The full impact of HIPAA on the practice of community pharmacy is yet to be fully determined.

Shifting Responsibilities

The many data elements to be evaluated at every prescription processing, combined with the variety of formularies and insurance variables, have created a distribution system that requires automation. Today virtually every community pharmacy in the country uses computers, on-line claims processing, and various other forms of automation. Some pharmacies also use automated dispensing systems to count doses, fill bottles, and print patient information and labels. The next decade will see a rapidly expanding use of automated filling systems to reduce the technical functions performed by pharmacists.

In addition to automation, pharmacy technicians are performing many clerical and technical tasks. Technicians have been increasing in numbers and assuming more responsibility over the past 20 years, and today they play a very important role in freeing pharmacists for more patient-focused activities such as counseling and disease state management. Allowing technicians to perform many distributive functions provides time for pharmacists to perform patient care activities. Four pharmacy organizations created the Pharmacy Technician Certification Board to develop, administer, and review a national certification program for technicians.[16] As of April 2003, 131,562 pharmacy technicians across the nation had passed the Pharmacy Technician Certification Examination, and approximately 30% to 40% of certified technicians worked in a community pharmacy setting.[17] Training and certifying pharmacy technicians expands their role, which ultimately allows the pharmacist to spend more time delivering pharmaceutical care services.

As the number of prescriptions dispensed continues to rise and the demand for cost containment remains strong, it is extremely important that community pharmacists focus their limited time on those aspects of practice that make the most effective use of their education and training. First and foremost among these are promoting appropriate drug therapy and avoidance of drug misadventuring. The potential health care cost savings associated with these aspects of practice are enormous. In order to deliver this level of care at community pharmacy sites, it is essential for increases in the use of automation and technical personnel to occur.

Pharmaceutical Care in Community Practice

With the influx of new medication classes, as well as the aging of the American population, the role of the pharmacist in providing effective medication therapy for their patients is more vital than ever. The only method for providing this vital service is in performing pharmaceutical care. This is the same pharmaceutical care that was defined by Hepler and Strand in 1989 as being "the responsible provision of drug therapy and other patient care services for the purpose of achieving outcomes related to the prevention or cure of disease, the elimination or reduction of a patient's symptoms, or the prevention, arrest, or slowing of a disease process."[18] There are several ways in which community practice is performing pharmaceutical care every day, from counseling and prospective drug utilization review at the time of dispensing all the way to disease state management and collaborative practice agreements. While counseling and prospective DUR are requirements of every prescription dispensed, it is disease state management and collaborative practice that are the leading edge of pharmacy practice in the community.

OBRA 90 requires that a minimum amount of pharmaceutical care be performed with each prescription dispensed. All medications must undergo a prospective DUR during which a comprehensive review of the patient's prescription order is performed as well as an evaluation of the appropriateness of the medication for the patient.[19] This application of pharmaceutical care provides for "the responsible provision of drug therapy" but fails to address the patient's outcomes. This level of pharmaceutical care requires a patient history and allergy information and the willingness of the patient to talk about their medications.

Disease state management addresses therapeutic outcomes. In this application of pharmaceutical care pharmacists monitor disease progression as well as problems with medication regimens. Pharmacists in community practice settings offer screening or wellness clinics where screenings tests and monitoring or certain disease states occur. Blood pressure and blood glucose are screening tests that are easily performed with an inexpensive piece of equipment and a little training. However, the technology now exists to perform hemoglobin A1C in diabetics as well as PT/INR and lipid testing in cardiac patients. At this point the results are relayed back to the prescriber who would then make adjustments in the drug regimen. Along with the monitoring, pharmacists can also make recommendations on nutritional support, immunization and OTC preparations, which should and should not be used in conjunction with the patient's drug regimen. This level of pharmaceutical care in addition requires the requisite equipment as well as physician support in the form of referrals and willingness to accept outside suggestions.

Collaborative practice takes disease state management and makes the pharmacist the driving force in medication planning decisions. The practice model that exists in this type of pharmaceutical care is one where a physician refers a patient with a specific condition to a pharmacist run clinic. This pharmacist would then do all medication care planning under the limits of the collaborative agreement and be responsible for all follow up and monitoring required. This level of pharmaceutical care requires the pharmacist to have an intimate knowledge of all the patient's medical history.

If collaborative practice and disease state management are the most advanced form of pharmaceutical care then pharmacogenomics is the next natural evolution. The ability to predict drug therapy outcomes before initiation by studying a patient's genetic profile will improve mediation efficacy, patient safety and quality of life while decreasing adverse reactions as well as help contain cost. Pharmacogenomics analyzes a patient's genetic profile to ascertain which medication will provide the best possibility of efficacy with the least risk adverse reactions. This genetic profile can assess receptor affinity as well as polymorphic pathways in the metabolic pathways of medications, thus allowing the provider to "predict" the outcome of drug therapy before initiation.

Embracing these new practice standards is not without problems and disadvantages. In an age of ever-increasing prescription volume it is difficult to divert pharmacists from their primary role. Also this new level of practice requires increased access to patient records as well as more advanced equipment, training, and floor space for the clinic area.[20] Physician involvement is not easy with the perception being that pharmacy is impinging on what has traditionally been the physician's role. And lastly there is a need for increased education of the existing population of pharmacists for this increased role.[21]

Economic Issues of Pharmaceutical Care

Community pharmacists have been hesitant to provide comprehensive pharmaceutical care primarily due to economic constraints. These economic issues, as we will see in the following discussion, are a key component in the evolution of the community pharmacy practice model. With little compensation for pharmaceutical services, there was little incentive for pharmacists to invest in advanced education, the restructuring of

their pharmacy, the hiring of more technical help, and the purchasing of technology to support advanced patient care. However, as stated previously, because of the diminishing margins for medications it is imperative that pharmacists broaden their practice model to include reimbursement for cognitive services. Therefore, it became necessary to convince patients, payers, and regulators that pharmaceutical care is of value. Let us further explore the primary challenge of this task.

There are three primary models for health insurance currently employed in the US: risk pooling, cost containment and demand. Of these, the demand model has the greatest potential for the development of a successful platform from which pharmacists may receive direct reimbursement for pharmaceutical care. The cornerstone of a successful demand model is the establishment of the value of the service(s) provided in the mind of the consumer. In essence, the consumer must perceive a sufficient value of the service provided, be willing to initially pay for it out-of-pocket, and demand payment for these services from third party payers. The third party carriers must in turn establish a uniform fee schedule upon which to base this reimbursement. Rather than wait for consumers to make the demand on insurance carriers to cover these cognitive services, pharmacist must initiate the process by establishing a private pay basis from which the private and public insurance carriers would draw.[22] There has been recent progress in this area to render this process more than an academic discussion.

The inpatient pharmacists at a large east-coast teaching hospital had been providing cognitive services (eg, in the areas of pharmacokinetic consultation, patient and family medication education, nutritional assessment for patients receiving metabolic support, adjustment of parenteral nutrient regimens and drug regimen reviews) for years without receiving direct compensation for same. A decision was made by pharmacy administration to discontinue the practice of pro bono care and charge private insurance carriers for pharmacist interventions. The fee schedule was based on the "charge level" system used by AMA and is based on the acuity of the illness or injury and the relative complexity of the issues (not based on the amount of time necessarily spent on intervention). All interventions are documented in a uniform format (SOAP) in patients' progress notes and no charge may be generated unless this entry completed. Specific software package developed specifically for this process for the purposes of establishing both audit trails for the interventions and tracking of successful reimbursements from private insurers. Audited results indicate that reimbursement by private insurance carriers was at 59% of the charged rate. Because of the success of this program, it has been expanded to included diabetes and asthma management for employees of the health system.[23] There has also been some progress in the area of cognitive services reimbursement at the federal level.

Medicare presently does not compensate the health care system for therapy (i.e. cognitive) services provided by pharmacists. A recently introduced bill (the "Medicare Pharmacist Services Coverage Act") would for the first time, recognize pharmacists as health care "providers" under Medicare and permit compensation for "high level drug therapy."[24] The areas proposed for inclusion in this program are anticoagulation, diabetes, asthma and hypertension management. Again, the impetus for this significant modification to the Medicare program has been driven on two primary fronts:

1. Clients of privately funded pharmacist managed programs value the service as an integral and previously missing component of their overall disease management and decreased levels of reimbursement and;
2. Decreased levels of reimbursement and managed care imposed algorithms have drastically decreased the amount of physician time before patients with the net result that medication matters related to various disease states are not addressed with patients.

To convince payers that pharmaceutical care has value and can save enormous amounts of money, numerous studies have been conducted.[25, 26] In a recent study at the University of Kansas, direct savings from community pharmacist interventions averaged $27.63 for each therapeutic substitution, $35.55 per drug discontinuation, $32.36 for drugs deemed not necessary to dispense, and $21.98 for each generic substitution.[27] To further demonstrate how pharmacists can reduce total health care costs and improve patient health, Project ImPACT (Improve Persistence and Compliance with Therapy): Hyperlipidemia was established.[28] Community pharmacists participating in this project offered cholesterol tests and regular counseling to patients with hyperlipidemia, a form of high blood cholesterol. Participating pharmacists spent up to 30 minutes per visit with patients, explaining laboratory test results, suggesting lifestyle changes, and stressing the importance of staying on their prescribed medication. According to preliminary results, 84 percent of the 469 enrolled patients are still taking their medicine as prescribed and about 50 percent of those patients have achieved their cholesterol-lowering goals. As a result of these findings, payers, both public and private, and patients are realizing that pharmaceutical care leads to improved patient health and offers substantial savings in health care costs. In other words, pharmaceutical care provided by community pharmacists is of value.

As payers and patients realize the value of pharmaceutical care, they are more willing to reimburse pharmacists for their pharmaceutical care services and disease management activities.[29] Financially, it is better to pay the pharmacist a fee to prevent a drug therapy complication than to pay for an emergency room visit or hospitalization due to a drug therapy complication. Therefore, programs are slowly being implemented to reimburse pharmacists for pharmaceutical care. An established program is the Mississippi Medicaid Waiver Program. The Health Care Financing Administration (HCFA) has approved a Medicaid Waiver in Mississippi to pay for pharmaceutical care in four disease states: asthma, diabetes, hyperlipidemia, and anticoagulation.[30] The waiver allows for licensed, credentialed pharmacists to receive reimbursement for disease management activities. Programs like this provide continuing evidence that payers as a direct result of patient advocacy are recognizing the value of pharmaceutical care and are reimbursing pharmacists for their services.

Community pharmacists are encouraged to provide pharmaceutical care as they are compensated for their services. Moreover, there is less economic risk involved in investing in the delivery of pharmaceutical care when reimbursement programs are in place. As the practice and business platforms for community pharmacy practice evolve from the predominant fee-for-dispensed-medication model to one of evidence-based pharmacotherapy, direct payment for cognitive services will become an even more critical component. This is especially true as the community pharmacist becomes more regarded as a healthcare resource for both medication and education in the evolution to a practice of true medication management.

REFERENCES

1. Gebhart F. *Drug Topics* 2003; 147(6):38.
2. Cranor CW, Christensen DB. *J Am Pharm Assoc* 2003; 43:149.
3. Cranor CW, Christensen DB. *J Am Pharm Assoc* 2003; 43:160.
4. Cranor CW, Bunting BA, Christensen DB. *J Am Pharm Assoc* 2003; 43:173.
5. Bluml BM, McKenney JM, Cziraky MJ. *J Am Pharm Assoc* 2000; 40:155.
6. Pharmacy Compounding Practices & Sterile Drug Products For Home Use, United States Pharmcopeia National Formulary, USP Rockville, MD, 1996.
7. Duncker A, Greenberg S. *A Profile of Older Americans*, AARP, Washington DC, 1997 (available at http://research.aarp.org/general/profile97.html)
8. The Third Strategic Planning Conference for Pharmacy Practice Report, Supplement to American Pharmacy, APhA, Washington DC, October 7–10, 1994.
9. Hepler CD, Strand LM. *Am J Hosp Pharm* 1990; 47(3):533.

10. Hatoum HT, Valuck RJ: Drug use and the health care system. In: Knowlton CH, Penna RP, eds. *Pharmaceutical Care*, 1996.
11. Manasse HR. *Am J Hosp Pharm* 1989; 46:929.
12. Strand LM. *Report at Podium Presentation, Pharmaceutical Care Outcomes Research Conference*, University of Georgia, Athens, AT, Sept 1996.
13. Maine LL, Penna RP. Pharmaceutical care: an overview. In: Knowlton CH, Penna RP, eds. *Pharmaceutical Care,* 1996.
14. Johnson JA, Bootman JL. *Arch Intern Med* 1995; 155:1949.
15. Pew Health Professions Commission Report: *Critical Challenges Revitalizing the Health Professions for the Twenty-First Century*. CA-UCSF Center for Health Professions, San Francisco, CA, 1995.
16. Knowlton HL. *J Am Pharmaceut Assoc* 1997; 38:12
17. Harteker LR. *The Pharmacy Technician Companion,* APhA, Washington DC, 1998.
18. Hepler CD, Strand LM. *Am J Hosp Pharm* 1990; 47:533.
19. Abood RR, Brushwood DB. *Pharmacy Practice and the Law*, 2nd ed, 1997.
20. Isett JI, McKone BJ. Practice changes facilitated by pharmaceutical care. In: Knowlton CH, Penna RP, eds. *Pharmaceutical Care*, 1996.
21. Amsler MR, Murray MD, Tierney WM. *J Am Pharm Assoc* 2001; 41:850.
22. Ganther JM. *J Am Pharm Assoc* 2002; 42:875.
23. Michalets EL, Williams E. *Am J Health-Syst Pharm* 2001; 58:164.
24. Young D. *Am J Health-Syst Pharm* 2002, 59:811.
25. Huffman DC (ed). Washington DC: NARD, 1996.
26. Johnson JA, Bootman JL. *Am J Health-Syst Pharm* 1997; 54:554.
27. Bochamer C (ed). *NCPA Newsletter* 1997; 119:1.
28. Bluml BM et al. *J Am Pharm Assoc* 1998; 38:529.
29. Knowlton CH. *J Am Pharm Assoc* 1997; 37:361.
30. Stevens WL (ed). *MS State Board of Pharmacy Newsletter* 1998; 4(4): June.

CHAPTER 5

Pharmacists in Industry

Teresa Pete Dowling, PharmD

The pharmaceutical industry in the United States is a for-profit environment. Its goal is to bring value to its shareholders, and it does this by doing good for people (Fig 5-1). Integral to the mission of a pharmaceutical company involved in research is the discovery of new chemical entities (NCEs), their toxicological testing, the development of these entities into dosage forms, clinical trials in humans of these investigational drugs or biologics, regulatory review and approval of the new products, and marketing of the products for appropriate use by health care professionals and consumers.

In 2003, the industry invested an estimated $33.2 billion in discovering and developing new medicines.[1] Hundreds of employees are involved as a new chemical entity moves through the stages of product development. Hundreds to thousands of people become subjects in the clinical trials depending on the proposed indications.

Many of the NCEs died on the road of discovery and testing. On average it takes 10 to 15 years and costs more than $800 million to advance a potential new medicine from a research idea to a treatment approved by the FDA.[2] When one of your company's NCEs is approved by FDA, the feelings of achievement and success are great among the product team members.

Pharmacists may choose many environments to practice pharmacy and to apply their knowledge and skills to the improvement of patient care. One area is the pharmaceutical industry where major advances in patient care, research to improve patient's lives, and education for health care professionals and patients are happening every day. The input into patient care is indirect rather than direct, and the products and programs have the potential to touch numerous patients' lives.

OPPORTUNITIES FOR PHARMACISTS

As of June 1996, the US pharmaceutical industry employed a total of 367,871 people worldwide. Of this total, 203,009 were employed in the US, and 164,862 were employed abroad.[3] Among those working in the US, 60,163 were involved in production; 58,082 worked in marketing; 50,802 were involved in medical R&D; and 28,642 worked in administration. The remaining 5321 were responsible for distribution activities. The Pharmaceutical Research and Manufacturers of America, the organization that collected these data, do not have it available as of 2004. It would be very interesting to see the impact on the number of employees in the US pharmaceutical industry when one considers the mergers, acquisitions, down-sizing, and growth (eg, in the biotechnology area) that has occurred over the last 8 years. However, the 1996 data can be used to give an estimate of number of positions within certain divisions of the industry.

It is difficult to obtain the percent of pharmacists that work in the pharmaceutical industry. Approximately 2.7% of pharmacists practice in the industry, according to the *National Pharmacist Workforce Study: 2000*.[4] It is estimated that there are 257,256 licensed pharmacists with in-state addresses based upon census data as of June 30, 2003.[5] If the percentage of pharmacists in industry stayed about the same, there would be approximately 7000 pharmacists working in the pharmaceutical industry.

Riggins and Plowman reported a survey of pharmacists employment and satisfaction trends at one pharmaceutical company (Table 5-1) that found pharmacists employed in many areas of the company.[6] These included drug discovery, manufacturing, marketing, medical information, product development, quality assurance, sales, and regulatory. A follow-up survey in 2001 revealed project management, health outcomes research, legal, information technology, training and development, and scientific communications as additional areas of employment for pharmacists.[7] These listings should not be considered complete. For example, one additional area is drug surveillance or safety; also, pharmacists move into other departments once they enter the industry, based upon their interests and skills.

Most of these positions would start at an entry level; however some, such as medical liaison and account representative, would require some years of clinical or sales experience. The entry-level salaries are often competitive with other areas of pharmacy practice, and the opportunities for long-range advancement, earnings, and fringe benefits are good in industry. Industry pharmacists are able to use their pharmacy training and skills and at the same time, experience professional growth, personal satisfaction, and a challenging environment.

Most companies are lean on full-time staff, and an individual will find that job responsibilities will be more than one full-time equivalent at times of peak team activity. The Career Pathways Evaluation Program, Pharmacist Profile Survey, formerly the Glaxo Pharmacy Specialty Survey, is maintained by the American Pharmaceutical Association and provides information about 17 career paths for pharmacists. The survey was administered in spring 2002 and included pharmacists in industry. One of the questions concerned work schedules. On average, the industry respondents stated that they work 49 hours/week. Flexible working arrangements and telecommuting help to bring some work-life balance to the job.

T. P. Dowling is an employee of AstraZeneca. All opinions expressed in this chapter are those of the author and do not represent those of AstraZeneca.

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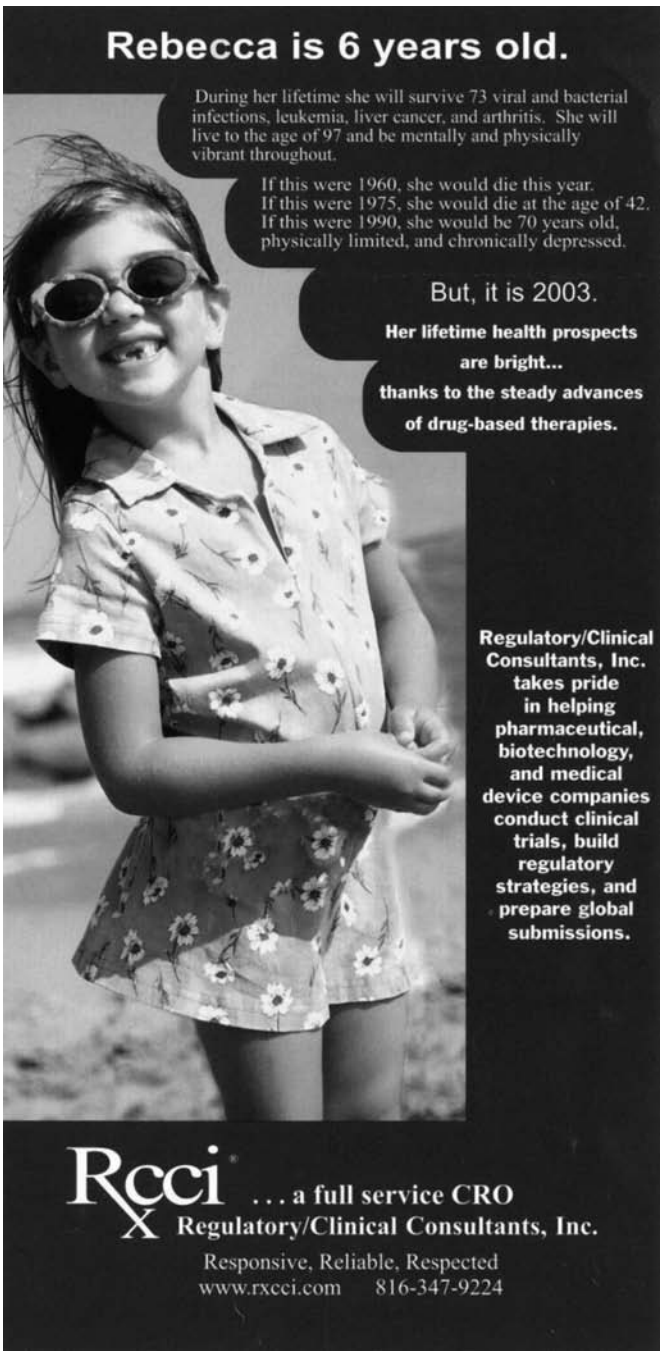

Figure 5-1. An example of the impact of pharmaceuticals to patients' lives. *Copyright 2004, Regulatory/Clinical Consultants, Inc. Used with permission. All rights reserved.* Regulatory/Clinical Consultants, Inc. used this ad to promote their services to the industry. The ad drew worldwide attention and was recognized for its strongly positive message about the progress of pharmaceuticals over the past 50 years.

When presenting potential roles within the industry, authors often select specific divisions within the company. Each company has developed its own titles for positions. It is often frustrating to realize that the same position can have many titles; however, this is important to remember when looking at positions within the industry. Also, these positions may be placed within different reporting divisions when comparing one company to another. The areas that will be highlighted within this chapter are sales, marketing, medical affairs (headquarters- and field-based positions), research and development, production and quality control, legal, regulatory affairs, and management and administration.

Table 5-1. Division in Which Lilly Pharmacists were Employed in 1998

DIVISION	NO. OF PHARMACISTS	PERCENTAGE
Discovery	18	2.7%
Manufacturing	25	3.7%
Marketing	52	7.7%
Medical	72	10.6%
Product development	37	5.4%
Product team	35	5.2%
Quality assurance and quality control	10	1.5%
Regulatory	35	5.2%
Sales	402	59.2%
Other	19	2.8%

Reprinted and adapted with permission from Riggins JL and Plowman BH: Pharmacists employment and satisfaction trends at Eli Lilly and Company. *Drug Information Journal*. 2000;34:1223–9, Table 5.© 2000, Drug Information Association.

Potential Positions within the Industry Sales

The sales area is one of the ways for pharmacists to get into the pharmaceutical industry. The sales representative (also called professional services representative, professional sales representative, or professional sales specialist) usually call upon physicians, pharmacists, nurses, and, in some cases, dentists and veterinarians with details on the products of their companies. The objective of these calls is to provide the various professional audiences with enough comprehensive information on a product to encourage the product's appropriate use by the health care providers.

Many companies prefer that candidates for a sales position have a science background, and thus they favor applications with pharmacy training. Equally important in being considered for a sales position are the personal traits and attitudes of the applicant, such as a congenial personality, effective oral communication skills, and a strong interest in selling.

Entry-level salaries for sales positions in most areas of the country generally are competitive with other pharmacy practice positions. In addition, most pharmaceutical companies offer excellent benefits packages such as company cars, expense reimbursement, travel to medical and pharmacy conventions, comprehensive medical insurance for the family, and reimbursement for education programs.

Marketing

The marketing department is responsible for developing and implementing marketing plans to promote the company's products to the appropriate audiences. Every company in the industry has, over time, developed its own unique marketing organization. In some firms, the department is organized by category, such as prescription-products marketing and OTC-products marketing. In other firms, marketing is divided into therapy areas, such as cardiovascular or respiratory products. In still others, brand teams are formed to drive the activities for the product. Whatever their structure, most marketing departments include:

- *Marketing Research*, which analyzes business trends, sales histories of the company's products, competitive information, prescribing and recommendation habits of practitioners, and new business opportunities within the market.
- *Marketing Strategy/Planning*, which is responsible for anticipating and developing products and services to meet the needs of the market place in the long term.

- *Product Management*, which oversees the overall marketing plan for a specific product, and is responsible for the profits or losses generated by that product.
- *Life Cycle Management*, which evaluates new uses for the product and supports research to study these uses, leading to new indications or to publications.
- *Promotion/ePromotion*, which develops the promotional pieces for the product.

A degree in pharmacy may be helpful but generally is not a requirement for a marketing position. Experience in the industry, usually gained in the sales department, plus an understanding of the health-care delivery system, general business principles, and a basic knowledge of R&D, manufacturing, quality assurance, and distribution are helpful in obtaining a position in the marketing department of a pharmaceutical company. The MBA would be an appropriate advanced degree, and many obtain the degree while in sales or in the marketing department.

Medical Affairs, Headquarters-based and Field-based Personnel

Within the company, a department provides information and services to health care practitioners in response to unsolicited inquiries, fosters research, gives presentations to practitioners, does sales training, and obtains the input of thought leaders. Most members of this department are health care providers and pharmacists are excellent for positions in Medical Affairs. A group of industry employees, most of who are pharmacists, published a supplement to discuss and describe this practice area.[9]

HEADQUARTERS-BASED PERSONNEL—MEDICAL COMMUNICATIONS GROUPS, MEDICAL INFORMATION MANAGERS

Health care providers recognize that the pharmaceutical company knows the most about its products. When the providers have questions about the products, they call the company and expect rapid, concise, accurate, and scientifically-balanced answers to their questions. These questions come to the Medical Communications group within Medical Affairs. Although previously staffed by physicians, this area has been a primary entrance position for clinical pharmacists in industry since the 1980s. It is a "spin-off" of the drug information center in the hospital setting.

Each company provides avenues for health care practitioners to ask questions and report adverse events. In industry, pharmacists are excellent for this position. They staff the company's 1-800 drug information telephone inquiry center, also staffed by nurses, responding to inquiries and capturing adverse events. Pharmacists with a Doctor of Pharmacy degree are often hired to develop the databases utilized by the company to answer these unsolicited inquiries. The responses in these databases are scientifically rigorous and balanced. Many of these pharmacists also teach the sales force, respond to questions from the marketing team, and review promotional pieces used by the company. Technology is a key requirement to aiding the company in responding to unsolicited inquiries. Managers in Medical Affairs develop an understanding of telephone response systems, fax-back programs, web-based information, and inquiry tracking and response systems.

FIELD-BASED PERSONNEL—MEDICAL LIAISONS, PRODUCT DEVELOPMENT SCIENTISTS, MEDICAL INFORMATION SCIENTISTS

Most pharmaceutical companies have deployed highly trained personnel to the field to provide support and information to opinion leaders, clinical investigators, and decision makers in health care organizations. Pharmacists with a Doctor of Pharmacy degree constitute the majority of pharmaceutical company personnel in these positions. The position requires the application of scientific and product knowledge to disease management in response to inquiries from health care professionals. Individuals are expected to develop working relationships with opinion leaders and to foster research. Good people skills and excellent presentation skills help these individuals succeed. Physicians and PhDs are also among the individuals utilized by this group. These teams are regionally located throughout the country.

Field-based personnel are aligned with the product teams or therapeutic areas and share information directly with these marketing teams. They also develop and deliver scientific training programs to the sales force.

Research and Development

Pharmacists in the industry are engaged in R&D of new drugs or new indication or dosage forms for existing products. This area of the industry is stimulating and challenging and is suited especially to pharmacists with strong scientific backgrounds.

PhDs are often required to progress in the area of dosage form development. PharmDs are becoming more involved with clinical research and protocol development, along with nurses and PhDs in biological sciences.

Individuals in research must be willing to move to new areas of research in the company as a project come to completion or is killed when the investigational drug does not preform as expected or desired. They work on tight timelines to conduct clinical trials in a timely manner with rapid enrollment and strict attention to *Good Clinical Practices*. When the study is completed, they draft the clinical study report for filing with regulatory agencies. Project management of the clinical trials program is an exciting opportunity for research-oriented pharmacists.

Health economics research is another area where pharmacists with specialized training are evaluating the cost-effectiveness of new medicines. These data are especially important to a company in its discussion with managed care plans. Research on patient-reported outcomes, what was grouped more into health-related quality of life, is also very important to companies as they evaluate their products.

Production and Quality Control

Pharmacists working in production often serve in managerial positions. They are responsible for anticipating the company's needs and planning for the plant facilities, equipment, and personnel who will be needed to meet the company's production goals. They are also responsible for establishing and administering manufacturing procedures and controls to ensure the production of high-quality products that will meet rigid company and FDA standards.

Pharmaceutical manufacturing is changing constantly by developing new technologies. Equipment often becomes obsolete in as short a time as 3 to 5 years. Thus, pharmacists and other production employees constantly must learn and adapt to new technology and procedures. Pharmacists who want to advance in careers in manufacturing usually will need advanced degrees beyond their entry-level pharmacy diplomas.

Research-intensive pharmaceutical companies constantly conduct thousands of assays and quality assurance (QA) tests each year to maintain the quality of their products. QA activities begin while the safety and efficacy of a new product are being established. The R&D, manufacturing, and QA departments of the company jointly establish final production and QA specifications for a new product.

The QA department establishes sampling and testing procedures to make certain that each lot of a product meets both company and FDA specifications. The system also ensures the

potency, purity, and dose-to-dose uniformity of the product, in addition to the chemical, physical, and biological data; stability of the finished trade package; and appropriate expiration dates. The QA department also checks not only for the quality and quantity of the active ingredients, but also for the uniformity and predictability of the nonactive ingredients. Pharmacists can work in many QA areas.

Legal Department or Regulatory Affairs Department

Some pharmacists decide to pursue a law degree. With this additional credential, they can consider positions as lawyers in the legal departments within companies. While there are many areas of law that are of value to the company, patent lawyers and lawyers that work with the product teams to provide legal consul on the laws and regulations for marketing pharmaceuticals within the US are very important. Pharmacists as lawyers understand the science behind the product and can fill both of these roles. Companies may want the lawyers that they hire to have legal experience prior to entering the company.

Regulatory Affairs is the department within the pharmaceutical company that handles the interactions between the company and the medicines regulatory body of the country in which the company is located. In the US, this regulatory body would be the Food and Drug Administration. Individuals within the company learn the regulations and processes that must be following for submitting an Investigational New Drug application (IND), a New Drug Application (NDA), and many other special documents including post-marketing surveillance reports. Regulatory Affairs individuals work within the company with all groups that have input into these documents. Many interactions are with R&D staff as the IND and NDA documents and other reports are developed and also with Marketing as the materials for promotion are developed. Regulatory Affairs will work with a cross-functional team to develop the draft Prescribing Information for submission to the FDA.

Pharmacists with their science background in drugs, diseases, and patient care can understand these documents as drafted by team members and work to improve them to the guidance of the regulations. They also can understand the regulatory agencies during the interactions that occur and help to establish regulatory strategy with the product teams.

Management and Administration

As pharmacists in the industry perform successfully at their positions, they move up within the department and within the company to positions in management and administration. Here, they ensure that the department functions smoothly and achieves its objectives. In some companies, managers are still involved with aspects of daily staff functions.

Bendis commented that a pharmacist's career path in management might span well over 10 to 15 years.[10] Using the sales and marketing area as an example, she outlined the following succession of positions illustrated by rank that may be achieved:

- Professional sales representative
- Coordinator, sales training
- District sales manager
- Product manager
- Regional sales director
- Vice president of sales
- Vice president of marketing
- President

While it doesn't happen often that people progress to president of the company, it does happen.

Pharmacy training provides a good basis for management and administration, but on-the-job experience is usually the key to success in management. Many of the people in management positions in the industry began their careers at entry-level positions and learned the organization from the inside. Qualities of discipline, hard work, and dedication go a long way in helping a pharmacist advance into a management position.

Selecting a Pharmaceutical Company

Not all pharmaceutical companies are the same. When deciding to investigate the pharmaceutical industry as a career choice, it is important to study the companies as well as the type of positions that you want (Table 5-2). *The Pink Sheet* may be a source of the information that you need. There is the potential for movement among the companies in the pharmaceutical industry as clinical research in one area is completed and is growing elsewhere or as a sales force ramps down in one area and expands in another. Here are questions that you may want to ask yourself and the individuals with whom you interview.

- How large is this company? The size of the company can be obtained from it Annual Report, usually posted on its corporate web site. Large companies usually have very defined job descriptions. Small companies will provide more opportunity to do a variety of jobs in a given area. You will be able to know most of the people at headquarters or the business unit where you work.
- What is the company's mission and shared values? The company mission statement will be found in its annual report and usually is posted on its Web site.
- Is this a US-based company or is its global headquarters based in Europe or Japan? There are cultural differences that come into play when you work for a European-based or Japanese-based company. Teams in the US may need to work differently to influence the global brand team and to understand their international colleagues. There may be the opportunity for international travel to team meetings. Also, there is the benefit of exposure to other cultures.
- How much travel is involved with this position? There are positions in clinical research and in field-based Medical Affairs that are 60% travel. How does this fit into your plans right now?
- Is relocation necessary?
- What are the company's major products? How many do they have? Are any of these products going off patent soon?
- What does the company have in its pipeline? How does its pipeline compare to other companies? Articles are published yearly in journals such as *Fortune* or *Medical Advertising News* that rank different aspects of pharmaceutical companies. It would be important to look at these over a few years to see improvements or declines. Ask about the trends that you see when you interview or with your faculty and preceptors.
- How does this company's sales force compare to others?
- What legal actions or investigations, if any, are underway concerning this company? Have they just finished any notable legal settlements? Many pharmaceutical companies have come under scrutiny of the States Attorneys General's Offices and the Plaintiffs' bar. This increased legal activity probably will continue for some time.
- What is the career progression for individuals who take this position? Where have individuals in the department moved within the company? Has the department attracted any staff from other departments within the company?
- How was this company ranked by Working Mother's Magazine? Are there lactation rooms? Is there a sponsored day care facility on site or close by?

Table 5-2. Potential Sources for Pharmaceutical Industry News

Drug Information Journal
Fortune
First Word (daily global e-news letter)
Medical Advertising News
Pharmaceutical Executive
The Pink Sheet
Science (check the Companies of Choice listing)
Scrip
Working Mothers (check the 100 Best Companies listing)

- Which degree programs does the company support if you wish to go back to school?
- What are your goals and desires? Do they match what this company offers?
- Is there any opportunity for you to do a summer internship, clerkship, residency or fellowship in the industry?

CONCLUSION

In 1995, Gmerek et al stated that "the pharmacist who will succeed in the pharmaceutical industry is the one who has a strong scientific background, is research-oriented, understands the business needs of the organization, and works well in a collaborative, or team situation."[11] The education that a pharmacist receives in the sciences, pharmacology, pharmacy, and therapeutics fosters success at many industry positions. No degree promises you success in your position. Hard work, dedication to quality, and having fun are drivers to success at any position. The pharmaceutical industry lets pharmacists apply their training in a team environment and grow with the company.

REFERENCES

1. www.phrma.org/whoweare, accessed March 31, 2004
2. DiMasi JA, Hansen RW, Grabowski HG. *J Health Econ* 2003; 22:151.
3. *PhRMA Industry Profile*, Washington, DC: Pharmaceutical Research and Manufacturers of America, March 1997.
4. The Midwest Pharmacy Workforce Research Consortium. *Final report of the national pharmacist workforce survey:2000*; Table 4.1. www.accp.org/DOC/MainNavigation/Resources/Section_4_PDF.pdf, accessed April 9, 2004.
5. *Survey of Pharmacy Law–2003–2004*. Park Ridge, IL: National Association of Boards of Pharmacy, 2003.
6. Riggins JL, Plowman BH. *Drug Information J* 2000; 34:1223.
7. Riggins JL. Data on file. Eli Lilly and Company, Indianapolis, 2001: file no. RSRiggs501.
8. Category 14. Pharmaceutical Industry. *Career Pathways Evaluation Program*. Washington, DC: American Pharmaceutical Association. 2002. www.aphanet.org/pathways/Pathways.html accessed on March 25, 2004.
9. DePew CC (guest editor). *Drug Information J* 2000; 34:991.
10. Bendis I. *Pharmacy Times* 1997; 63:86.
11. Gmerek AM, Bakker-Arkema RG, Texter MJ, et al. *Int Pharm J* 1995; 9:150.

CHAPTER 6

Pharmacists in Government

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The emphasis on effective and efficient health care services for the population of the United States, and the recent terrorist attacks upon its populace, are increasing the importance of pharmaceutical managed patient-care services and pharmacist participation in complex health programs. New and exciting possibilities for adaptive pharmacy practice and careers are offered in government sectors, with the federal sector offering the broadest range of opportunities.

The trend toward systems of managed care administration has set into motion several initiatives that have already reformed the provision of health care in the US. While commitments and action steps at the end of the last century sought to reduce the overall size of the federal establishment, it became abundantly clear at the beginning of this century that certain parts of that establishment that had been designed to protect against terrorism actually needed to be expanded. Both the form and effect of changes in the federal sector will be spread over several years. It can be anticipated that federal-sector health systems will be extremely dynamic through the turn of the century and beyond.

Pharmacists and the profession of pharmacy are at the crossroads of health care. Opportunities for the creation of new forms of practice abound. Nowhere is this truer than in the federal sector, which offers numerous opportunities for innovation through novel clinical delivery systems, research, and in policy and regulatory mechanisms. While it used to be true that pharmacists practicing within the several federal services were not the highest paid practitioners in the profession, changes due to federal legislation providing for an accession bonus, special pay, loan repayment, and board certified pay for pharmacist officers have made it more competitive with the private sector. Pharmacist officers and federal civilian pharmacists also enjoy a benefits package that is highly competitive with the private sector. In addition, pharmacists desiring to practice advanced forms of clinical activities usually find greater fulfillment in federal practice than in most of the private sector. Federal uniformed service also offers the unique opportunity to pursue a career in which one's seniority and retirement program remains intact throughout one's career moves. Those pharmacists who are not product-oriented, but rather hold values and educational backgrounds oriented toward patient care and public health, find a particularly rewarding form of practice in federal service. Finally, even if pharmacists do not choose a full-time federal career, there are ample opportunities for intermittent federal service throughout the nation.

PHARMACISTS AND GOVERNMENT SERVICE

Pharmacists and their predecessors, the apothecaries and druggists, have served their country and government with distinction since the founding of the colonies. Although direct employment of large numbers of pharmacists is a relatively recent phenomenon, more subtle and indirect assistance has been provided for centuries. Pharmacists, apothecaries, and druggists have responded uniformly to the call of their country to perform critical tasks in support of causes ranging from defense to improving national social equity.

As health care and medical technologies have advanced and become increasingly complex, pharmacists have been called upon to perform tasks that are pivotal to the achievement of improving the health of the individual patient as well as the collective health of the nation. Paradoxically, most of the demands placed on the profession and its practitioners are expanding the pharmacist's role into new and different institutional and consulting territories, while at the same time intensifying demands for those performing in the more traditional community dispensing and distributive role. The ability of the pharmacist to be the health professional uniquely equipped to respond to these changing needs and demands rests with the nature of pharmacy and, to a large extent, the educational system that has evolved from the traditions of the apothecaries.

Pharmacy education and practice rests on a foundation of a synthesis of sciences. Pharmacists enter the practice world with a background and education that prepares them to be highly skilled and expert in several different intellectual and practical areas. This training and experience allows the pharmacist to move farther into the generalist role or choose to pursue a specialist role. Whichever role is chosen, the pharmacist remains a broadly educated member of society, offering a flexibility of performance of functions that is unseen in any other health profession. Pharmacists have gone to extraordinary measures to reach out to other disciplines in the health care team, and this has invariably opened up new opportunities for pharmacists and has led to a deeper reliance upon a pharmacist's expertise. It is precisely this high level of flexibility that makes the pharmacist an exceptionally valuable resource in government practice. Today, given the rapidly changing social and political environments into which government is interwoven, such flexibility is an essential element in adding value to the health system.

All opinions expressed in this chapter are those of the authors who are participating on their own personal time and do not represent those of the Department of Health and Human Services or the United States government.

CAREER OPPORTUNITIES

Opportunities in the federal sector are not merely employment opportunities, but are truly career opportunities. Federal service offers more variety and differentiation in the types of positions that a pharmacist may fill than does the private sector. In addition, the federal sector offers the pharmacist opportunities for which there is no comparison in the private sector. In the federal sector, it is not unusual to find a pharmacist in a position that neither calls for the specific expertise of a pharmacist nor is normally filled with a pharmacist. Federal pharmacists often occupy important positions of this nature because of their greater level of understanding of health care; this is the culmination of the skills they possess along with the on-the-job and federally funded training that they receive.

For most pharmacists, entry into federal service is through the traditional roles of dispensing and preparation of pharmaceuticals, then advancing to greater responsibilities in scope and magnitude. At some point in their career, most federal pharmacists must choose between accepting more distribution-oriented supervisory duties, or branching into a less traditional, more management and administrative path. For many pharmacists occupying high-level positions, advancement removes them entirely from traditional dispensing and other direct patient-oriented tasks. These posts generally are upper management or policy-making positions, where the specific requirement for experience in pharmacy practice is indirect or nonexistent.

In many respects, this pattern is similar to that which can be expected in some forms of multi-unit and chain-type community stores and in larger institutional practice in the private sector. Pharmacists in federal leadership positions have considerably greater, more far-reaching impact than do their peers in the private sector. The practice profile probably more closely resembles the events of a career in industry. The functional difference between federal and industry/multi-unit practice is that the federal climate offers the broadest range of types of practice, spanning the entire continuum from staff pharmacist functions through high-level management, administration, and policy making.

The federal agencies that offer career opportunities for pharmacists are the Department of Veterans Affairs (DVA), which employs the greatest number; the U.S. Public Health Service (PHS); and the Department of Defense (DOD), through the Army, Navy, and Air Force. The PHS and the three services within the DOD offer positions as either civil service or commissioned officers. The DVA and other federal agencies have primarily focused upon civil service appointments, but there are some PHS commissioned officer pharmacists who have been detailed to these agencies, and one needs to fully investigate such possibilities when job-hunting.

In the PHS, and in the Army, Navy, and Air Force, commissioned officers are used as rapidly mobile professional experts. Civil service is used as an ancillary method of recruitment, and offers significantly more geographic stability. Within the PHS, pharmacist officers of the Commissioned Corps provide the majority of pharmacy services; civil service recruitment is used in limited instances.

UNIFORMED SERVICE REQUIREMENTS

Of the seven uniformed services, four provide commissioned officer opportunities for pharmacists. The Air Force commissions pharmacists as members of the Biomedical Service Corps. The Army categorizes pharmacists as officer members of the Medical Service Corps. The Navy commissions pharmacists as members of the Medical Service Corps, and assigns some members of their health professional staffs as support for the Marine Corps. The Commissioned Corps of the PHS commissions pharmacists as members of a distinct pharmacist category, and these pharmacists primarily serve in Department of Health and Human Services agencies such as the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Indian Health Service. PHS commissioned officer pharmacists are also assigned to several other federal Departments, such as the Department of Justice, where they provide medical and health support to the Bureau of Prisons, and the Department of Homeland Security, where they provide medical and health support for the Coast Guard and National Disaster Medical System. PHS commissioned officer pharmacists similarly provide medical and health support for the National Oceanic and Atmospheric Administration in afloat and ashore establishments.

It is important for the pharmacist applicant to understand that accepting a commission as a member of one of the uniformed services obligates the individual to a higher order of service. Anyone seeking a career as a health professional and commissioned officer must keep in mind that professional pharmaceutical knowledge and expertise do not by themselves characterize a good officer. The individual must possess other qualifications and skills as required of any commissioned officer, whether serving in a health corps or in a combat arms corps. These qualifications include dedication to a larger cause; excellent judgment, leadership, efficiency, and effectiveness; and devotion to organizational purpose. These qualifications also include the willingness to take certain risks, such as working in a theatre of combat operations, pre-positioning in an area about to be devastated by a hurricane, or venturing into a contaminated area after a bioterrorist attack. The extent to which an officer exhibits and activates these attributes is carefully considered by promotion boards in addition to the skillful application of professional prowess.

Most successful applicants can expect to be commissioned as an extended duty reserve officer when first called to active duty. Applicants must possess a baccalaureate degree in pharmacy from an institution accredited by the American Council on Pharmaceutical Education (ACPE) and be licensed by exam to practice in one of the states or territories of the US or the District of Columbia. Generally, the licensure that is claimed must have been earned by examination, and not by reciprocity.

All applicants must be of good moral character, at least 21 years of age, and physically qualified. All applicants are required to undergo a government-provided, comprehensive physical examination prior to commissioning. In all cases, applicants must provide adequate information for a complete background and security check and be willing to undergo a credentialing process. In most cases, appointees with advanced degrees and/or specialized training and education are awarded added credit for rank purposes, in recognition of their attainment.

US ARMY

The Continental Congress established a hospital for the care of wounded and disabled in 1775 and simultaneously established the position of "Apothecary" as a member of its officer complement. In 1776, Congress created the office of "Druggist," whose duty it was to "receive and deliver all medicines, instruments and shop furniture of the United States." The Medical Department was reorganized in 1777 and the country divided into four districts. Congress provided that there would be one Apothecary General for each district. Each district Apothecary General was charged to "receive, prepare and deliver medicines and other articles of his department to the hospitals and Army, as shall be ordered by the director general."

During the Revolutionary War, a central laboratory was established for the manufacture of various pharmaceuticals needed to support the operations of the Continental Army. The first Apothecary General, Andrew Craigie, manufactured the majority of these products. His shop in Carlisle, Pennsylvania, was one of the first large-scale manufacturing operations in the colonies.

Professional recognition of the Apothecary, Druggist, and Pharmacist in the Army has been varied, but has improved over the past two centuries. During the Civil War, medical officers controlled the acquisition and preparation of medicinals in both the Union and Confederate Armies. Druggists frequently were found in supporting roles, especially among Union volunteer regiments, but they did not occupy commissioned positions. Between the end of the Civil War and the period immediately after World War II, pharmacists served in capacities for which some received commissions; others were assigned to the enlisted ranks. During World War I, several pharmacists served in support roles in the Army's Sanitary Corps.

Most recently, active and reserve Army pharmacists have risen to numerous challenges in supporting the Army War Fighter ensuring the projection and sustainment of a healthy and medically fit force. Army pharmacists have deployed both home and abroad in support of our nation's global war on terrorism for Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) in addition to other worldwide deployments.

Army Pharmacy

The degree of professional recognition of pharmacists, as well as pharmacy practice, is radically different in today's Army. Pharmacists are vital members of the Medical Service Corps and serve throughout the world in support of the mission of the Army Medical Department, which is to ensure the health of the soldier during times of peace and war. To accomplish this mission, the Army operates 106 ambulatory care clinics, 20 general hospitals, and 8 medical centers, as well as several fixed and mobile ambulatory-care medical activities.

There currently are approximately 153 commissioned pharmacist officers on active duty and approximately 260 Reserve pharmacist officers. The reserve officers are comprised of Reserve Troop Program Unit Members (TPU), Individual Ready Reserve (IRR), and Individual Mobilization Augmentee's (IMA). The Reserve officers are used to supplement the active duty force and are available for deployment on very short notice. Reserve officers can be called to active duty as part of an entire unit or as an individual to fill a specific vacancy.

Most pharmacist officers, active duty or reserve, are assigned to Army medical centers and general hospitals in the US. Army general hospitals have all the characteristics of the modern community hospital, but restrict their operations to providing for the care of active duty and retired personnel and their dependent beneficiaries. All eight of the medical centers conduct advanced education, training, and research programs and are equipped with much of the same sophisticated technology to be found in university-affiliated teaching hospitals.

Service as a pharmacist officer in the Army provides the opportunity for international travel and service. The Army has pharmacist officers stationed outside the US in hospitals in Germany, Korea, Panama, Japan, Italy, Belgium, and Southwest Asia. Career-status pharmacists can anticipate having the opportunity for a foreign-duty assignment at least once during their career. During an armed conflict, active duty pharmacists join ranks with their reserve counterparts in being assigned to and deploying with combat support hospitals (CSH), mobile army surgical hospitals (MASH), field hospitals (FH), medical logistics battalions, and medical logistics centers that are located in the theatre of operations.

An active pharmacy technician program supports pharmacist officers. The Army conducts pharmacy technician training at the Academy of Health Sciences at Fort Sam Houston, Texas, via a program of studies accredited with the American Society of Health-System Pharmacists (ASHP). A total of more than 600 pharmacy technicians are now on duty. Army pharmacists and technicians dispense in excess of 75,000 ambulatory-care prescriptions and 55,000 inpatient medication orders daily.

Army medical activities also use the civil service system to employ pharmacists. The Army employs some 400 civilian pharmacists in a variety of General Schedule (GS) grades, plus an additional 300 civilian technicians. Most of these civilian pharmacists are employed within the continental US and can expect geographic stability.

The Army provides several opportunities for advanced education, training, and research. Each of its medical centers conducts research programs. Four medical centers (Brooke AMC, Madigan AMC, Tripler AMC, and Walter Reed AMC) operate hospital pharmacy residency programs that are fully ASHP-accredited. In addition, a hematology–oncology and nuclear pharmacy residency is offered at Walter Reed Army Medical Center. Continuing education courses and opportunities are offered through military-provided programs of study, as well as attendance at civilian pharmacy programs; the expenses are covered under military reimbursement.

The Army is active in providing external education opportunities for its pharmacists. Each year, highly motivated officers are selected for Army-sponsored graduate studies in civilian institutions and Army-sponsored Training with Industry opportunities with national pharmaceutical organizations. Officers customarily pursue graduate education in institutional pharmacy leading to either a Master of Science or Doctor of Pharmacy degree. There is a limited opportunity for officers to pursue studies directed at earning a PhD degree in pharmacology. Officers selected for the training with the industry program are offered fellowship-learning opportunities within the healthcare community, including the pharmaceutical industry, regulatory agencies, and professional organizations. After training, Army pharmacists are positioned in key leadership roles to apply their knowledge and skills to advance the practice of pharmacy within the Army Medical Department. While attending sponsored education, officers receive full pay and allowances as well as tuition assistance.

The career path for all pharmacist officers extends from the rank of Second Lieutenant (O–1 grade) through Colonel (O–6 grade). It is possible for officers to be promoted through these ranks over a career of 21 years, based upon the promotion methods now in effect. All promotions are competitive.

Army pharmacy practice presents several unique opportunities. The Army Medical Material Development Activity manages and directs the development of pharmaceuticals and particularized delivery systems. The functions of the pharmacist assigned to duty in this activity are the assurance of program performance in terms of cost, schedule, logistics, quality, and adherence to specifications. Many, if not most, of the projects within this activity are unique to the military and are not seen in civilian practice. Delivery systems for combat casualty care, chemical warfare pretreatment, treatment devices and antiparasitic agents are examples of some of the areas in which the pharmacist would be expected to work.

As mentioned previously, the Army trains pharmacy technicians at their own school. The school offers an 18-week program, conducted on a rotating basis, approximately six times a year; the class size averages 40 to 60 students. Classes provide interservice education for active Army, Reserve, and National Guard components, and foreign military services. The school is supervised by a pharmacist officer and has a staff of an additional eight pharmacist officers and more than 20 senior enlisted military pharmacy technicians. This staff offers other more specialized courses of study in sterile products preparation and therapy and drug distribution. A course orienting all newly commissioned pharmacist officers to the organization and operation of Army pharmacy services, career opportunities, and expectations of performance is presented periodically by the staff.

Army pharmacists continue to provide value every day as contributing members of the Army and Department of Defense Health Care Team. With the implementation of futuristic initiatives such as pharmacy informatics, a pharmacist-lead Department of Defense Military Vaccine office, and the continued quality care improvements in the delivery of clinical services

that ensure medication-use safety for all patients, Army pharmacists will continue to be a vital link between the Medical Service Corps and the Army Medical Department in conserving the fighting strength and compassionately and effectively managing the medication-use aspects of the health of our Soldiers and Army family.

US AIR FORCE

Today's US Air Force (USAF) was preceded by the Army Air Corps. The Air Force Medical Service (AFMS) was authorized and activated on July 1, 1949. In March 1965, the Medical Service Corps (MSC) was reorganized into two distinct corps. The component including officers who conduct medical administration, supply, and non-clinical patient support activities remained in the MSC. The new added corps, the Biomedical Service Corps (BSC), consists of officers representing 17 areas of health practice who carry out clinically oriented functions. Pharmacists were transferred into the BSC, and this is the service in which they are now commissioned.

The mission of the AFMS and the BSC is to provide the medical support needed to maintain the highest possible degree of readiness of Air Force combat forces. The general mission is quite similar to that of the Army and the Navy, but differs in the methods and locations of delivery of services. As is the case with all other uniformed services facilities, during peacetime the Air Force provides health services to retired and active-duty service members and their dependents.

The Air Force operates 78 pharmacist-staffed medical facilities worldwide. In the US, these range from small ambulatory clinics to large medical centers. The service has additional hospitals and major clinics located overseas. The service also provides supplemental health services to beneficiaries in smaller support operations throughout the Air Force system. The Air Force operates a global network of aircraft and professionals for the purpose of aeromedical evacuation of members of all services. There are four aeromedical staging units in the continental US and another one located overseas.

Air Force hospitals range in size from 10- to 500-bed facilities, whose character depends upon the nature of the mission of the command in which they are located. The size and range of services are determined by the composition and quantity of those requiring support. Each of the major commands administers hospitals and clinics of the full range of sizes. The Air Force Medical Center is the largest and provides a full range of general, specialist, and tertiary support. Medical centers sponsor internships and residencies in most medical specialties and also offer broad integration of pharmacy services into the teaching mission. Research occupies an important focus in the day-to-day activities of most medical centers. There are five medical centers located in the continental US; the largest is Wilford Hall at the USAF Medical Center in San Antonio, Texas, with a full clinical teaching program.

Medium-sized hospitals of the USAF tend to be smaller than 100 beds and are designed to provide a full range of community-oriented care to beneficiaries within a geographically circumscribed area. Patients with conditions that cannot be handled at a USAF hospital commonly are referred to a multi-specialty civilian facility in the area or, in many cases, referred to other uniformed treatment facilities. Although they are geographically separated from the medical-center class of hospitals, these medium-sized hospitals remain linked to medical centers through parallel programs of patient care, medical education, and research. There are nine hospitals of this class in the US, plus two overseas facilities.

Air Force Pharmacy

As one would expect, given the varying characteristics of the different facilities of the Air Force, the specific qualities of pharmacy practice are variable from command to command and location to location. All treatment facilities offer ambulatory-care services, so pharmacy practice is a combination of inpatient institutional and outpatient dispensing. Workload statistics show that 23 facilities dispense more than 1000 ambulatory-care prescriptions a day; of these, 8 dispense over 2000 prescriptions per day, and one processes and dispenses in excess of 4000 prescriptions a day.

Pharmacist officers supervise, review, and monitor all functions of the dispensing activity. To deal with this volume and to provide the pharmacist with professional tools such as an up-to-date patient profile on each patient, the Air Force service is heavily computerized. Currently all DOD, retail network, and mail order pharmacies are linked through a centralized screening system that allows monitoring of patient medication profiles regardless of where the patient accesses the system. Additional automation, in development and testing, will also integrate inpatient pharmaceuticals, giving the pharmacist a complete spectrum of patient-specific drug information. Prescription digital imagery and barcode technology are currently utilized for outpatient prescriptions in all Air Force facilities to further improve patient safety.

Larger facilities employ specialist pharmacists. Most medical centers use pharmacists as drug information specialists who provide consultative services to medical and allied support staffs. In other large facilities, some pharmacist specialists devote a portion of their time to distributive functions. In all cases, pharmacists serve as active members of the pharmacy and therapeutics committees, which possess more far-reaching authority than in the civilian community. The pharmacist's role in selecting therapeutic alternatives and substitutable pharmacologically active entities is broader than in civilian practice.

The BSC currently has on active duty approximately 255 pharmacist commissioned officers, supported by approximately 1100 enlisted highly trained technicians. Additional pharmacy support is provided by pharmacists and technicians employed under the civil service system. Technician support spans several roles, from basic pharmacy administration to the supervised preparation of intravenous additives and solutions.

The career path for Air Force pharmacist officers is similar to that of the Army and Navy. Pharmacists serve as commissioned officers in grades from Second Lieutenant (O–1) through, and including, Colonel (O–6). With completion of the entry-level PharmD degree, direct commissioned pharmacists will enter active duty in the grade Captain (O–3). All new officers are provided a formalized orientation program upon entry. This 4-week program orients the pharmacist to the Air Force and to the Air Force medical community. Additional instruction in military courtesies, career development, and the operation of readiness programs also is provided.

Within the first 2 years of service, all pharmacists are required to return for advanced training. A 3-week course in management, concentrating on the finer skills of managing a clinical administrative career, serves as the foundation for future advancements in position and rank.

Sometime after the initial 2 years of service, pharmacist officers may be selected to attend the Squadron Officers School, which offers a full 7-week course in leadership. During the course, the pharmacist officer is integrated with other mixed-skills officers and receives information that helps build understanding of the Air Force mission, how it integrates with national objectives, and the roles and requirements of the career officer in the Air Force.

Air Force pharmacist officers are expected not only to maintain their skills, but also to improve them by constantly engaging in knowledge-enhancing activities. All pharmacists in the Air Force must achieve a minimum number of continuing education hours that reflect customary state requirements for the maintenance of licensure. All forms of ACPE-approved continuing education are supported through paid attendance.

Advanced academic education is encouraged by the Air Force. Under the sponsorship of the Air Force Institute of Technology program, highly motivated pharmacists are selected for

attendance at several different types of civilian institutions. The Air Force sets aside funds for advanced education specifically for the purpose of personnel earning advanced credentials, including specialty training, graduate degrees, certificates of proficiency, and ASHP-accredited residencies. While in attendance at an approved program of study, pharmacists remain active-duty officers and receive full pay and allowances.

US NAVY

The organization and mission of health care in the Navy is very different from that of the Army and the Air Force. All three share the common element of being a part of the armed forces, but the basic requirements of supporting a naval and marine force on land and on sea change central elements in providing support to the active and reserve establishments. Services on ships of the line, in amphibious forces, and on fully deployable hospital ships and fleet hospitals give Navy practice a character all its own.

The status of pharmacists in the Navy has been, in much the same fashion as in the Army and Air Force, variable over the years; there have been significant improvements since the 1960s. For many years proceeding the turn of the century, pharmacists were a component of the Hospital Corps. In 1898, Congress provided for the appointment of pharmacists within the Hospital Corps and for their rank to be equal to that of warrant officers, and a total of 25 pharmacist warrant officers were authorized. Since the passage of the Medical Service Corps Act in 1947, pharmacists have been commissioned members of the Navy.

The mission of the Naval Medical Department is Force Health Protection. In order to fulfill that mission, the Naval Medical Department strives to create a healthy and fit force and deploy along with that force to protect them, restore the health of the deployed and non-deployed force, and support the DOD TRICARE for Life initiative.

Naval facilities in San Diego, California; Bethesda, Maryland; Pensacola, Florida; Jacksonville, Florida; Camp Pendleton, California; and Portsmouth, Virginia, conduct active teaching programs. All hospitals, regardless of size, operate active ambulatory-care dispensing programs, which prepare and deliver from 100 to more than 4500 prescriptions a day and provide a full range of medication management consultative services. All hospitals operate unit-dose dispensing and distribution systems and intravenous admixture services.

Unique to the Navy in combat support is the operation of hospital ships. Two hospital ships operated by Military Sealift Command are designed to provide emergency, on-site care for US combatant forces deployed in war or other operations. USNS Mercy (T-AH 19) and USNS Comfort (T-AH 20) each contain 12 fully-equipped operating rooms, a 1000-bed hospital facility, radiological services, medical laboratory, a pharmacy, an optometry lab, a cat scan, and two oxygen producing plants. Both vessels have a helicopter deck capable of landing large military helicopters, as well as side ports to take on patients at sea. Both hospital ships are converted San Clemente-class super tankers. Mercy was delivered in 1986 and Comfort in 1987. Normally, the ships are kept in a reduced operating status in Baltimore, Maryland and San Diego, California, by a small crew of civilian mariners and active duty Navy medical and support personnel. Each ship can be fully activated and crewed within 5 days

Unique to the Navy is Fleet Hospitals. Fleet Hospitals are re-locatable, self-contained facilities designed to provide medical, surgical, and acute care services in support of the fleet and the fleet marine forces engaged in combat operations. A Fleet Hospital has the capability of a 250- to 500-bed hospital and is fully equipped with ward facilities, operating rooms, and an intensive care unit. They are different from a traditional Army MASH unit in that they are able to give the patient a wider range of care, from trauma surgery to physical therapy to pharmacy services.

Navy Pharmacy

The Navy currently has 160 pharmacist officers who serve primarily within hospitals. Navy pharmacist officers are augmented by nearly 120 pharmacists who are employed under the civil service system or by contracts, and slightly more than 900 technicians. Over 50% of Navy pharmacists possess advanced degrees, have completed an ASHP-accredited residency program, or both. Career officers are afforded the opportunity to apply for postgraduate education. The Navy annually sponsors officers for postgraduate education to earn a Master degree in one of the following: Hospital Pharmacy, Pharmacoeconomics, Health Policy, or Pharmacy Systems or a Post Doctor of Pharmacy degree. Officers selected for postgraduate education remain on active duty and receive full pay and allowances for up to 2 years of study. Additionally, the Navy operates ASHP-accredited residency programs at San Diego and Bethesda.

Navy pharmacist officers also have the opportunity to attend specialized schools, which are service-oriented or train with industry leaders in pharmacy benefit management to enhance their knowledge and value as a professional officer. They may apply for Director's Training with Industry; the Navy War College at Newport, Rhode Island; the Naval Postgraduate School at Monterey, California; or most any of the schools operated by the Department of Defense. Most of these ancillary schools offer year-long programs and prepare the Navy pharmacist for assignments and responsibilities over and above those of the customary practice of pharmacy.

The career path for Navy pharmacist officers is similar to that of the other Department of Defense services. Pharmacists serve in grades from Ensign (O–1) through Captain (O–6). Almost all officers enter as a Lieutenant (O–3), unless the person does not have a PharmD degree. If this is the case, they may enter as either an Ensign (O–1) or Lieutenant Junior Grade (O–2). Professional degree and years of experience determine entry grade. All new pharmacist officers attend Officer Indoctrination School at Newport, Rhode Island. Here, basic instruction is given in military courtesy, organization of the Navy, and other military indoctrination subjects. Pharmacy opportunities differ from other services basically in the nature and location of the usual Navy duty station.

The Navy offers several nontraditional opportunities for the pharmacist. Pharmacist officers serve as staff officers, at the Naval School of Health Sciences, the DOD Pharmacoeconomic Center and the TRICARE Management Activity. It is also possible for Navy pharmacist officers to expand their horizons into a more administrative roles through appointment as Chief of Ancillary Services where they are responsible for multiple services, including pharmacy, laboratory, radiology, and social work. All pharmacist officers who achieve the rank of Captain are asked to screen for executive leadership positions; these include Executive Officers and Commanding Officers of Medical Treatment Facilities.

The operational nature of the Navy gives rise to a concern with methods of supply and logistics. Pharmacists, who are familiar with storage standards and are additionally equipped with a Navy education, serve in several joint-command situations. Opportunities in medical supply and logistics are available at the Defense Supply Center Philadelphia and the Joint Readiness Clinical Advisory Board, at Fort Detrick, Maryland. In addition, medication management needs require pharmacist officer staffing on the hospital ships and in the fleet hospital units.

US PUBLIC HEALTH SERVICE

The US Public Health Service (PHS) of the Department of Health and Human Services (DHHS) is the oldest health arm of the federal government. It is the successor to the US Marine Hospitals Service, which was established by Congress in 1798 to provide services to "merchant seamen, naval and marine officers, and naval and marine enlisteds." The progenitors to

today's pharmacists were employed in the Marine Hospitals system from its very beginnings. All varieties of practitioners and titles (Apothecaries, Chemists, Druggists, and Pharmacists) have been employed. An unusual aspect of the employment of these Apothecaries was that, even in earlier periods, they were dedicated to the preparation and dispensing duties that are now associated with the operation of a contemporary pharmacy; Apothecaries in most other federal services had to do "double duty," tending to patients as well as preparing pharmaceuticals. Pharmacy practice has been a respected specialty in the PHS service since its very beginning.

The US Marine Hospitals Service was reorganized in 1871, placed under the supervision of a centralized office, and given leadership in the form of the "Supervising Surgeon." The Service was fully moved administratively within the Department of the Treasury. In 1875, the Office of the Supervising Surgeon was changed to that of Supervising Surgeon General, and his official title similarly changed. This second reorganization added the requirements that the Supervising Surgeon General be appointed by the President, with the advice and consent of the Senate.

In 1871, Dr John M Woodworth, Supervising Surgeon General, made the establishment of a mobile corps of health professionals to respond to health needs and crises within the US a top priority. He established rules, regulations, appointment standards, and examination requirements that paralleled those of military organizations, except that the standards relating to professional practice were set higher. Just as military officers were expected to display the highest level of military professionalism, Woodworth expected and demanded a commensurate level of excellence and dedication targeted specifically to patient care. A system of ranks and promotions was established; officers were appointed with the understanding that they would serve at the pleasure of, and for the good of, the service. Woodworth clearly established the Commissioned Corps as a meritocracy. As a battle-tested veteran—a Union surgeon of the Civil War—he understood the benefits of military-style discipline and organization, and gave them special meaning in the requirements for organized health care.

On January 4, 1889, Congress statutorily established the Commissioned Corps of the Marine Hospitals Service, legally organizing it with rank, benefits, obligations, and management methods parallel to Army and Navy officer corps. Additional statutory changes in 1902 and 1912 strengthened the position of the Commissioned Corps as the fundamental professional personnel system for the service. Statutory changes made during these periods changed the focus of the service from a hospital and health service for the Merchant Marine to a true preventive health and research organization of national scope.

For career and grade purposes, the Parker Act of 1930 provided for the appointment and promotion of pharmacists up to the grade of a Naval Lieutenant (O–3); all rank restrictions were subsequently removed by the PHS Act of 1944. Since 1944, pharmacists have been able to compete for all grades within the Commissioned Corps, up to and including Rear Admiral, Upper Half (O–8), with the title Assistant Surgeon General. By current statutory requirement, one Commissioned Corps pharmacist officer serves as an Assistant Surgeon General, Rear Admiral, Lower Half (O–7), and functions as the service's Chief Pharmacist Officer.

Organization

The PHS is the principal health agency of the Federal Government. Its mission is to protect and advance the health of the American people. The service is directed and overseen by the Secretary of Health and Human Services, with the consultation of both the Assistant Secretary for Health and the Surgeon General, who provide leadership and guidance on all health-related activities including research and development, education and training, and the organizing and financing of healthcare delivery services. The Assistant Secretary for Health also serves as a convener of various cross-departmental working groups. The Assistant Secretary for Health is the statutory chairperson for many of these working groups. The Assistant Secretary for Health can also hold the position of Surgeon General, or each position may be filled by a different official.

The PHS is organized into line-operating divisions, each with its own particular mission and focus. The PHS consists of the Office of Public Health and Science, with Regional Health Administrators located in PHS regional offices geographically dispersed throughout the US; the Administration for Children and Families (ACF); Agency for Healthcare Research and Quality (AHRQ); the Administration on Aging (AoA); the Agency for Toxic Substances and Disease Registry (ATSDR); the Centers for Disease Control and Prevention (CDC); the Centers for Medicare and Medicaid Services (CMS); the Food and Drug Administration (FDA); the Health Resources and Services Administration (HRSA); the Indian Health Service (IHS); the National Institutes of Health (NIH); the Program Support Center (PSC); and the Substance Abuse and Mental Health Services Administration (SAMHSA). Opportunities are available to the pharmacist in most of these agencies. Both civil servants and commissioned officers staff the PHS. Approximately 845 pharmacist officers and 250 civil servant pharmacists are employed in the service, and Figure 6-1 shows the relative distribution of those 845 pharmacist officers.

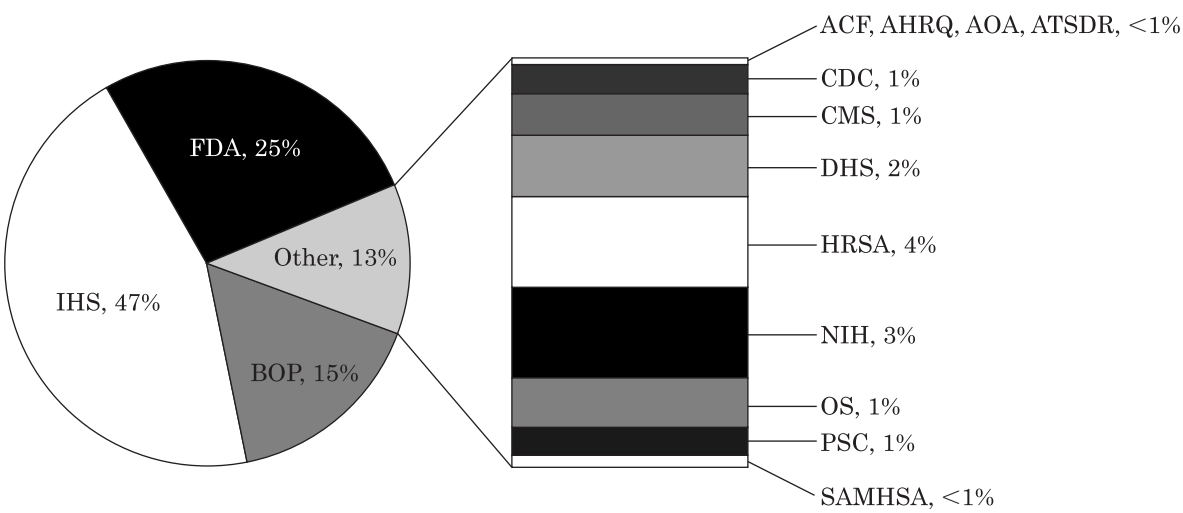

Figure 6-1. Distribution of USPHS Pharmacist Officers.

The Administration for Children and Families (ACF) is responsible for federal programs that promote the economic and social well-being of families, children, individuals, and communities.

The Agency for Health Research and Quality (AHRQ) identifies strategies to improve health care access, foster appropriate use, and reduce unnecessary expenditures, and is the federal government's principal agency for the conduct of health services research. The agency conducts broad-based outcomes and quality research, mainly through the awarding of grants to qualified researchers. The agency also issues periodic authoritative statements on treatment modalities and their effectiveness. The agency focuses heavily on the dissemination of the results of its research.

The Administration on Aging (AoA) is one of the nation's largest providers of home- and community-based care for older persons and their caregivers. Their mission is to promote the dignity and independence of older people and to help society prepare for an aging population.

The Agency for Toxic Substances and Disease Registry (ATSDR) implements the health-related provisions of Superfund (the Comprehensive Environmental Response, Compensation and Liability Act of 1980). ATSDR is charged with assessing health hazards at specific hazardous waste sites, helping to prevent or reduce exposure and the illnesses that result, and increasing knowledge and understanding of the health effects that may result from exposure to hazardous substances.

The Centers for Disease Control and Prevention (CDC) provides leadership in the control and prevention of diseases and monitors the immunization status of the population. It develops advanced methods for testing and preventing communicable and vector-borne diseases and conducts a substantial program for improving the performance of clinical laboratories. The CDC is extremely active in assisting state governments and local health authorities in preventing and controlling diseases within their respective jurisdictions. Through its National Institute of Occupational Safety and Health (NIOSH), the CDC monitors and researches safety standards in the workplace.

CDC has the responsibility for managing the Strategic National Stockpile Program (formerly called the National Pharmaceutical Stockpile Program) to ensure the availability and rapid deployment of life-saving pharmaceuticals, antidotes, other medical supplies, and equipment necessary to counter the effects of nerve agents, biological pathogens, and chemical agents. The Strategic National Stockpile Program employs pharmacist officers who stand ready for immediate deployment to any US location in the event of a terrorist attack using a biological toxin or chemical agent directed against a civilian population.

The Food and Drug Administration (FDA) is charged with protecting the nation's health as it relates to foods, pharmaceuticals, biological and vaccine products, medical devices, radioactive health products, cosmetics, food additives, poisons, and certain pesticides. The agency ensures that pharmaceutical products meet safety and efficacy standards, foods are unadulterated and wholesome, cosmetics are nontoxic, and that products in both the food and pharmaceutical industries do not present a hazard to the public.

The FDA has pharmacist officers working in a variety of regulatory positions, but the majority of these pharmacists serve as either Project Managers or Consumer Safety Officers. Their roles are to serve as primary focal points for industry questions, and to make sure that Congressionally established drug approval process timelines are followed. Pharmacists who have been successful at traditional dispensing roles are especially adept at these positions, as they have usually honed their multitasking skills, and such multitasking is necessary when they coordinate the simultaneous review of numerous New Drug Applications. In addition, FDA pharmacists serve in other key regulatory positions, including as biopharmaceutical reviewers, drug safety experts, drug information experts, and as inspectors at pharmaceutical plants. Some FDA pharmacists work with national and international standards-setting organizations in order to streamline the drug approval process and to simplify drug labeling.

FDA pharmacist officers have formalized appointments as preceptors for schools of pharmacy throughout the nation and have established an extremely dynamic integrated program in order to maximize the exposure of pharmacy students to the regulatory process. One goal of this program is to attract pharmacy students to the PHS as a career goal. In the past, PHS pharmacist officers were likely to take a position with the FDA only after first serving in some other PHS agency (eg, IHS or NIH), but this paradigm is rapidly changing. However, most FDA supervisors still believe that in order to be truly effective at an FDA position, several years' worth of traditional pharmacist experience is necessary, and such pharmacist officers usually have the competitive edge in both FDA job placement and PHS promotions.

FDA pharmacist officers are afforded a substantial amount of continuing education, both to help them to be highly effective in their regulatory position, and to help them maintain their clinical skills. This includes courses in regulatory law, biotechnology, and data management, as well as in disease state management. FDA has supported its pharmacist officers in their pursuits of advanced degrees, especially the Masters in Public Health degree that is offered through the Uniformed Services University of the Health Sciences, which is available at no cost and which equips the pharmacist officer to manage regulatory health care issues. In addition, because of the non-clinical nature of most positions, FDA pharmacist officers are usually encouraged to practice clinical pharmacy for several hours each week and are often allowed time away from their job in order to accomplish this professional development.

The Health Resource and Services Administration (HRSA) provides leadership in the identification and deployment of health personnel and in the educational, physical, financial, and organizational resources necessary to achieve optimal health services for all persons in the nation. As such, many of the agency's programs are targeted specifically to serve populations who are disadvantaged. The agency contains a component that is concerned specifically with issues of maternal and child health. The HRSA also participates in initiatives and studies that address the integration of public and private resources to improve the responsiveness of the health system to various populations of the country. The HRSA supports service delivery programs through grants and contracts and provides for improved access to health-care systems in both rural and urban environments. An arm of the agency provides the health-care personnel who serve as the medical and health support cadre for the Bureau of Citizenship and Immigration Services, which is under the Department of Homeland Security.

The National Institutes of Health (NIH) provides leadership and direction in advanced areas of medical and biomedical research. The NIH, which is consistently on the leading edge of medical discoveries and new techniques, is composed of 19 institutes that are arranged topically to correspond with particular pathogenetic concerns (such as the National Cancer Institute; National Heart, Blood and Lung Institute; and National Institute of Allergy and Infectious Diseases). It conducts and supports research in the causes, diagnosis, prevention, and cure of disease in humans, in the processes of human growth and development, and in the biological effects of environmental pollutants; the NIH also engages in considerable basic life-science research. It supports the training of research personnel, construction of research facilities, and development of promising research resources. The NIH actively funds extramural research in universities, teaching hospitals, and research centers throughout the country.

Many PHS pharmacists who work at NIH are assigned to the NIH Clinical Center Pharmacy Department, which provides pharmaceutical care and research support to patients, health care providers, and investigators. Pharmacy staff members conduct and participate in research programs that

enhance knowledge regarding optimal dosing and appropriate use of investigational and commercially available agents. Pharmacists at the NIH Clinical Center manage commercially available and investigational drugs in approximately 1000 drug protocols. This includes managing the equivalent of a small pharmaceutical production plant where oral and parenteral investigational drug products are manufactured.

In order to keep PHS pharmacists who work at the NIH Clinical Center Pharmacy Department on the cutting edge of medicine, they must take annual performance improvement training and must take an annual competency examination. Since the professional atmosphere on the NIH campus closely mimics that of a large university, there is ample opportunity to attend highly specialized lectures on a wide variety of medical topics. As a result, NIH pharmacists are looked upon as highly knowledgeable, integral members of the health care team; they perform drug utilization reviews, and routinely participate on patient medical team rounds, as blinded investigators for drug protocols, and on institutional review boards. In addition, NIH pharmacists are greatly encouraged to publish in the refereed medical and pharmaceutical journals. One publication in particular led to the adoption of national standards for personal protective equipment for health care workers that handled chemotherapeutic drugs.

NIH Clinical Center Pharmacy Department has a robust drug information center and highly trained staff of clinical specialists who answer thousands of drug information questions each year. It also has a highly competitive ASHP-accredited Residency Program, where one can focus upon Pharmacy Practice, Drug Information and Pharmacotherapy, Oncology, and Primary Care.

The Substance Abuse and Mental Health Services Administration (SAMHSA) focuses its efforts on substance abuse prevention and treatment and provides funding for programs which have interlinkages between drug treatment activities and primary-care programs. A major concern of SAMHSA programming is injection drug use as a cofactor in the transmission of HIV. Several SAMHSA programs seek to use the treatment of substance abusers as an opportunity to provide both primary and secondary prevention counseling. Pharmacist officers who have been detailed by SAMHSA to the District of Columbia Government usually practice at St. Elizabeth's Hospital, which is a psychiatric hospital.

The Indian Health Service (IHS) provides direct health services to 1.5 million American Indians and native Alaskans who are members of approximately 557 federally recognized tribes in 35 states.

The IHS operates the largest health maintenance organization (HMO) in the US. The IHS cares for most of the American Indians and native Alaskans who live primarily on or near Indian reservations and lands.

Pharmacy practice in the IHS is the one of the primary entry points for new PHS pharmacists, and its form of practice is very advanced and unique among all of the federal services. Although the original focus of the IHS was to promote the elimination of infectious diseases such as tuberculosis, great strides in the IHS' programs have nearly solved that issue; thus, the focus now is on comprehensive care, prevention, and rehabilitation.

The IHS direct-care establishment consists of 49 general hospitals, 155 service units, and 545 ambulatory facilities. Although the service population is spread across 35 states, the concentration of beneficiaries resides in the western half of the nation and in Alaska.

The IHS facilities are small compared to the average size of the DVA or military hospitals. Of the 49 hospitals, 33 have less than 50 beds, 12 have between 50 and 99 beds, and 4 have more than 100 beds. The largest facility operates 170 beds. All IHS hospitals operate unit-dose or modified unit-dose programs and provide central intravenous admixture services. The larger of the IHS hospitals have drug information services staffed by pharmacists who have formalized appointments with colleges of pharmacy and serve actively as preceptors. All IHS hospitals provide both ambulatory and inpatient care. The care activity associated with a patient's inpatient and ambulatory history is documented in a single record system that readily is accessible to the pharmacist. Pharmacists routinely monitor drug therapy and have all the necessary information to render clinical judgments on a patient's drug therapy and other clinical issues. All prescriptions are filled directly from entries in the patient's permanent health record. The nature of the IHS system creates a situation where the pharmacist usually is the last health-care professional to see the patient before discharge and frequently is the only professional regularly seen in an ambulatory environment. The IHS pharmacists have virtually total responsibility to ensure that patients understand their diagnosis, treatment, and follow-up requirements. Compliance with treatment plans is reviewed with the patient during each pharmacist consultation.

In most IHS settings, pharmacists provide primary-care services to patients and many pharmacists are certified with prescribing authority as an integral part of their practice. In most IHS facilities, there are formalized programs under which an appropriately educated and trained pharmacist is authorized to assess and treat patients with selected acute and chronic conditions, obtain patient histories, evaluate vital signs, order laboratory tests, and perform physical assessment techniques. These pharmacists are expected to exercise independent judgment in modifying, initiating, or otherwise altering drug therapies.

Pharmacists entering the IHS will find that practice differs significantly from traditional practice and that added training is necessary to accommodate the new roles. To develop these skills, a comprehensive clinical pharmacy training program has been developed, which is an integral portion of the IHS pharmacist's career development pathway.

Added educational opportunities are offered through service-sponsored attendance at professional meetings and continuing education seminars. Annually, all officers who are interested in further formal training are asked to complete a request for training out of service, which is granted based upon the anticipated needs of the service and funds available. There is no fixed limit on the number of pharmacists who may be sponsored. While officers pursue sponsored education, they remain on active duty and receive full pay and allowances. A commitment to serve twice the number of years of training accrues to the sponsored officer.

Commissioned Corps Readiness Force (CCRF) pharmacist officers are from most of the DHHS operating divisions. The CCRF is a cadre of US Public Health Service (PHS) officers, uniquely qualified by education and skills, who can be mobilized in times of extraordinary need during disaster, strife, or other public health emergencies and in response to domestic or international requests, to provide leadership and expertise by directing, enhancing, and supporting the services of the PHS and other DHHS Operational Divisions (OPDIVs), other US government agencies, and/or other respondents. CCRF pharmacist officers deploy to both natural disasters and to terrorist attacks and are therefore held to much higher readiness and proficiency standards than the average PHS pharmacist officer. They receive specialized training in emergency preparedness and response, including mass vaccinations, responding to weapons of mass destruction, and the management of the National Strategic Stockpile Program. CCRF pharmacists are often consulted upon, and routinely recommend, therapeutic substitution because of the very limited and ever changing formulary during an emergency. Recently, CCRF pharmacists have deployed in response to the terrorist attacks upon the World Trade Center, and in response to the bioterrorist anthrax attacks that quickly followed.

PHS Agreements with Other Departments

The PHS provides pharmacists for the health-care programs of the Bureau of Prisons (BOP) and US Marshals Service under agreement with the Attorney General and the Department

of Justice. The pharmacist officers in the BOP program are assigned to most of the intermediate- and large-size federal prisons and operate both inpatient and ambulatory services. Pharmacy operations within the BOP are unique and offer challenges not seen in other components of government. All pharmacists serving in this program are provided specially tailored training and education in the psychology of working within the prison environment. Additionally, all officers assigned to BOP, including pharmacists, are required to participate in firearms training and must establish a qualifying level of proficiency; periodic retraining sessions are required.

The PHS provides pharmacists for the health-care programs of Department of Homeland Security, and this is particularly noteworthy since it houses both the Coast Guard and the National Disaster Medical System (NDMS), the latter which had been under DHHS until 2003. NDMS is a joint partnership with PHS, DHHS, DOD, and the Department of Veterans Affairs. Many PHS pharmacists serve under NDMS, both in the Commissioned Corps, and as civil servant intermittent appointees. Most of these pharmacists assist the nation in responding to natural disasters and acts of terrorism through Disaster Medical Assistance Teams and are integral to the overall federal medical response.

Pharmacist officers in the PHS also can serve in international assignments with the World Health Organization, the Pan-American Health Organization, the Agency for International Development, and as support to the government of Micronesia.

PHS Pharmacy

The PHS offers the most variegated forms of pharmacy practice of any of the federal services. Pharmacists have the opportunity to practice in a traditional manner, engage in regulatory affairs, or compete for high-level policy and planning positions. Because the PHS is the prime supplier of health personnel to the DHHS, it is possible for pharmacists to access opportunities up to the departmental level.

The PHS offers unique opportunities for training and education. The pharmacist corps of the PHS offers pharmacy students as well as graduate pharmacists opportunities to learn. Pharmacy students may apply for participation in the Commissioned Officer Student Training and Externship Program (COSTEP). The junior COSTEP offers the pharmacy student a paid externship experience lasting from 30 to 120 days in one of the DHHS operating divisions, during which the student serves as, and is paid as, a commissioned officer holding the rank of Ensign (O–1). The senior COSTEP also offers the pharmacy student a commission as an Ensign, but not a short-term assignment. Instead, the pharmacy student receives pay while attending their sixth year of pharmacy school, and in return, is automatically promoted to the rank of Lieutenant (O–3) upon graduation and is obligated to remain on active duty for an additional 2 years.

Pharmacist officers customarily are eligible for transfer to other positions after the completion of an initial 2-year tour of duty. Although pharmacist officers in the PHS are not limited to positions of traditional pharmacy practice, it is the service's philosophy that pharmacist officers must clearly evidence that they are highly competent pharmacists prior to the service considering any reassignment into a nontraditional position.

The potential career pattern for commissioned officer pharmacists differs markedly from other uniformed services as all ranks from the entry level of Ensign (O–1) through Rear Admiral, Upper Half (O–8) are available. Pharmacists who graduate with a Doctor of Pharmacy degree are first commissioned at the rank of a Lieutenant (O–3 grade) and can progress through the rank of Captain (O–6 grade). One pharmacist is selected to serve a 4-year term as the service's Chief Pharmacist Officer and holds the rank of Rear Admiral, Lower Half (O–7 grade). Pharmacist officers succeeding in attainment of the rank of Rear Admiral, Upper Half (O–8 grade), normally do so by competing successfully for high-level program management or policy-making positions, either in the service or the department.

DEPARTMENT OF VETERANS AFFAIRS

The roots of the Department of Veterans Affairs (DVA) health-care system, as is true of many other federal health-care programs, are to be found in the PHS. In November 1918, PHS Surgeon General Rupert Blue was wrestling with two pressing issues. The first, and most immediate, was that a serious, virulent influenza was taking its toll in the American population. This strain, termed the Spanish Flu, gave rise to severe symptoms and took essential war material workers off the production lines for extended periods. Blue was also an exceptional strategic planner, and by mid-1918 he sensed that the war was drawing to a close, and knew that significant numbers of disabled and injured veterans would require care. He was concerned for the health of those who had served and would need additional care. He actively promoted legislative action to ensure that appropriate assistance would be available to the war-disabled upon their return home.

On March 3, 1919, Congress passed legislation empowering the Surgeon General of the PHS to provide for "discharged sick and disabled soldiers, sailors and marines; Army and Navy nurses, male and female." The Hospitals Division of the service expanded dramatically to meet the needs of these added beneficiaries; several existing Army hospitals and facilities were absorbed into the system. The PHS was given complete charge of veterans' health, including what would later be provided under the War Risk Insurance program.

In accordance with provisions of the Sweet Act, which established a distinct Veterans Bureau in the Department of the Treasury, a presidential executive order was issued directing that, effective May 1, 1922, all hospitals and outpatient facilities that had been opened or operated under the Surgeon General for the purpose of treating veterans were to be transferred to the new bureau. The Surgeon General transferred 57 hospitals; 17,000 beds; 13,000 inpatients; 9 additional new hospitals under construction; and in excess of 2300 physicians, pharmacists, nurses, and other health professionals to the health operations of the Veterans Bureau.

In 1946, the successor to the Veterans Bureau, the Veterans Administration (VA), underwent a major reorganization. The importance of pharmacy practice was recognized and the position of Chief Pharmacist of the VA's Bureau of Medicine and Surgery was established. This position continues today as the Director of Pharmacy Services, with a Central Office Pharmacy Staff. The DVA now operates the largest multi-institutional system of pharmacy services in the US.

In 1989 the Veterans Administration, through an act of Congress, became the Department of Veterans Affairs. The old Department of Medicine and Surgery became the Veterans Health Administration (VHA).

The mission of the VHA is to provide medical care to its statutory beneficiary population. Its largest beneficiary population consists of veterans of US uniformed services; however, certain dependents of veterans also comprise a substantial number of beneficiaries.

Veterans who were discharged from one of the uniformed services, under conditions other than dishonorable, are eligible to receive services. Beneficiary classes are broken down into "primary" and "other." The primary classification consists of veterans who were discharged or retired because of an injury or disability incurred or aggravated in the performance of their duties. Ex-service members who seek care for treatment of a disease or injury incurred in the line of duty are given first priority.

DVA Pharmacy

Pharmacy service in the DVA operates under the VHA. The VHA administers the largest multi-treatment facility health-care system in the United States. Pharmacy services, available in nearly all of these facilities, represent the largest multi-site pharmacy system in the United States. The treatment facility system encompasses 163 medical centers, which provide comprehensive, full-service inpatient care as well as ambulatory care; over 800 ambulatory-care centers and 131 nursing-care facilities; and 33 domiciliaries that offer a range of services from custodial to extended care for the neurologically disabled. These are organized into 21 distinct health care networks that comprise the DVA's health enterprise. There are approximately 8600 full-time pharmacy staff members and an additional 600 who serve part time. Of the full-time staff, approximately 4,600 are pharmacists, representing 55% of the full-time staff; an equal proportion of part-time staff are pharmacists as well.

Of major significance, especially to those interested in practicing pharmacy in a creative, research-based environment, is that the DVA operates the largest health professional training effort in the US. Nearly 110,000 health professional students receive clinical education in a DVA facility. The DVA offers nearly 3000 medical residency positions, representing virtually all medical specialties dealing with adult and geriatric medicine. Opportunities for part-time experience through affiliated rotations are made available to approximately 30,000 medical residents and 24,000 medical students. Over the past several years DVA pharmacy services have made a successful effort to integrate pharmacy operations and investigations into the overall medical research effort. Consequently, new and exciting vistas, especially in the practice of clinical pharmacy, have been opened.

Education and training possibilities in DVA pharmacy correspond with the extensive potential in the DVA system in general. Most schools of pharmacy have established formal relationships with pharmacies and pharmacists in DVA facilities. The DVA offers approximately 256 ASHP-accredited residency positions in 66 locations. DVA pharmacies routinely provide training to over 2000 pharmacy students annually. The DVA staff dispensed over 120 million ambulatory-care prescriptions in fiscal year 2002. DVA continues to provide comprehensive IV admixture services but does not tabulate the data nationally. Clinical pharmacy activities continue to grow significantly and 1400 clinical pharmacists have some form of prescriptive authority and expanded Scope of Practice Statement approved by the medical staff.

Pharmacists perform a full range of professional tasks and, with a professional to support ratio of almost 1:1, are provided with adequate time to discharge the professional duties. DVA pharmacists are exceptionally active in the areas of clinical pharmacy practice and quality assurance. The policies of the DVA pharmacy services central office encourage all pharmacists, regardless of their functional duties or their particular educational background, to practice in a highly patient-oriented manner. Pharmacists increasingly are becoming providers of technical information and consultative services to medical and dental staffs.

DVA has developed comprehensive automated systems to provide care to veterans. DVA has established 7 highly automated Consolidated Mail Outpatient Pharmacies (CMOP) that can fill up to 15 million prescriptions per site with significant reduction in staffing and improvements in medication errors. The dispensing accuracy of DVA CMOPs approached 99.997% in 2002. During this time, the CMOP program dispensed 75 million of the 120 million prescriptions filled that year.

In addition to the CMOP system the DVA automated pharmacy system provides Electronic Order entry for physicians as well as a comprehensive electronic medical record. DVA physicians use electronic order entry for approximately 95% of all medication orders and prescriptions. On the wards, the VA has implemented a Bar Code Medication Administration System (BCMA) to document medications and reduce medication errors.

DVA medical centers have implemented comprehensive quality assurance programs that involve pharmacists. The DVA uses several different quality assessment formats, including a systematic internal review along with a paralleling systematic external review procedure. The former is conducted by each individual institution as a self-assessment technique, whereas the latter involves peer assessments. DVA pharmacists are heavy contributors to assessments and policy-making processes in the selection of drugs, patient profiles, drug interactions, and adverse drug experience detection and prevention.

Veterans Affairs Employment

Unlike the uniformed services, the Veterans Health Administration uses civilian employees only. Since December 1989, all VHA pharmacists are appointed under a Hybrid Title 38 personnel classification system. This is a system by which positions are graded in accordance with the functions of the position as defined by applicable criteria. Hybrid Title 38 provided VHA pharmacists the opportunity to have non-supervisory, clinical roles with appropriate grades.

Generally, pharmacists occupy positions graded as GS-11 through GS-14. Most entry- and staff-level professional staff are graded at GS-11. Supervisory Pharmacists, Clinical Pharmacists/Pharmacy Specialists, and Assistant Chief Pharmacists generally are graded at GS-12 through GS-14, depending upon the size and type of medical facility and scope of pharmacy services. Pharmacy Directors range from GS-12 to GS-15 grade. All sites currently have special pay authorized for the staff pharmacist level and DVA may offer recruitment, retention, or relocation bonuses as well. Other incentives include a loan repayment plan as well as tuition support of second clinical and management degrees.

As described above, Hybrid Title 38 provides the vehicle to enable VHA pharmacy practice to transform from a purely distributive role to one that recognizes the pharmacist's place in quality patient care. Career progression within the DVA health-care system can now be achieved through administrative and clinical means. The opportunity to remain at one facility or relocate to other VHA health-care facilities is very attractive to many young professionals.

VHA pharmacy practice offers the pharmacist interested in all facets of professional practice an opportunity to experience many varieties of personal-career patterns. Growing, dynamic programs in ambulatory care and geriatrics, as well as acute medicine, provide practitioners a multitude of practice opportunities and the ability to contribute to a continuum of care wherever they choose to practice.

STATE, COUNTY, AND MUNICIPAL GOVERNMENT AGENCIES

In addition to employment in federal government agencies dealing with regulation of the distribution of drugs, numerous opportunities exist for similar service with state departments of health, state boards of pharmacy, state bureaus of controlled drugs, state and county welfare administration departments, and similar agencies. This applies also to the larger municipalities.

The coordination of municipal, state, and federal drug enforcement procedures, especially for regulation of controlled drugs and dangerous drugs and poisons, opens a great opportunity for pharmacists who are especially interested in regulatory activities. Very often those who start in federal positions and acquire considerable experience at that level have the opportunity to take over administrative functions of a similar nature in state and municipal agencies, where their coordination

efforts are enhanced greatly by past experience at the federal level.

The administrative functions of state, county, and local organizations that enforce health and welfare regulations frequently include specific duties that require a background of pharmaceutical training.

Many of these agencies deal with such matters as disease prevention and medical care. State governments have increasingly assumed the administration of welfare medical-care programs. In carrying out this function state and local appropriations are being augmented or matched by federal appropriations. In such instances, pharmacists frequently are employed to supervise the administration of pharmaceutical services in welfare medical-care programs, especially those involving what has become known as "vendor payments" for prescription drugs and pharmaceutical services. These agencies usually appoint advisory committees that consist of representatives of the various health professions, including pharmacists, to aid in developing and enforcing their programs.

Some pharmacists are employed by these agencies on a full-time basis and usually are designated as Pharmacy Advisors or Consultants. State welfare agencies, which are called on to pay for the millions of prescriptions that are supplied annually to indigent or medically indigent and aging patients, will employ such consultants on a full- or part-time basis or will create positions under the civil service for pharmacists. These positions provide an expert review of the pricing of prescriptions to keep them within the range of payment prescribed by the agency. These pharmacists are expected to give advice on the best methods of reducing drug costs to the welfare agency. They also are expected to work with medical consultants and members of the medical profession in devising limitations and extensions of medical-care services as may be indicated.

Although government service does not pay as well as employment in the private sector, it has compensations in the form of retirement benefits, medical services, and annual and sick leave benefits that are very attractive. In recent years, government agencies have also tended to provide time for formal education in various specialties, enabling the incumbents of these positions to improve their status.

LOCATING CURRENT INFORMATION

The information presented in this chapter is accurate as of the time of its publication, but the nature of the governmental system changes rapidly. Those interested in pursuing a career in federal or other government service should seek current information. The best way to do this is to discuss one's interest with the personnel responsible for placement at a college of pharmacy. Placement officers invariably know how to access recent information. When a pharmacist desires to proceed further than the information stage, college personnel can offer referrals to government agency representatives for detailed, in-depth information and discussion.

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BIBLIOGRAPHY

A History of the Hospital Corps and The Dental Technician Rating, Naval School of Health Sciences, Portsmouth, Virginia, NAVEDTRA 13130, 2003, https://www-nshspts.med.navy.mil/Courses/History/manual/intro.htm

USNS Mercy T-AH 19, 2003, http://www.mercy.navy.mil/

USNS Comfort T-AH 20, 2003, http://www.comfort.navy.mil/

Babb J, Tosatto R, Hayslett J. *J Am Pharm Assoc (Wash)* 2002; 42(5 suppl 1):S50–1

Bayles BC, Hall GE, Hostettler C, et al. *Am J Health-Syst Pharm* 1997; 54:778.

Carmona RH. *Preparedness and Pharmacy Science.* American Pharmaceutical Association (APhA) Conference - Academy of Students of Pharmacy (ASP) Opening Session, New Orleans, Louisiana, 2003, http://www.surgeongeneral.gov/news/speeches/pharmaconf032903.htm

Floyd D. Spence National Defense Authorization Act for Fiscal Year 2001 (aka HR 4205, which later became Public Law No: 106-398), SEC. 628.

Furman B. *A Profile of the United States Public Health Service, 1798–1948.* Publ No NIH 73-369. Washington, DC: Department of Health, Education, and Welfare, 1973.

Gill H. *The Apothecary in Colonial Virginia.* Williamsburg, VA: Colonial Williamsburg Fund, 1972.

Herrier RN, Boyce RW, Apgar DA. *Hosp Formul* 1990; 25(1):67–8, 76–8, 80.

Huntzinger PE. *Mil Med* 2000; 165(11):855.

Kremers E, Urdang G, Sonnedecker G. *Kremers and Urdang's History of Pharmacy,* 4th ed., reprinted by the American Institute of the History of Pharmacy, Madison, WI, 1986.

Montello MJ, Ames T. *Am J Health-Syst Pharm* 1999; 56:236.

Mullan, F., *Plagues and Politics: The Story of the United States Public Health Service.* New York: Basic Books, 1989.

Normark JW, Williams RF, Hostettler CF, et al. *Am J Health-Syst Pharm* 1999; 56:568.

Ogden JE, Muniz A, Patterson AA, et al. *Am J Health-Syst Pharm* 1997; 54:761.

Paavola FG, Dermanoski KR, Pittman RE. *Am J Health-Syst Pharm* 1997; 54:766.

Spain J. *Mil Med* 1999; 164:693.

Williams RF, Moran EL, Bottaro SD 2nd, et al. *Am J Health-Syst Pharm* 1997; 54:773.

Young JH. *Am J Health-Syst Pharm* 1997; 54:783.

CHAPTER 7

Pharmacists and Public Health

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Public health is a societal effort to protect, promote, and restore the public's health.[1] It is a combination of sciences, skills, and beliefs that are directed to the prevention, maintenance, and improvement of the health of all the people through collective or social actions. The programs, services, and institutions involved emphasize the prevention of disease and the health needs of the population as a whole. Public health activities change with changing technology and social values, but the goals remain the same: to reduce the amount of disease, premature death, and disease-produced discomfort and disability in the population. Public health is thus a social institution, a discipline, and a practice. The Institute of Medicine defines the mission of public health as "fulfilling society's interest in assuring conditions in which people can be healthy."[2]

Public health programs in the US were established initially to handle the epidemics of communicable diseases and high levels of infant and maternal mortality that were prevalent during the late 1800s and early 1900s. Much of the problem related to a lack of sanitation, overcrowding, and a failure to adhere to appropriate hygienic measures; by the 1960s, most of these problems were under control.

HISTORY

The first public health organizations in America developed in the late 18th century in the port cities along the Eastern coastline, largely in response to early infectious disease threats such as the 1793 yellow fever epidemic in Philadelphia. By the middle of the 19th century, reformers advocated the collection of vital statistics, birth/death registrations, and more comprehensive data on the health of the population, especially as communicable disease outbreaks continued. One such reformer, Lemuel Shattuck, a schoolteacher, publisher, and bookseller, was primarily responsible for instituting a vital statistics registry in Massachusetts.

The *Report of the Sanitary Commission of Massachusetts, 1850* is a classic and comprehensive document of recommendations for organizing public health.[2] In 1872, the American Public Health Association (APHA) was formed to "advance sanitary science and promote the practical application of personal hygiene."[3] By 1880, permanent state and local health departments and boards had been formed; their financial backing, and hence their impact, was very limited. After 1912, when the US Public Health Service (PHS) was increased in size and responsibilities, a network of federal, state, and county/city health departments began to emerge. The primary unit to administer programs was the city or county health department with its team of a physician, nurse, sanitarian, and administrative staff.

The PHS, originally named the Marine Hospital Service, was created on July 16, 1798, when President John Adams signed the Act for the Relief of Sick and Disabled Seamen. From the beginning, the PHS has been at the forefront of addressing the public health issues facing this country, from curtailing the spread of contagious diseases in 19th century, to providing health care to those with special needs. Today, PHS activities include not only regulation of food, drugs, and toxic substances, but also supporting disease control and prevention, biomedical research, health care to underserved populations, mental health, substances abuse prevention, health promotion, and international health.

Prior to World War II, traditional programs formed the bulk of public health work: disposal of sewage, provision of pure water, communicable disease control, and the care of mothers and infants. Health education was the main weapon of attack. This changed, however, with the advent of antibiotics and the expanded development of vaccines, both of which reduced the danger of infections.

As chronic diseases began to assume a major role in morbidity and mortality, hospital care replaced care in the home. Comparable changes in public health accelerated as federal funding increased; health departments provided an increasing amount of direct patient care in the clinic and in the home. Funding shifts at the national and state levels have reversed this trend somewhat, but trends continue to point to the emergence of an organized medical care service with an emphasis on keeping people well, a forerunner of a national health service.

The first permanent county health department in America was not formed until the early years of the 20th century. At that time, the primary aim of public health services was to control communicable disease by enforcing sanitary codes that eliminated contamination of food, water, and milk by human excreta. With the advent of immunization, communities instituted programs for disease prevention with vaccines; gradually, more personal health services were added, such as maternal and child health. In many areas of the country, the primary provider of these community-based services has been the public health nurse. Pharmacists should become acquainted with local public health nurses and the variety of services they provide to their patients.

Since the 1970s, new public health issues have emerged. These include infectious disease outbreaks such as AIDS, West Nile virus, or Severe Acute Respiratory Syndrome (SARS); access to quality health care for all Americans; environmental problems such as exposure to and disposal of toxic chemicals and wastes, nuclear wastes, and smog and air pollution; and societal problems such as care of a growing elderly population, teenage pregnancy, and substance abuse. The health of the public has been and continues to be influenced by governmental policies and Medicare; discussions continue to call for overall reform of the health-care system in the United States. Over the past 50 years, the public health infrastructure has

expanded to include everything from occupational safety to environmental protection; however, worldwide socioeconomic issues have created an enormous public health problem worldwide. Public health is at a major crossroads because of the convergence of problems related to social and biological factors, community and individual problems, and widespread economic and social policy issues. In the face of world problems of an economic, political, population control, and environmental nature, as a discipline, public health continues to experience changes, both in its organization and accomplishments. American pharmacy and medicine have diminished or eliminated teaching public health as an entity.

During the past few decades, because traditional acute health-care services have had a limited effect on improving the overall national health status, health professionals have initiated health promotion and disease prevention (wellness) strategies in their respective practices. Pharmacists, with a renewed emphasis on the clinical care of the patient,[5] have been encouraged to use pharmaceutical care strategies to uphold the health of the patients that they serve. Prevention is a major component of that philosophy. Pharmacists, in a unique position to promote public health because of their easy access and good communication skills, remain the most trusted health profession.

HEALTH GUIDELINES

The first set of national health targets was published in 1979 as *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention.*[6] The series of Department of Health and Human Services (DHHS) *Healthy People 1990, 2000* and *2010* reports (www.healthypeople.gov) put a strong emphasis upon comprehensive preventative programs that are office, community, or population based,[7] serving to improve the health of the people of this country. With a growing influence, national pharmacy organizations, and the pharmacy leadership in the US Public Health Service submitted new objectives for consideration in the development of the *Healthy People 2010* report (Table 7-1).

The *Guide to Clinical Preventive Services,* developed by the United States Preventive Services Task Force (USPSTF),[8] is an evidence-based review of over 100 interventions to prevent 60 different medical conditions. The guide offers some of the most comprehensive, evidence-based, graded prevention recommendations that pharmacists or other clinicians can provide to patients. The USPSTF grades its recommendations according to one of five classifications (www.ahrq.gov/clinic/3rduspstf/ratings.htm) which reflect the strength of available evidence and the magnitude of the net benefit.[9] Some of these conditions are routinely seen, triaged, or managed by pharmacists, including cardiovascular conditions; infectious and sexually transmitted diseases; various forms of cancer, trauma, and injuries; and alcohol, tobacco, and other substance abuse. Pharmacists in primary care settings have frequent opportunities to screen for many of these conditions, educate patients, and encourage them to attempt to change their health behaviors.[10]

Table 7-1. Pharmacy-Oriented Objectives in Healthy People 2010

1. Reduce by 50% Medicare admissions to short stay acute hospitals due to drug therapy management problems.
2. Increase to 75% the proportion of Medicare enrollees with diabetes receiving appropriate educational and preventive services.
3. Increase to 25% the proportion of pharmacies providing administration of influenza and pneumococcal immunizations to adults.
4. Decrease the number of pharmacies who sell tobacco and tobacco-related products to no more than 20% and increase the number of pharmacists who provide tobacco cessation counseling, support, and referrals to smokers to 90%.
5. Substance abuse: add prescription medications to alcohol and other drugs that contribute to substance abuse.
6. Increase the number of pharmacies that offer patient counseling on diabetes and other chronic diseases.
7. Reduce by 50% the number of courses of antibiotics prescribed for the common cold per population.
8. Increase the number of medical, nursing, public health, pharmacy, dentistry and allied health academic training programs that include a unit on the prevention and control of emerging, re-emerging and drug-resistant infectious diseases.

Pharmacists can utilize two excellent sources of evidence-based health care information, the National Guidelines Clearinghouse (NGC; www.guideline.gov), a comprehensive database of evidence-based clinical practice guidelines, and the National Quality Measures Clearinghouse (NQMC; www.qualitymeasures.ahrq.gov). The NGC, a comprehensive database of evidence-based clinical practice guidelines and related documents, provides health care providers, health plans, integrated delivery systems, and others an accessible mechanism for obtaining objective, detailed information on clinical practice guidelines and to further their dissemination, implementation, and use. Key components of NGC include structured abstracts about specific guidelines and their development, links to full-text guidelines, where available; a Guideline comparison utility that gives users the ability to generate side-by-side comparisons for any combination of two or more guidelines, guideline comparisons (aka Guideline Syntheses) which compare guidelines covering similar topics, highlighting areas of similarity and difference. These syntheses often provide a comparison of guidelines developed in different countries, providing insight into commonalities and differences in international health practices; and an annotated bibliography database where users can search for citations for publications and resources about guidelines, including guideline development and methodology, structure, evaluation, and implementation

The National Quality Measures Clearinghouse (NQMC; www.qualitymeasures.ahrq.gov), is sponsored by the Agency for Healthcare Research and Quality (AHRQ), for information on specific evidence-based health care quality measures and measure sets to promote widespread access to quality measures to health care practitioners. Its mission is to provide practitioners, health care providers, health plans, integrated delivery systems, purchasers and others an accessible mechanism for obtaining detailed information on quality measures, and to further their dissemination, implementation, and use in order to inform health care decisions. Key components of NQMC include a structured, standardized abstracts (summaries) containing information about measures and their development; a utility for comparing attributes of two or more quality measures in a side-by-side comparison; and links to full-text quality measures.

Similarly, the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, offers *CDC Recommends*, quick access to documents containing CDC recommendations for the prevention, control, treatment, and detection of infectious and chronic diseases, environmental hazards, natural or human-generated disasters, occupational diseases and injuries, intentional and unintentional injuries and disabilities, and other public health conditions. This compendium of documents allows public health practitioners and others to quickly access CDC recommendations from a single point, independent of where they were originally published. Presently, there are over 400 documents containing recommendations and 80 documents archived for research or historical purposes maintained in the system.

Healthy People (www.healthypeople.gov) is the national prevention initiative designed to improve the health of all Americans. It identifies three national public health goals: increase the span of healthy life, reduce health disparities among Americans, and achieve access to preventive services for all Americans. Detailed in the latest report are 300 specific objectives for health promotion and disease prevention programs in 22 separate priority areas (Table 7-2), with quantitative targets

Table 7-2. Healthy People 2010 Priority Areas

1. Physical Activity and Fitness
2. Nutrition
3. Tobacco
4. Substance Abuse: Alcohol and Other Drugs
5. Family Planning
6. Mental Health and Mental Disorders
7. Violent and Abusive Behavior
8. Educational and Community-Based Programs
9. Unintentional Injuries
10. Occupational Safety and Health
11. Environmental Health
12. Food and Drug Safety
13. Oral Health
14. Maternal and Infant Health
15. Heart Disease and Stroke
16. Cancer
17. Diabetes and Chronic Disabling Conditions
18. HIV Infection
19. Sexually Transmitted Diseases
20. Immunization and Infectious Diseases
21. Clinical Preventative Services
22. Surveillance and Data Systems

to be achieved by the year 2010. The mission of public health is defined further as being directed on four fronts: optimizing public health service delivery, protecting the community against environmental hazards, assisting and reinforcing the community health-care provider system, and assisting individuals (consumers) to achieve optimal health status through promoting medical self-help principles.

In 1981, a policy statement of the APHA focused on the role of the pharmacist in public health and the importance and need for increased involvement of pharmacists in public health settings.[11] The report states the problem, underutilization of the patient-oriented pharmacist; gives the purpose, the need to maximize the use of existing health-care professionals and facilities; and provides positions and recommendations, to identify current and future roles for pharmacists in public health, provide essential background information about these roles, and describe means of implementing or maximizing these functions. This policy statement identifies the need for public health pharmacists to become public health educators and role models, and it also provides detailed suggestions for pharmacist public health activities. These activities are to be achieved not only at the *micro* level, such as speaking to community groups on drug topics and providing hypertension screening, but also at the *macro* level (ie, with managerial level health planning, evaluation, and administration).

Few pharmacists have asserted themselves and established a functional and visible role in public health. The average community pharmacist, however, does not participate on a regular basis in community health-promoting activities. The APHA policy statement emphasizes that community pharmacists are an underused source of health data that could assist health planners in these areas.

In general and individual disease prevention and health promotion programs, the public health activities of the pharmacist could include community preventive health care, primary care, referral, health education, drug information, toxicology, and health planning. Pharmacists should consider increased involvement with immunization programs, substance abuse education and monitoring, sexually transmitted disease education, family planning, fluoridation, poison prevention, disaster preparedness, environmental protection, workplace safety, peer review, and health data collection. With program targeted to individual patients, activities suggested for improvement are increased patient education, screening and referral, medication maintenance, compliance counseling, patient monitoring, and family counseling.

A particular set of functions for pharmacy services in public health settings include planning for health care for wide geographic areas or communities; managing, administering, and evaluating health-care programs, systems, and facilities; providing direct-person health-care service (eg, education and maternal and child care) and environmental health; developing and promoting legislation and deriving regulations pertaining to the public's health; and training health-care workers needed to carry out these functions. Community pharmacists are both knowledgeable in and can easily embrace community-oriented activities, such as speaking to groups on health-related matters, referring patients to community agencies, and participating in community-based programs on sexually transmitted diseases, mental health, substance abuse, poisoning, and cancer signals.

Regional or state health planning boards should use community pharmacists to provide epidemiological data on prescribing patterns, local illness patterns and various socioeconomic factors related to prevalent disease states. Finally, the position paper encourages more exposure of pharmacists to public health in their training and to promote the pursuit of advanced degrees (ie, Master of Public Health [MPH] or Doctor of Public Health [DrPH]) in schools of public health.

Advocates have urged pharmacists to document their roles in several specific practice areas and have provided data where pharmacists have shown leadership and significant contributions to the field of community health.[12, 13] Most pharmacists are employed in the community setting where they have a significant impact on the health status of the population, however, there is an ongoing need to focus both education and incentives in the direction of public health. At the *macro* level, pharmacists usually are salaried, and work in private and public institutions, agencies, and organizations that focus health care on defined population groups. This type of pharmacist requires a wide breadth and depth of knowledge, usually administrative and organizational skills (eg, health planning, monitoring state Medicaid drug programs, providing in-service education, developing health-promotional materials, and planning community health campaigns).

In 1972, Gibson,[14–16] in a review of public health instruction in colleges of pharmacy, found uniform deficiencies in the following: a definition of public health in pharmacy, a perceived relevance of public health to pharmacy, textbook(s) focusing upon the role of pharmacy in public health, faculty qualified to teach the subject, and sites where students could become involved with public health projects and personnel. In 1985, this issue was addressed by an Ad Hoc Committee on Public Health within the American Association of Colleges of Pharmacy (AACP).[17]

Pharmacy educators should develop community practitioners who can interface between the profession of pharmacy and community health planning agencies. Currently, these pharmacists frequently provide health promotion and disease prevention (HPDP) activities such as providing drug and nutrition counseling, screening for hypertension and diabetes, providing weight control programs, counseling on the appropriate use of prescribed and/or over-the-counter (OTC) medications, referring patients to specific health-care providers, and performing drug and medical histories. Having the majority of pharmacy practitioners involved in these types of programs continues to evolve through federal legislation such as the Omnibus Budget Reconciliation Act (OBRA) of 1990, which mandated pharmacists to consult and counsel patients on drug and health matters.

While most reimbursement for pharmacists remains product-related, pharmacists have been getting more involved in providing cognitive services that are now becoming reimbursable from third-party beneficiaries. These services include innovative disease management arrangements, intensive patient counseling and education, and physician-initiated pharmacotherapeutic consultations.

Involvement can be initiated directly with local health departments and with assistance from national pharmacy organizations such as the American Pharmacists Association (APhA),

American Society of Health-System Pharmacists (ASHP), American College of Clinical Pharmacy (ACCP), or their state affiliates. Pharmacists can volunteer their services, share their ideas, perspectives, and knowledge, and be available for collaborative community health efforts. Initial involvement of a minor nature often leads to greater potential for future mutually beneficial public health endeavors.

Through the National Center for Health Statistics (NCHS), pharmacists can become aware of sources of health data (eg, Vital Statistics System (www.cdc.gov/nchs/nvss.htm); National Notifiable Disease Surveillance System (www.cdc.gov/epo/dphsi/nndsshis.htm), Morbidity and Mortality Weekly Report (www.cdc.gov/mmwr), and National Health Interview Survey (NHIS; www.cdc.gov/nchs/nhis.htm) and how epidemiology plays an important part in overall public health strategies. Health services must be viewed on all levels, from international to local. With increasingly shorter travel times and an increasing number of people traveling, it is vital to have a global awareness of health and disease.

In addressing the challenges of public health for the 21st century, Frenk proposed an effort to integrate tradition and progress with new directions, including research to provide scientifically validated information relevant to the problems of decision-makers at all levels, support of continued academic education in public health to promote excellence and broaden university milieu, application of the population approach to all related fields of health on a multinational level, and a greater openness to concepts from the social, biological, and behavioral sciences.[18] A review of the public health literature of the last 10 years demonstrates some of the major public health concerns:

- The epidemiologic and biostatistics studies associated with infectious diseases - HIV disease, AIDS, tuberculosis, SARS, etc.
- The appropriate amount of physical activity for good health, and diet, hormones, and cancer.
- Environmental and occupational health (eg, health effects of low-level ionizing radiation, occupational health concerns, worksite drug testing, and hazardous waste generation and safe disposal).
- Global change (eg, ozone depletion, greenhouse warming and public health policy toward toxic or nuclear waste disposal).
- Public health practice: global immunization, polio eradication from the Western Hemisphere, health issues for college students, mortality of Native American infants, the public health practice of tobacco control and lessons learned, the changing epidemiology of asthma morbidity and mortality, mammography use and cost-effectiveness.
- Behavioral aspects of health: depression and public health, obesity, poverty and cultural diversity challenges for health promotion among the medically underserved or non-English speaking members of the community, smoking in pregnancy, and heterosexual transmission of HIV.
- Health services: unnecessary surgery, low pre-school immunization coverage, access and cost implications of state limitations on Medicaid reimbursement for pharmaceuticals, containing costs while improving quality of care, the insurance gap, retiree health benefits, emergency medical services, improper use of antibiotics, aging, and national health systems throughout the world.
- Bioterrorism, with its growing influence of viral, bacterial, biochemical, and nuclear toxins (eg, anthrax, botulism), and its management/prevention across all sectors of the health care field.
- The exponential growth in the interest in and practice of complementary/alternate medicine, nutrition, and lifestyle.

HEALTH SERVICES PROGRAMS

Federal health legislation is based upon the federal government's constitutional right to "promote the general welfare," but the states retain sovereign rights in guarding the health of their inhabitants. Within the states, health departments provide a wide spectrum of services to the community under the rubric of public health.

Usually, local health departments are affiliated with their state's health department. In the more sparsely settled states with adequate local coverage, the state health department acts in a consultant capacity; in states with inadequate local services, personnel from the state central office often provide direct services. The state may, in turn, call upon federal health consultants for advice and assistance.

A health director, usually with an advanced degree in public health, is responsible for the overall management of a health department. As a part of the health department team, public health nurses provide the bulk of the personal health services, both in clinics and in the home; they deal with the care of people ranging from newborn infants to elderly patients with multiple medical conditions. Their primary concern is to apply the principles of prevention to the patients, to promote health or to retard the progress of a disease where a return to health is not possible. Environmental health specialists are responsible for the control of disease by environmental techniques. Animal control officers serve to control endemics within a broad number of animal species.

Public health has often been popularly regarded as a health care service for the financially, socially, or geographically disadvantaged, but in reality, public health services are for all members of the community (eg, epidemics, or post-natural disaster care such as after hurricanes, tornadoes, or blizzards), as they are supported by the county or state tax base. Pharmacists should become acquainted with their local health department and its wide range of services and avail themselves of these services whenever the need arises. Further, pharmacists can get involved locally in public health, as many county boards of health are required by state or local statutes to have a pharmacist on the Board.

EPIDEMIOLOGY

Epidemiology is the study of the distribution and determinants of health-related events in specific populations and the applications of this field in the control of these events. Epidemiology relates to the interaction of hosts and their environment, with attention to those particular agents in the environment that are causal factors of disease. Originating in the investigation of outbreaks of communicable disease in the 19th century, epidemiology is being applied increasingly to those non-communicable, chronic diseases that are of the most significance in today's aging population such as cardiovascular disease, cancer, and stroke. The alert pharmacist who can apply the basic principles of epidemiology in their community will become a significant member of the health team.

In the US, a longer lifespan can be achieved by direct measures that are initiated early in childhood and sustained throughout adulthood, especially with the current recognition of the contribution of psychosocial and behavioral risk factors to the prevalence of disease. To this end, a 1979 report of the Surgeon General[6] recommended action in the following areas, many of which can actively involve pharmacists: family planning, pregnancy and infant care, immunizations, sexually transmissible diseases, control of toxic agents, occupational health and safety, control of accidental injuries, fluoridation of community water supplies, reduction in the spread of communicable and infectious diseases, tobacco cessation, reduction of drug/alcohol use/abuse, improved nutrition, and exercise and fitness and stress modification. The continued and remarkable decrease in the number of smokers during the past quarter century is an example of what can be accomplished if a sufficient percentage of the community get involved in a coordinated plan.

Pharmacists should fulfill not only a referral role for patients suspected of having a particular illness, but also can collaborate with the local health departments or health planning agencies in epidemiology. Through their daily and multiple interactions with many patients, pharmacists can contribute to the knowledge base of disease patterns prevalent in the community. More than any professional group, pharmacists become aware of community-based epidemic infectious diseases in its earliest stages. The arrival of an unusual number of people with diarrheal disease for OTC products may be the result

of an outbreak of food-borne disease. The monitoring of numbers and types of prescriptions often points to an epidemic, and the focused pharmacist can set up a systematic monitoring system for more scientific validity.

Pharmacoepidemiology, a subspecialty of epidemiology that is pertinent to pharmacy, involves the safety or risk assessment of a new drug, starting with its early use and continuing through its longer use cycle. It involves generating information about pharmaceutical outcomes and monitoring associated risks, particularly in the postmarketing environment. There are three major parts to these studies: a knowledge base, a conceptual framework, and an interpretive framework. With these perspectives, a pharmacoepidemiologist can establish a surveillance system, understand a posed research question, select strategies, apply methodologies, and interpret the results of purposeful investigations. Population-based studies are designed in an unbiased manner to include all patients (or a representative sample of patients) who may have been exposed to a common risk factor, have an identified disease, or a medical condition in a given population during a given time period. This type of study of a population is expected to provide an unbiased view of the examined medical condition/disease in the population as a whole.[19]

The ready availability of statistical software packages has made multivariate analysis more available to public health researchers. Further, there are numerous sources for public health statistics on the Internet (eg, http://www.lib.umich.edu/govdocs/sthealth.html or www.lib.berkeley.edu/PUBL/stats.html). Public health research studies focus on generalized linear models, so that the types of outcomes common in public health (eg, continuous measures binary indicators of disease counts, times to events) can be handled in a uniform manner.

DISEASE PREVENTION

Three levels of prevention exist: primary, secondary, and tertiary:

Primary prevention is helping people maintain their health or improve the quality of their lives through a healthy lifestyle. An example of primary prevention is the control of infections through immunization. Also, adopting healthy lifestyle practices may lead to increased longevity as well, for example, eating foods low in saturated fat, salt, and simple sugars; refraining from tobacco use; limiting alcohol consumption; controlling weight; sleeping 7 to 8 hours a night; being physically active; and eating in moderation. The aim of primary prevention is to modify lifestyles to the benefit of the individual and, ultimately, to the community.

Secondary prevention is the early diagnosis and treatment of an already existing disease. For example, the use of penicillin in the treatment of a streptococcal infection prevents the onset of rheumatic fever. Thus, a pharmacist can perform a vital service by advising patients who present a febrile illness characterized by a sore throat to see a physician.

Tertiary prevention largely consists of rehabilitation. Most chronic diseases cannot be cured, but their progress can be retarded with maximum benefit to the patient. Much can be done, for instance, with rheumatoid arthritis to make patients more comfortable and more productive in their daily lives.

HEALTH MEASUREMENT

The pharmacist is the health professional in most frequent contact with the general public, and this function as a community health educator makes the pharmacist's role unique. By staying abreast of local health statistics, pharmacists can function as a valuable resource person to researchers conducting epidemiological studies in the community.

All events that are measurable must be related to the population in which they occur, usually known as the *population at risk.* Events to be measured must be reduced to a common factor of population.

The *crude birth rate* is only a crude measurement of births because the population at risk includes all the men, women, and children in the geographical area of concern; most of this population cannot bear children. A more accurate measurement would be to confine the population at risk to women, a sex-specific rate. Including only the women of child-bearing age who can conceive would be a further refinement of the group, an age/gender-specific rate. The *fertility rate* is a far more accurate measurement of births.

Death rates follow the same pattern as birth rates, ranging from the crude death rate to age and sex-specific rates. The most commonly used indicator of health services is the *infant death,* or *mortality, rate.* This age-specific rate, which measures the number of deaths occurring in infants below the age of one year, is often used as an indicator of the effectiveness of a nation's health services; the implication is that the care of the mother and baby reflects the availability and efficiency of medical care. *Incident rates* show the number of new cases of a disease that occur in a population during a period of time, usually one year. *Prevalence rates* provide the number of new and old cases that are present in a community at a particular point in time.

HEALTH EDUCATION

The objective of health education is to provide the individualized information necessary for patients to modify their behavior, all in an effort to live a healthier life. Pharmacists actively promote good health practices through their own personal example, and by reaching out to provide professional information to the public. Many pharmacies participate in patient health education through the use of pamphlets and bulletins that cover every medical subject imaginable, including all the major chronic diseases, drug classes, drugs of abuse, drug and food interactions, sexually transmitted diseases, immunizations, family planning, health promotion, fluoridation, poison prevention, alternative therapies, disaster preparedness, environmental protection, and workplace safety.

The Internet serves as a primary site for review and receipt of health information. Occasionally, the material received through this medium may be misleading and is usually generalizible without the ability to be put into a patient's specific context. Pharmacists can offer an invaluable service by refuting misinformation or by reframing the information into the patient's specific situation.

Participation of pharmacists in community health education programs must be recommended, but it is in the everyday person-to-person contact that the pharmacist serves most effectively. To display pamphlets with health information is admirable, but it is substantially better to augment this with verbal instruction. People can always benefit from a few words of advice or direction on health matters, and the greater availability of the pharmacist in the community is a vital link to the health of individuals, or of the community in general.

The primary emphasis of the health education activities of the pharmacist is awareness of the early signs and symptoms of the major diseases within their community, and a willingness to provide those citizens who may require such information, often in association with various health agencies, both official and voluntary. These groups have basic differences in governance, financial support, legal responsibilities, and primary focus. In general, official agencies are governed by appointed officials, and supported by taxes to provide direct services to the public, while the scope of activities are dictated via legislative fiat. Voluntary and philanthropic agencies have greater flexibility to support new programs than do state or federal agencies, with no legal authority to enforce health rules and regulations. Pharmacists need to understand the basic origins and differences of these agencies to derive the greatest benefits for the patients and populations that they serve.

The following sections illustrate examples of areas of health care where pharmacists can have a positive impact on the health outcomes of their communities:

COMMUNICABLE DISEASE CONTROL

During the 20th century, control of infectious diseases has been accomplished in large measure by the environmental control of food, milk, water, and sewage. Although some serious communicable diseases have been practically eradicated, others such as tuberculosis (TB) and syphilis are still common and are now appearing in drug-resistant forms.[20] The estimated number of cases of sexually transmitted diseases (STDs), hospital-acquired infections, influenza, and other acute respiratory illnesses number in the millions. The most common STD, *chlamydia*, has reached epidemic proportions. Certain viral diseases, including acquired immunodeficiency syndrome (AIDS), West Nile virus, and Severe Acute Respiratory Syndrome (SARS), remain resistant to eradication, or sufficient treatment modalities have not been identified, to date.[21,22] Further, the threat of bioterrorism, with smallpox and its high rate of transmission and potential mortality, requires a new level of planning, training, monitoring, and vaccination practices.[23]

In some areas of the US, such as inner cities, and the world (such as Third World countries), greater than 9 out of 10 individuals are either at risk of being infected, or are currently infected with HIV. Pharmacists can become involved in educational programs promoting safer sexual practices, particularly the use of condoms. Many pharmacies have prominent displays that offer ready accessibility to condoms, all in an effort to minimize barriers to their purchase and use.

As a part of developing a comprehensive national HIV prevention strategy, federal agencies and professional health-care organizations have recommended that injection drug users (IDUs) be given greater access to clean syringes and drug treatment programs. The once-only use of sterile needles and syringes remains the safest and most effective approach to limit the transmission of HIV among IDUs who cannot or will not stop injecting drugs.

The CDC, the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), and the National Institute on Drug Abuse (NIDA) jointly have published the *HIV Prevention Bulletin: Medical Advice for Persons Who Inject Illicit Drugs* (http://www.cdc.gov/idu/pubs/hiv_prev.htm). The primary recommendation of this document was to provide counseling to IDUs to stop using and injecting drugs, if possible by entering and completing a substance abuse treatment program that includes relapse prevention. For those who continue to inject drugs, HIV prevention strategies include not reusing or sharing syringes, water, or drug preparation equipment; using only syringes that come from a reliable source, such as pharmacies; using a new, sterile syringe to prepare and inject drugs; and safely disposing of the syringe after one use. While politically volatile, numerous states have passed legislation to address the availability of syringes to reduce the spread of HIV transmission. As the absolute number of individuals worldwide who are HIV-infected has not reached a plateau, use of highly active antiretroviral therapy (ie, a combination of double or triple combination antiretroviral drug regimens) continues to improve outcomes in this country, and worldwide, provided that adequate public health resources (ie, the medications, and the means to deliver them) are available in sufficient supply.

The role of the pharmacist in the control of communicable diseases consists of an awareness of the natural history of these diseases in both the individual and the community, and referral of patients to health care facilities, when indicated. The pharmacist is in a position to dispel much of the ignorance and myths attached to these diseases, especially STDs, particularly in high-risk sectors of the population (eg, youth). In this aspect of community disease control, pharmacists can have their greatest impact, and one of the best opportunities for health education, via written, visual, oral, or via audio or video, is when a patient is waiting to be seen in a clinic, or waiting for a prescription to be filled.

The pharmacist's role in educating the public about effective health measures cannot be overemphasized, but it is vital that the pharmacist has the most current information to carry it out. The control of communicable diseases is based upon adequate case finding and the supervision and prophylactic treatment of close contacts. As community health educators, pharmacists can remove barriers to care by involving themselves with sociosexual and psychosocial problems as they relate to public health, understanding their patients' subcultures, and knowing how sexual activities and other social behavior vary from one group to another. Patients should be counseled freely and advised on STD prevention methods, available methods of treatment, and the necessity for receiving the treatment.

Immunization has controlled the childhood infections of measles, mumps, rubella, poliomyelitis, diphtheria, and whooping cough. New changes in recommended regimens should be expected as new products are developed. Pharmacists should remain up-to-date with immunization schedules and advise parents, particularly those who have infants or young children, of the importance of adhering to the recommended times.

Independent of those times when vaccines are in short supply or back order, the pharmacist often will have many vaccines in stock for immediate or urgent administration by private physicians that local health departments need only on an occasional basis and, therefore, do not stock routinely. Where mass community immunization clinics (eg, at local health departments) are used to immunize the public, the pharmacist is the primary health care professional responsible for obtaining, storing, preparing, and administering the vaccine.

An increasing number of states and within the PHS, pharmacists are acquiring the knowledge and the requisite skills to administer the vaccines directly, pursuant to an order from another health-care practitioner who is licensed to prescribe. This can provide increased access to immunizations. The information necessary for a vaccination program can be found in *Epidemiology & Prevention of Vaccine-Preventable Diseases,* available from the CDC, an excellent first step for acquiring these skills. *The Report of the Committee on Infectious Diseases,* published periodically by the American Academy of Pediatrics, provides a sensible immunization schedule.

The Control of Communicable Diseases Manual, published by APHA,[24] concisely summarizes all known communicable diseases with the etiology, treatment, and control of each disease. Pharmacists who wish to keep current on communicable disease patterns should subscribe to the CDC's *Morbidity and Mortality Weekly Report* (MMWR; www.cdc.gov/mmwr). The MMWR contains epidemiologic notes, reports of disease outbreaks, and current statistics by disease and geographical location at home and abroad.

UNIVERSAL PRECAUTIONS FOR PREVENTION OF TRANSMISSION OF HIV AND OTHER BLOOD BORNE INFECTIONS

Universal precautions, as defined by the CDC (www.cdc.gov/mmwr/preview/mmwrhtml/00000039.htm), are a set of precautions designed to prevent the transmission of HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), and other blood borne pathogens to first-aid or health-care providers. Under universal precautions, all blood and certain body fluids are considered potentially infectious.

Universal precautions apply to blood, other body fluids containing visible blood, semen, and vaginal secretions, as well as to tissues and to the following fluids: cerebrospinal, synovial,

pleural, peritoneal, pericardial, and amniotic. These precautions do not apply to feces, nasal secretions, sputum, sweat, tears, urine, and vomitus unless they contain visible blood. Further, these precautions do not apply to saliva except when it is visibly contaminated with blood or in the dental setting where blood contamination of saliva is predictable.

Universal precautions involve the use of protective barriers such as gloves, gowns, aprons, masks, or protective eyewear, which can reduce the risk of exposure of the clinician's skin or mucous membranes to potentially infective materials. In addition, it is recommended that all clinicians take precautions to prevent injuries caused by syringes, scalpels, and other sharp instruments or devices.

Pregnant health-care practitioners are not known to be at greater risk of contracting HIV infection than are clinicians who are not pregnant; however, if a clinician develops HIV infection during pregnancy, the infant is at risk of infection by perinatal transmission. Because of this risk, pregnant health practitioners should be especially familiar with, and strictly adhere to, precautions to minimize the risk of HIV transmission.

Even though universal precautions took the place of and eliminated the need for the isolation category "Blood and Body Fluid Precautions" in the *CDC Guidelines for Isolation Precautions in Hospitals* (www.cdc.gov/ncidod/hip/isolat/isolat.htm),[25] implementing universal precautions does not eliminate the need for other types of isolation precautions. These guidelines (standard precautions) include isolation in hospitals, droplet precautions for influenza, airborne isolation for pulmonary tuberculosis, and contact isolation for drug-resistant *Staphylococcus aureus*. Standard precautions were developed for use in hospitals and may not necessarily be indicated in other settings where universal precautions are used, such as child-care settings and schools.

INTERNATIONAL/GLOBAL HEALTH

Globalization has decreased the distinctions between the issues of community or domestic health, and international health.[26,27] Pharmacists should have an understanding of the complexity of diseases encountered in international travel. When considering or suspecting an infectious disease in a patient, pharmacists should ask them if they have traveled nationally or abroad within the past 2 weeks, and if so, where. The epidemic of Severe Acute Respiratory Syndrome (SARS) provides an excellent example of how global transmission of a virus can occur.

The World Health Organization (WHO; www.who.int), with 192 member nations, is the only official international health organization. Apart from reporting disease trends, WHO controls many aspects of international health. By international agreement, there are only three diseases to which quarantine regulations still apply: cholera, plague, and yellow fever. One WHO program that is of particular significance to pharmacy is the international standardization of immunological agents, vaccines, and toxoids.

Pharmacists can be of invaluable assistance to international travelers in advising them what to take in the way of medications, especially for infectious conditions such as malaria and traveler's diarrhea. Referral to the local health department may be easier for those pharmacists who lack the facilities or knowledge base, but they should retain some degree of interest in travelers' requirements, if only as a public service. Information on creating a traveler's medical chest is available in several publications; generally included are a broad-spectrum oral antibiotic, adhesive bandages, remedies for travel sickness, acetaminophen/ibuprofen/aspirin, a thermometer, and antibiotic cream or ointment. Immunizations also must be up to date. Annually, several of the professional pharmacy journals update travelers' needs in the areas of immunizations and emergency drugs for trips. The CDC provides this information at the National Center for Infectious Diseases Traveler's Health web page (www.cdc.gov/travel/)

CHRONIC DISEASE MANAGEMENT

Patterns of diseases over the past 100 years have been shaped by the improvements in diagnosis, treatment, and prevention in health care. Because the control of infectious diseases has resulted in a longer life expectancy, chronic diseases have become the primary causes of mortality in this country. Accidents and cardiovascular, oncologic, and neurovascular conditions are the current primary causative factors of mortality. With no readily foreseeable solution to the control of chronic conditions, pharmacists should still encourage patients to avail themselves of the few proven techniques for chronic disease prevention, and they can recommend methods of preventing disease, particularly cardiovascular disease.[28]

The pharmacist's role in the control of chronic disease[29] can range from the support of proven community programs such as screening and disease management clinics for diabetes,[28] to surveillance for the first signs of diseases associated with an occupational hazard (eg, environmental toxin spill). The pharmacist is unique in having a basic understanding of disease processes and in being in daily contact with the public. The pharmacist's ability to prevent or to intervene in the initial stages of illness in chronic disease is unparalleled.

In economic terms, cancer remains the most important health problem in the US, followed by affordability of health care, AIDS/HIV disease, obesity, and heart disease.[30] In 2000, the CDC reported that, according to the *Annual Report to the Nation on the Status of Cancer, 1975–2000* (www.cdc.gov/cancer), death rates from the four leading cancers (lung, breast, prostate, and colorectal) show a decline nationally and in most states during the late 1990s. For certain cancers such as stomach cancer, an appropriate diet can help in prevention, although in general these conditions must be dealt with by early diagnosis and treatment. Techniques such as the Pap smear serve as specific preventive methods as well, although secondary prevention is the main point of attack.

Pharmacists should be acquainted with the warning signals of cancer and advise any patient who exhibits them to seek medical advice immediately. Pharmacists can encourage patients to obtain routine physical examinations, pap smears, mammograms, colorectal examinations, or other tests. Further, patients can be taught self-performed techniques such as breast or testicular examinations. Local cancer societies can provide health education literature for professional and public education.

The mortality rates for both heart disease and stroke have decreased for the past 10 years, probably as a result of such well-promoted measures as stopping tobacco use, controlling hypertension, lowering cholesterol (including saturated and trans-fat) intake, increasing physical activity, and having a good overall health awareness.[31–33] Stroke prevention, in particular, is correlated primarily with the control of hypertension and associated risk factors.

With secondary and tertiary prevention, early diagnosis, and treatment and rehabilitation, respectively, are the primary measures in chronic disease management. Pharmacotherapeutic innovations within the past 10 years have had a positive impact, resulting in the lower mortality rates from cardiovascular and cerebrovascular disease. As medications comprise the basis of modalities for hypertension, pharmacists should be at the forefront of monitoring, especially in encouraging compliance with prescribed regimens. Because they are in a unique position to measure their patients' blood pressure and advise them about its normal variations, pharmacists are becoming more involved in hypertension screening and referral.[34] Pharmacists should be well acquainted with the community-based services that offer diagnosis, treatment, and rehabilitation.[33] As

appropriate, local medical societies and heart associations should be consulted as pharmacists become involved in blood pressure screening and monitoring programs.

Guidelines for the involved pharmacist can be found in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), released in May 2003 by the National Heart, Lung, and Blood Institute. This report was developed using evidence-based medicine and consensus to make clinical decisions.[35] An update to the Sixth Report (JNC VI, published in 1997), it provides a contemporary approach to hypertension prevention and control, including data from the second phase of the third National Health and Nutrition Examination Survey (NHANES), updated information on the US government's Healthy People 2010 objectives, a discussion of new pharmacotherapies including combination agents, the role of managed care in hypertension treatment, and information from recent randomized controlled trials on hypertension prevention and treatment.

The report also provides a guide to assist in risk stratification into three stages of blood pressure ranges, in an effort to individualize treatment. Strategies for individualizing treatment in special populations are provided in a revised treatment algorithm. Of particular interest are the new recommendations for lifestyle changes independent of risk group: diet, weight reduction, alcohol limitation, smoking cessation, and regular physical activity.

The fourth most common cause of death in the US today is accidents. Injuries are the leading cause of death for children and young adults. Accident prevention relies on a few specific actions, such as the use of automobile seat belts. With accidental poisonings, the pharmacist should be a leader in control and prevention. In small communities, the pharmacist should be considered as the prime consultant for advice in poisoning cases and should be able to refer the caller to the nearest poison control or information center when unable to deal with the matter personally. Pharmacists must be aware of the dangers arising from industrial toxins and be alert to their manifestations in patients who seek relief in OTC medicines.

As a part of community educational services, the pharmacist should be viewed as a leader in disseminating information about poisoning and its prevention, especially during National Poison Prevention Week in the third week of March. Many pharmacists run poison control centers nationally, usually within larger regional hospitals or academic medical centers.

MATERNAL AND CHILD HEALTH

Mother and child health was the first public health program of the 20th century. Infant and child mortality rates were exceptionally high, largely because of diarrhea and respiratory diseases; many of the latter were propagated by non-pasteurized milk, an ideal medium for bacterial proliferation. The first move to combat this form of infant mortality came in the form of milk stations, where purified milk was provided to mothers and their children. Gradually, the concept of maternal and child health expanded to the formation of direct patient care and health education programs aimed at both the mother and child (or fetus), provided both in clinic settings and at home. Since the end of World War II, maternal mortality has declined some 45%, and infant mortality has been reduced by about 75%, thus demonstrating the utility of these programs. One of the major programs in America that has had a positive impact on outcomes is the Special Supplemental Nutrition Program for Women, Infants, and Children, also known as the WIC program (www.fns.usda.gov/wic/aboutwic/default.htm). The WIC target population are low-income, nutritionally at risk: Pregnant women (through pregnancy and up to 6 weeks after birth or after pregnancy ends), breastfeeding women (up to an infant's first birthday), non-breastfeeding postpartum women (up to 6 months after the birth of an infant or after pregnancy ends), infants (up to their first birthday), and children up to their fifth birthday. WIC serves 45% of all infants born in the US. WIC participants receive supplemental nutritious foods, nutrition education and counseling at WIC clinics, and screening/referrals to other health, welfare, and social services.

The basic premise behind maternal and child health is to assist the mother and her child through the time when they are exposed to the greatest risks of disease and mortality: during pregnancy, the puerperium (the first 6 weeks after birth), and through the first year of life. The prognosis and overall health of the infant are directly influenced by its care *in utero*. The earlier that prenatal care is initiated, even in the pre-conception phase, the more beneficial is the effect, not only to the mother but also to the child. Pharmacists who understand the normal course of pregnancy and infancy, and all of the attendant health-care issues, are in constant demand.

Mothers can be instructed on simple matters of diet, hygiene, and overall management of their pregnancy and infant. This is of particular importance with mothers who have an incomplete understanding of the importance of receiving coordinated and continuous prenatal care. Pharmacists who are able to discuss the various available contraceptive methods in an intelligent and professional manner are important, especially in the postpartum period. Before delivery, parents can be advised to obtain an infant car seat, and instructed on its proper instruction within the car and the correct method of seating and securing the child into the seat. Many city/county health departments have infant car seat loan programs for a nominal fee. Based upon the immunologic and nutritional benefits supplied, breast-feeding is still the best option for the baby, and pharmacists should encourage breast-feeding, whenever possible.

A primary aspect of disease control in the infant is childhood immunizations. All infants should be immunized fully to avoid the dangerous diseases associated with the first years of childhood. Primary immunization should begin at birth (with hepatitis B vaccine) and must continue until the fourth dose of triple vaccine (ie, diphtheria, tetanus, pertussis) is given at 12 months, with a follow-up dose at 4 to 6 years (www.cdc.gov/nip/recs/child-schedule.pdf, or www.cispimmunize.org).

Mortality from sudden infant death syndrome (SIDS) continues to decrease at a steady rate. The SIDS rate for 1995 was 0.87 deaths per 1000 live births. One measure contributing to the decline is the implementation of prevention recommendations that are based upon the best available evidence. SIDS has long been associated with women who smoke during pregnancy. Infants who were in the presence of second-hand smoke in the home after birth were twice as likely to die from SIDS, and constant smoke exposure both during and after pregnancy triples a baby's risk for SIDS. Also, babies who died of SIDS were less likely to been breast-fed.

The American Academy of Pediatrics recommends that healthy infants sleep on their backs or sides to reduce the risk for SIDS (www.healthychildcare.org/section_SIDS.cfm). These recommendations are considered to be primarily important during the first 6 months of age, when a baby's risk of SIDS is greatest. The US Public Health Service, American Academy of Pediatrics, SIDS Alliance, and the Association of SIDS Program Professionals jointly sponsor the *Back-to-Sleep Campaign*, a program to reduce the risk of SIDS. In this program, parents are advised to place their babies on their back or side to sleep when being put down for a nap or to bed for the night.

Worldwide, overpopulation is the most serious public health problem. *Family planning,* as population control is alternatively called in the Western countries, consists not only in spacing births by deliberate contraceptive use, but also in helping women who cannot conceive to bear children. Contraceptives, both prescription and OTC, are available in community pharmacies, and pharmacists should be at the vanguard of family planning.

In addition to family planning, other programs that have received much attention recently are lead poisoning prevention for children, infant, and preschool child health-care services, services for handicapped children, and nutritional education

and support for children. The increase in working mothers in this country and the concomitant increase in use of child-care centers has focused interest in these programs.

NUTRITION

Good nutrition, including a diet that is low in saturated fats and contains five or more servings of fruits and vegetables each day, plays a key role in maintaining good health. Improvements in the American diet have the potential to extend the productive lifespan of Americans, and reduce their risk of chronic diseases (eg, heart disease, stroke, various types of cancers, diabetes mellitus, and osteoporosis. A direct relationship between obesity and morbidity is well established, as well as an inverse one with both length and quality of life. For this reason, pharmacists should be aware of normal nutritional requirements and the problem of malnutrition or poor nutrition among the patient population that they serve. Pharmacists can make significant contributions in nutrition by advising patients about basic food needs; helping to correct improper food habits, especially in children; advising on special requirements for nutrients during prenatal and maternal periods, suggesting special dietary instructions for patients with diabetes and people with food allergies; and participating in supporting school lunch programs and food stamp plans.

Sufficient data exist regarding dietary risk factors for chronic diseases, providing an excellent opportunity to promote specific healthy behaviors to the US population (www.cdc.gov/NCCdphp/burdenbook2002/03_nutriadult.htm). Generally, these include such simple measures as lowering the fat intake in the diet (especially saturated fat), using less salt, and increasing green and yellow vegetables and whole grain cereals/fiber in the diet (www.nutrition.gov). For maximum benefit, these measures should be coupled with maintaining body weight within recommended limits, avoiding obesity, keeping good physical activity, and avoiding both alcohol and tobacco.

Over 20% of Americans greater than 20 years of age are at least 10% over their ideal body weight, putting them at increased risk of developing diabetes, digestive system diseases, and cardiovascular disease (www.ahrq.gov/clinic/3rduspstf/obesity/obesrr.htm).[37] Many people who lose weight when in good health, regain this weight. The popular notion that there are magic drugs to control weight has been dispelled with the removal of products containing ephedra (OTC), fenfluramine (Pondimin) and dexfenfluramine (Redux) from the market over the last decade.

Pharmacists can recommend nutritional education and guidance offered through the many materials available from voluntary health organizations and local and state health departments. As people lose weight better in peer support groups, pharmacists can become acquainted with the local organizations aimed at helping people of all ages lose weight, such as Weight Watchers, TOPS (Take Off Pounds Sensibly), and YMCA and YWCA programs.

ORAL HEALTH

A large proportion of Americans suffer from tooth decay or periodontal disease. Untreated tooth decay remains a problem. About one-third of persons across all age groups have untreated decay. Among adults aged 35 to 44, 48% have gingivitis, and 22 percent have destructive gum disease. Tobacco use increases the risk of gum disease. In the US, 30,000 people are diagnosed with mouth and throat cancer each year, and 8,000 die of these cancers. *A National Call to Action to Promote Oral Health* marks the latest in an ongoing effort to address the country's oral health needs in the 21st century. Reflecting the work of a partnership of public and private organizations, the *Call to Action* builds on *Oral Health in America: A Report of the Surgeon General* (May 2000) and the *Healthy People 2010* focus area on Oral Health. The *Call to Action* seeks to expand on these efforts by enlisting the expertise of individuals, health researchers and care providers, communities, and policymakers at all levels of society (www.nidcr.nih.gov/sgr/nationalcalltoaction.htm). Pharmacists have numerous opportunities on a daily basis to positively affect this trend. Most oral conditions are preventable by appropriate self-care and use of fluoridated toothpastes, oral fluoride supplements, dental sealants, flossing, avoidance of tobacco use (especially oral tobacco products such as chewing tobacco or snuff), and regular dental visits.

The American Dental Association has published pamphlets for dentists and pharmacists that cover oral structures and diseases, prevention of caries, OTC and prescription dental drugs, and how these two professions can collaborate. The American Dental Hygienists Association's Oral Health Information page (www.adha.org/oralhealth/index.html) has numerous pieces of information and publications on preventive oral care. Presently, patients should be counseled to visit a dentist at least annually (if not more frequently for more high-risk patients), and to floss daily, brush their teeth daily with a fluoride-containing dentifrice, and use fluoride for caries prevention and chemotherapeutic mouth rinses for reduction of plaque.

In 2003, 65.8% of the US population on public water supplies has access to fluoridated water systems population; the objective for the year 2010 is to increase that number to at least 75%. Fluoride supplementation is recommended for children living in areas with inadequate water fluoridation. Resistance to water fluoridation began in 1950 and continues to raise controversy in some segments of the population. The charges raised by opponents tend to be more sophisticated variations on themes used since the inception of fluoridation, namely the alleged adverse health consequences (eg, cancer or AIDS) and infringement on freedom of choice. Although various anti-fluoride advocacy groups have gained much publicity in their attempt to create the illusion of a scientific controversy about fluoridation, claims of a health hazard from water fluoridation remain unfounded. The American Dental Association cites extensive research demonstrating that fluoridation does not increase the incidence or mortality rate of any chronic condition, including cancer, heart disease, intra-cranial lesions, nephritis, cirrhosis, and Down syndrome. No correlation between fluoride in the water supply and cancer in human beings has been demonstrated by studies to date. Fluoridation of drinking water supplies at a level of 1 ppm (part per million) protects against dental caries, and in such concentrations is not associated with any known adverse health effects. Fluoride toxicity from water sources would be improbable because of the large quantities of water that would need to be consumed at any one time.

ENVIRONMENTAL HEALTH

All elements of the natural environment can be altered, sometimes with harmful results. Air, food, water, and the earth can all become sources of illness, in the home, public, or work environments. With increased industrialization, air, in Western, as well as developing countries, now contains noxious substances that are either direct results of combustion or produced by photochemical change. *Smog* (a term first coined from "smoke" and "fog" in 1905) is the classic example of the latter; it results from the interaction of the ultraviolet rays in sunshine and the unburned hydrocarbons of automobile engines or factories and smokestacks. These products, when trapped by the thermal inversion engendered by local topography, cause damage to mucous membranes and lungs when inhaled. There is a close correlation of such diseases with age, especially in persons whose heart, lungs, and immune system may already be compromised. Acute episodes of air pollution have been found to exacerbate illness and even cause death in people who already have respiratory and cardiovascular diseases. Supporting evidence exists demonstrating that second-hand tobacco smoke increases the risk of cardiovascular diseases or cancer as well.

Food remains a significant vehicle of disease organisms. Although pasteurization has eliminated milk as a medium for disease distribution, the same cannot be said for other foods. Food-borne disease, more commonly but often incorrectly called "food poisoning," is grossly underreported: the 400 to 500 outbreaks comprising some 5000 to 10,000 persons per year probably can be increased by a factor of 10 to represent its true magnitude. In most instances the illness produced by contaminated food is mild and of short duration, but more severe outbreaks (such as hepatitis A, most commonly seen in public restaurants) can occur. Epidemics of food-borne disease are dramatic and sudden, and most people become sick within 6 to 24 hours after consuming the contaminated foodstuffs. The epidemic pattern of food-borne disease presents differently from the gastrointestinal symptoms (eg, nausea, vomiting, and diarrhea) induced by intestinal enteroviruses. When pharmacists note a sudden increase in OTC sales of anti-nausea and anti-diarrhea agents, the local health department should be notified immediately so that they can initiate a rapid case investigation to prevent further spread.

Water-borne infectious disease is uncommon today, but this does not mean that all public water supplies are pure and potable. Many complaints about the taste, appearance, and physical qualities of locally supplied water have led to a brisk US trade in bottled water. A modern concern of many citizens is the presence of chemical toxins in the environment and in the diet. Well-documented data exist documenting cancer development in animals from ingested materials, but there also is little proof that many of these substances ever produce human cancer. Host factors may have a significant and vital role in disease of any type, and pharmacists, especially those in the community, should stay aware of developments pertaining to toxic and carcinogenic substances. Water contamination with ground-source chemicals (eg, pesticides, fertilizers) remains an ongoing possibility, and pharmacists should remain aware of outbreaks and refer patients to local health departments for assistance, when necessary.

Occupational illnesses provide evidence that the workplace can play an immense role in disease occurrence. For example, for hundreds of years, pneumoconioses in the form of silicosis have been known to occur in miners as black lung disease; more recently byssinosis, brown lung disease, was observed in textile workers. Asbestos exposure has been associated with cancer. All occupations that expose workers to dust are hazardous to a degree, depending on the size of the dust particles and their consequent ability to penetrate into the lung substance, combined with their concentration and the length of the workers' exposure time.

Pharmacists should be aware of the local occupations, companies, and factories and to be cognizant of the initial symptoms of disease. Again, pharmacists should become acquainted with the local community and to adapt the principles of health and medical care to the particular situations encountered. The pharmacist's continuing education requirements should include watching the local pattern of society and its diseases, and changing the emphasis toward evolving disease patterns and their control.

Included in the current environmental issues are the workplace and the future of occupational safety and health regulations, hazards of local ambient environments, such as hazardous and other waste dumps, radioactive waste from weapons production, air emissions, and groundwater contamination of unknown magnitude; the Clean Air act and other and regulatory initiatives; waste reduction and minimization, and radioactive waste and weapons production; global pollution, chlorofluorocarbons and the land ozone layer, the greenhouse effect, and global climate change; and conserving the tropical forest and biological diversity.[38]

With constant change to the physical, biological, cultural, social, and economic environment, both pharmacists and citizens should cultivate an informed awareness of these changes, and pharmacists should adapt their methods of health education, disease prevention, and disease control to the changes in each community.[38] This is especially true of air and water pollution, which require concerted community action for their control, but pharmacists may play a much more fundamental and personal role in controlling food-borne diseases; often, the first indication of an outbreak of food-borne disease is time-limited, with an unusually large number of people seeking relief from nausea, vomiting, and diarrhea. The pharmacist's role in environmental health is related primarily to being alert to the conditions prevailing in the community and of working with others to adequately control any of the attendant hazards.

MENTAL HEALTH

The topic of mental illness and its causation, manifestations, and control is vast. It is estimated that there are an approximate equivalent number of beds in this country for patients with mental health conditions as for all other ailments combined. It has been estimated that approximately 10% of the population in this country are affected with some form of emotional disorder requiring treatment. An estimated 2.4 million chronically mentally ill individuals have been identified in the US (excluding the mentally retarded and chronic substance abusers). Out of this number, about half (1.1 million) live at home, some 700,000 are residents of nursing homes, 450,000 live in single rooms or congregate-care facilities, and at least 150,000 are found in psychiatric hospitals. Of the 450,000 homeless persons, an estimated one-third of them have a serious mental illness. Pharmacists should be aware of their local community mental health services, especially those catering to ambulatory patients. The timely referral of patients exhibiting unusual behavior to these facilities may be life saving, especially in those persons who demonstrate suicidal tendencies.

Suicide is the one outcome of a mental illness that can be measured directly. Fortunately, many suicide attempts are merely gestures, but this does not negate the importance of prevention whenever possible. Suicide has been demonstrated to occur most commonly in older, unmarried, and affluent males. Although women attempt to commit suicide more often than men, they are not as successful. The agents used in suicide vary with their availability. In the US, firearms figure most prominently, as they are readily available; in the United Kingdom where there are stringent gun-control laws, medications such as acetaminophen are the primary etiologic agents.

With these and other epidemiological facts at their disposal, pharmacists can be alert to potential suicide victims among patients and should do everything possible to bring aid to them. An individual's quiet plea for help, potentially offered in the form of overt or covert references to low personal self-esteem and to the uselessness of life, should never be neglected. Even a solitary phrase expressing self-disgust with the implication that the best way out is to end it all should never be ignored, as it may be a clue to contemplation of suicide. Depression, whose cardinal symptoms are as readily recognizable to observant laypeople as they are to health professionals, can be the forerunner of attempted suicide. Pharmacists should never be reluctant to ask patients directly whether they have ever considered, or are now considering, committing suicide or harming themselves or others. Whenever a pharmacist detects a potentially suicidal patient, he or she should talk to the patient and seek aid from family and community mental health services—no patient's plea for help should be ignored. Pharmacists who have interest in this area of practice should become familiar with any of the depression scales (eg, the Zung Self-Rating Depression Scale) that can be used for screening for depression.

ALCOHOL/SUBSTANCE ABUSE

Abuse of alcohol, tobacco, and other substances, in general, is a worldwide public health problem of enormous dimensions.[36] In

the US, between 450,000 and 600,000 premature deaths annually are related to these substances, representing nearly one-third of all deaths. Substance abuse has become a common in American society, and the societal need to stay informed has never been greater. Again, the expert knowledge of the pharmacist should be used to good advantage in both an individual and community context.

Alcoholism is estimated to affect millions of men and women in the US. Alcoholism is a biopsychosocial disorder with many causes and many ramifications. Alcoholics Anonymous (AA) is a voluntary organization founded by a recovering alcoholic for individuals suffering from and recovering from alcoholism. The organization has branches for the spouses of alcoholics (Al-Anon) and their children (Ala-Teen) as well. AA groups exist in nearly all cities and many smaller towns, and individuals in recovery are always ready to help. Other types of clinics and treatment centers are available through government agencies' health, social services, mental health services, or public assistance departments.

Abuse of other agents has received more acceptance among younger people. Particularly in younger people, marijuana has been implicated as a gateway drug, such that harder drugs such as crack cocaine, amphetamines, or controlled prescription medications may follow the use of the milder ones. The trend of misuse/abuse of prescription medications (eg, opiates (OxyContin), benzodiazeines (alprazolam, Xanax), or stimulants (methylphenidate, Ritalin)) continues to rise. Again, the pharmacist is in the unparalleled position of being the most competent professional member of the community who can advise local agencies about substance abuse (including prescription, OTC, social, and illicit drugs) and its effects. The knowledge and participation of pharmacists adds to their professional reputation.

For general information on substance abuse, the Federal government and professional health organizations are often a valuable resource. The National Institute on Drug Abuse (NIDA; www.nida.nih.gov) has produced a science-based guide to drug addiction treatment, *Principles of Drug Addiction Treatment: A Research-Based Guide* (www.nida.nih.gov/PODAT/PODATindex.html). Based upon a comprehensive review of 25 years of treatment research findings, it describes the conditions required for truly effective drug abuse treatment. It also delineates the most common types of drug addiction treatment, identifies treatment approaches for which there is strong scientific evidence of efficacy, and answers the questions about treatment that are asked most frequently by providers, policy makers, patients, and the public.

The National Clearinghouse for Alcohol and Drug Information's PREVLINE (Prevention Online, www.health.org) contains the most current information on alcohol and drug use and abuse, with searchable bibliographic research databases, web pages especially designed for children, and an on-line catalog of substance abuse education materials.

Dealing with the diseases of alcoholism and substance abuse are peculiarly within the purview of the pharmacist. No other disease entities, with the possible exception of poison control, lend themselves more readily to intervention by pharmacists. Pharmacists have many opportunities to help individuals who become dependent upon alcohol, even though many will resist help. All community agencies, professional and voluntary, should be called into play, including church, voluntary, and government groups.

PUBLIC HEALTH RESEARCH

If the pharmacist evinces a sincere interest in community health programs, there may be opportunities to participate in public health research programs, especially those concerned with drugs and their control. In general, investigation of community disease is based on two methods, retrospective and prospective surveys.

Retrospective studies, based upon historical data, are readily obtained by asking questions of the population under investigation. Prospective studies actually observe the events that occur in the population over time. The retrospective method is inexpensive, takes little time, deals with a stable population, and requires a minimum amount of work, however, it relies on memory (recall bias), is difficult to conduct with a control group, and because the investigator knows what to look for, the introduction of observer bias is an issue. Conversely, prospective studies may take years to complete, are more expensive, contend with shifting populations, and require a vast amount of resources; but they are easy to use with a control group, do not rely on memory, and can minimize observer bias.

A classic example of the use of these methods comes from an observation by an Australian ophthalmologist in 1941 who saw an unusually large number of congenital cataracts in infants.[39] A retrospective investigation revealed that all the women concerned had had rubella (German measles) during their pregnancies, a retrospective discovery. This finding caused some women to obtain medically supervised abortions when they revealed to their physicians that they had had rubella during their pregnancies and were afraid of having a baby with a congenital deformity. Although rubella epidemics have largely been eliminated because of vaccination programs, it still exists in the US population, and therefore, pregnant women may be at risk if their immunization status is not current. The incidence of congenital rubella syndrome has increased since 1986, and in at least half of cases, the cause was determined to be missed opportunities for vaccination.[40] Pharmacists should offer their preventative services in the investigation of disease patterns in their community, especially with those of an infectious etiology, in the management of pharmacotherapy and its outcomes.

SUMMARY

Pharmacists are the most accessible and highly trusted health-care professionals. The pharmacist routinely sees the patient at the time of a prescription refill, which can be an opportune time to discuss public health issues; pharmacists can also use this time to identify early signs and symptoms of disease, if counseling and patient assessment are performed. New opportunities in this venue include provision of immunizations and performing smoking/tobacco cessation programs.

The role of the pharmacist has been and continues to undergo change. Early in the new millennium, this profession has some unique opportunities to acquire roles in the public health arena and to build partnerships with health departments, other health-care providers, and the community at large.

The availability of information such as the *Healthy People* reports, the *Guide to Clinical Preventive Services,* and the CDC Guideline Database, provide opportunities for pharmacists to take a more active role in preventive services and health promotion activities. Issues presented in the 1981 APHA statement on the role of the pharmacist in public health still exist, such as the underuse of patient-oriented pharmacists and the need to use existing health-care professionals and facilities. Thus, the pharmacist's role in public health remains unfulfilled. At this point in the professional evolution of the practice of pharmacy, it is time to address seriously the public health issues that affect everyone through the inclusion of the pharmacist as an engaged primary care member of the health care team.

REFERENCES

1. Last JM. *A Dictionary of Epidemiology,* 4th ed. New York: Oxford University Press, 2001.
2. Institute of Medicine, Committee for the Study of the Future of Public Health. *The Future of Public Health.* Washington, DC: National Academy Press, 1988.
3. Shattuck L. *A General Plan for the Promotion of Public and Personal Health, Devised, Prepared, and Recommended by the Commissioners*

Appointed under a Resolve of the Legislature of the State. Report of the Sanitary Commission of Massachusetts, 1850. Cambridge: Harvard University Press, 1948.
4. Cavins HM. *Bull Hist Med* 1943; 13:419–425.
5. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *Am J Hosp Pharm* 1990; 47:533–543.
6. *Healthy People: The Surgeon General's Report on Health Promotion and Disease Prevention*. Washington, DC: Department of Health and Human Services/Public Health Service, 1979.
7. U.S. Department of Health and Human Services. *Healthy People 2010: Understanding and Improving Health. 2nd ed.* Washington, DC: U.S. Government Printing Office, November 2000.
8. U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services: An Assessment of the Effectiveness of 169 Interventions: Report of the U.S. Preventive Services Task Force.* Baltimore: Williams & Wilkins, 1989.
9. U.S. Preventive Services Task Force Ratings: Strength of Recommendations and Quality of Evidence. *Guide to Clinical Preventive Services,* 3rd ed. *Periodic Updates*, 2000–2003. Agency for Healthcare Research and Quality, Rockville, MD.
10. Calis KA, Hutchison L, Elliott ME, et al. American College of Clinical Pharmacy *White Paper: Healthy People 2010: Challenges, Opportunities, and a Call to Action for America's Pharmacists,* 2003.
11. Pharmacists formally recognized for their role in public health. *Am Pharm* 1981; NS21: 9.
12. Cain RM, Kahn JS. *Am J Public Health* 1971; 61:2223–2228.
13. Bush PJ, Johnson KW. *Am J Pharm Educ* 1979; 43:249–253.
14. Gibson MR. *Am J Pharm Educ* 1972; 36:189–200.
15. Gibson MR. *Am J Pharm Educ* 1972; 36:561–570.
16. Gibson MR. *Am J Pharm Educ* 1973; 37:1–27.
17. Beardsley RS, Bootman JL, Christensen DB, et al. *Am J Pharm Educ* 1985; 49:413–417.
18. Frenk J. *Annu Rev Pub Health* 1993; 14:469–490.
19. Choi BCK. *Chronic Diseases in Canada* 1998; 19:145–151.
20. Cohen ML. *Nature* 2000; 406:762–767.
21. Morse DL. *N Engl J Med* 2003; 348:2173–2174.
22. Varia M, Wilson S, Sarwal S, et al. *CMAJ* 2003; 169:285–292.
23. Ferguson NM, Keeling MJ, Edmunds WJ, et al. *Nature* 2003; 425:681–685.
24. Chin J, ed. *Control of Communicable Diseases Manual,* 17th ed. Washington, DC: American Public Health Association, 2000.
25. Garner JS. *Infect Control Hosp Epidemiol* 1996; 17:53–80.
26. Frenk J, Gómez-Dantés O. *Lancet* 2002; 325:95–97.
27. Board on International Health, Institute of Medicine. *America's vital interest in global health: protecting our people, enhancing our economy, and advancing our international interests.* Washington, DC: National Academy Press, 1997:1.
28. Rothman R, Malone R, Bryant B, et al. *Am J Med Qual* 2003; 18: 51–58.
29. Wagner EH. *Br Med J* 2000; 320:569–572.
30. Health Pulse of America 2003 Survey. The Roper Center for Public Opinion Research, University of Connecticut, for the Henry J. Kaiser Family Foundation, July 2003.
31. Fletcher GF. *Circulation* 1997; 96:355–357.
32. Whelton PK. *J Human Hypertens* 1996; 10 (suppl 1):S47–S50.
33. Carter BL, Zillich AJ, Elliott WJ. *J Clin Hypertens* 2003; 5:31–37.
34. Grundy SM, et al. *Circulation* 1997; 95:2329–2331.
35. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; 289:2560–2572.
36. Giovino GA. *Oncogene* 2002; 21:7326–7340.
37. U.S. Preventive Services Task Force. *Screening for Obesity in Adults: Recommendations and Rationale*. November 2003. Agency for Healthcare Research and Quality, Rockville, MD.
38. Bloom BR. *Nature* 1999; 402 (suppl):C63–64.
39. Gregg NM. *Trans Ophthalmol Soc Aust* 1942; 3:35.
40. Lee SH, Ewert DP, Frederick PD, et al. *JAMA* 1992; 267:2616–2620.

BIBLIOGRAPHY

General Public Health

Baker EL, et al. *JAMA* 1994; 272:1276–1272.
Brown ER. *Am J Public Health* 1997; 87:554–557.
Garrett L. *The Coming Plague: Newly Emerging Diseases in a World Out of Balance.* New York: Farrar, Strauss, & Giroux, 1994.
Ibrahim MA, House RH, Levine RH. *Fam Commun Health* 1995; 18:17–25.
Institute of Medicine, Committee for the Study of the Future of Public Health. *The Future of Public Health.* Washington, DC: National Academy Press, 1988.
Institute of Medicine, Committee on Public Health. *Healthy Communities: New Partnerships for the Future of Public Health.* Washington, DC: National Academy Press, 1996.
Kondratas R. *Images from the History of the Public Health Service.* Washington, DC: Department of Health and Human Services/Public Health Service, 1994.
Scutchfield FD, Keck CW. *Principles of Public Health Practice.* Albany, NY: Delmar, 1997.
Pew Health Professions Commission. *Critical Challenges: Revitalizing the Health Professions for the Twenty-First Century*. University of California at San Francisco, 1995.

Epidemiology

Bailar JC III, et al, eds. *Assessing Risks to Health: Methodological Approaches.* Westport, CT: (www.greenwood.com), Auburn House, 1993.
Cook RJ, Sackett DL. *Br Med J* 1995; 310:452–454.
Gehlbach SN. *Interpreting the Medical Literature: Practical Epidemiology for Clinicians,* 4th ed. New York: McGraw-Hill, 2002.
Hartzema AG, Porta MS, Tilson HH, eds. *Pharmacoepidemiology: An Introduction,* 3rd ed. Cincinnati, OH: Harvey Whitney, 1998.
Sackett DL. *Br Med J* 1996; 312:71–72.
Sackett DL, et al. *Clinical Epidemiology: A Basic Science for Clinical Medicine,* 2nd ed. Boston: Little, Brown, 1991.
Strom BL. *Pharmacoepidemiology*, 3rd ed. West Sussex: John Wiley & Sons, 2000.

Public Health and Pharmacy

Bush PJ. *The Pharmacist Role in Disease Prevention and Health Promotion*. Bethesda, MD: ASHP Research & Education Foundation, 1983.
Lambert RL, Wertheimer AI, Dobbert DJ, et al. *Am J Public Health* 1977; 67:252–253.

Environmental Health

Bingham E, Meader WV. Governmental regulation of environmental hazards in the 1990s. *Annu Rev Pub Health* 1990; 11:419–434.
DiBerardinis LJ, ed. *Handbook of Occupational Safety and Health*, 2nd ed. New York: Wiley–Interscience, 1998.
Greenberg M. *Public Health and the Environment*. New York: Guilford Press, 1987.
Levy BS, Wegman DH, eds. *Occupational Health*. Boston: Little, Brown, 1983.
Zuckerman B, Jefferson D, eds. *Human Population and the Environmental Crisis.* Sudbury, MA: Jones & Bartlett, 1996.

Administration

Brown RE, et al. *National Expenditures for Health Promotion and Disease Prevention Activities in the United States.* Washington, DC: Medical Technology Assessment and Policy Research Center, Battelle, 1991.
Ware JE Jr. *Annu Rev Public Health* 1995; 16:327–354.
Roper WL, Thacker SB. *Ann NY Acad Sci* 1993; 703:33–39.

Prevention

Cardiology

Dajani AS, et al. *Circulation* 1997; 96:358–366.
Gomel M, et al. *Am J Public Health* 1993; 83:1231–1238.
Hennekens CH, Dyken ML, Fuster V. *Circulation* 1997; 96:2751–2753.
Jeffery RW, et al. *Am J Public Health* 1993; 83:395–401.
Joint WHO/ISFC Meeting on Rheumatic Fever/Rheumatic Heart Disease, with Emphasis on Primary Prevention. Strategy for controlling rheumatic fever/rheumatic heart disease, with emphasis on primary prevention (Memorandum). *Bull WHO* 1995; 73:583–587.
Jones PH, Gotto AM Jr. *Am J Cardiol* 1995; 76:118–121C.
Maron DJ. *Clin Cardiol* 1996; 19:419–423.
Ramsay LE, et al. *Lancet* 1996; 348:387–388.
Rimm EB, et al. *JAMA* 1998; 279:359–364.
The Medical Research Council's General Practice Research Framework. *Lancet* 1998; 351:233–241.

Endocrine

ABTC Cancer Prevention Study Group. *Ann Epidemiol* 1994; 4:1–10.
American College of Physicians. *Ann Intern Med* 1992; 117:1038–1041.
Engelgau MM, Narayan KM, Saaddine JB, et al. *J Am Soc Nephrol* 2003; 14 (suppl 2): S88–S91.

Hosking D, et al. *N Engl J Med* 1998; 338:485–492.
Kelsey JL, Bernstein L. *Annu Rev Public Health* 1996; 17:47–67.
Kerlikowske K, et al. *JAMA* 1995; 273:149–154.
Manson JE, Spelsberg A. *Am J Prev Med* 1994; 10:172–184.
Newton KM, et al. *J Women Health* 1997; 6:459–465.
The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2002; 26:S5–S20.
Smith-Warner SA, et al. *JAMA* 1998; 279:535–540.
Worden JK, et al. *Prev Med* 1990; 19:254–269.

Infectious Diseases

Ameratunga SN, Lennon DR, Martin D. *N Zeal Med J* 1994; 107:193–194.
Cooper ER, et al. *J Infect Dis* 1996; 174:1207–1211.
Lobel HO, Kozarsky PE. *JAMA* 1997; 278:1767–1771.
Mant D. *Lancet* 1994; 344:1343–1346.
Patel R, Kinsinger L. *Am J Prev Med* 1997; 13:74–77.

Prevention

Butler-Jones D. *Can J Public Health* 1996; 87(suppl 2): S75–S78.
Simpson JM, Klar N, Donner A. *Am J Public Health* 1995; 85:1378–1393.
Wall S. *Int J Epidemiol* 1995; 24:655–664.

Dietary and Other Lifestyle Issues

American Academy of Pediatrics. *Pediatrics* 1995; 95:777.
Boushey CJ, et al. *JAMA* 1995; 274:1049–1057.
Byers R. *N Engl J Med* 1995; 333:723–724.
Cushman R, James W, Waclawik H. *Am J Public Health* 1991; 81: 1044–1046.
Fletcher GF, et al. Statement on exercise. *Circulation* 1996; 94:857–862.
Heart Protection Study Collaborative Group. *Lancet* 2003; 361:2005–2016.
Jeffery RW, French SA. *Am J Public Health* 1998; 88:277–280.
Kleinman DV, Hickey DJ, Lipton JA. *J Am Coll Dent* 2003; 70:16–21.
Kuczmarski RJ, et al. *JAMA* 1994; 272:205–211.
Kujala UM, et al. *JAMA* 1998; 279:440–444.
Rimm EB, et al. *JAMA* 1998; 279:359–364.
Robinson JK, et al. *Prev Med* 1997; 26:364–372.
Task Force on Infant Positioning and SIDS, American Academy of Pediatrics. Positioning and SIDS. *Pediatrics* 1992; 89:1120–1126.
Vivekananthan DP, Penn MS, Sapp SK, et al. *Lancet* 2003; 361:2017–2023.

Pulmonary

DiFranza JR, Lew RA. *Pediatrics* 1996; 97:560–568.
The Health Benefits of Smoking Cessation: A Report of the Surgeon General. Publication CDC 90-8416. Rockville, MD: Department of Health and Human Services, 1990.
Jonas MA, et al. *Circulation* 1992; 86:1664–1669.
Lando HA, et al. *Am J Public Health* 1990; 80:554–559.

Substance Abuse

Aguirre-Molina M, Dorman DM. *Ann Rev Public Health* 1996; 17:337–358.
Department of Health and Human Services. Preventing Tobacco Use among Young People: A Report of the Surgeon General. Publication S/N 017-01-00491-0. Washington, DC: US Government Printing Office, 1994.
Ellickson PL, Bell RM, McGuigan K. *Am J Public Health* 1993; 83:856–861.
Perry CL, et al. *Am J Public Health* 1992; 82:1210–1216.
Yesalis CE, et al. *Arch Pediatr Adolesc Med* 1997; 151:1197–1206.

CHAPTER 8

Information Resources in Pharmacy and the Pharmaceutical Sciences

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Pharmacists and pharmaceutical scientists have a constant need for reliable and current information, and in the modern world information is everywhere. It is presented on television and radio, sent from computer to computer over the Internet, and passed from person to person using telephones and fax machines. The great challenge is sorting out the current information from the dated, the reliable from the questionable, the actual from the imagined. Practitioners and scientists must be able to find and identify different types of information in a variety of formats and media. In addition to meeting their own information needs, pharmacists must also be able to assist patients in meeting their information needs with regard to drugs, therapies, and diseases. This chapter will discuss primary and secondary literature and how to find each, the specialized reference sources in pharmacy and the pharmaceutical sciences, and the use of the Internet. The primary focus is on the literature and the information it contains. For a discussion of the critical evaluation of literature see Chapter 9.

TYPES OF LITERATURE AND HOW TO FIND THEM

Primary Literature

As with other sciences, the primary literature of the pharmaceutical sciences is the scientific journal. For more than three centuries, the scholarly journal has been the channel through which scientific research has been reported, evaluated, and disseminated.

Scientific research enters the primary literature by a prescribed route. When researchers have concluded a study, they usually write the results in a standard format that includes an abstract or summary, a review of past research in the area, a description of the methodology used, the results, a discussion of what the results mean, and a list of references. The finished article is then submitted to a scholarly journal, which may be published by a professional organization or by a commercial scientific publisher. The journal editor then sends the manuscript to be peer-reviewed by one or more researchers in the same field as the authors. Usually the reviewers are unaware of the authors' identities. Manuscripts that are found to meet criteria of sound research are accepted for publication and are published in the journal.

Nearly all scientific journals are now produced in digital form as well as in print. Because of the high costs of printing and mailing, and the dwindling number of subscribers to many specialized journals, research publications of the near future may exist only online.

Several different types of professional journals may contain primary literature of interest to those in pharmacy. Pharmaceutical scientists read and publish in basic science journals such as

European Journal of Pharmacology (Amsterdam, Netherlands: Elsevier Science)
Journal of Natural Products (Columbus, OH: American Chemical Society)
Pharmaceutical Research (New York: Kluwer/ Plenum)

Clinical pharmacists use major medical journals such as

Annals of Internal Medicine (Philadelphia: American College of Physicians)
JAMA: Journal of the American Medical Association (Chicago: AMA)
New England Journal of Medicine (Boston: Massachusetts Medical Society)

or journals that specialize in a particular disease or in drug therapy, such as

American Journal of Cardiology (Amsterdam, Netherlands: Elsevier Science)
American Journal of Health-System Pharmacy (Bethesda, MD: American Society of Health-System Pharmacists)
Annals of Pharmacotherapy (Cincinnati, OH: Harvey Whitney Books)
Diabetes (Alexandria, VA: American Diabetes Association)

Researchers in pharmacy administration have available to them such journals as

Journal of Pharmaceutical Marketing and Management (Binghamton, NY: Pharmaceutical Products Press)
Pharmacoeconomics (Auckland, New Zealand: Adis International)
Social Science and Medicine (Amsterdam, Netherlands: Elsevier Science)

Finally, those who teach pharmacy have

American Journal of Pharmaceutical Education (Alexandria, VA: AACP)
Journal of Pharmacy Teaching (Binghamton, NY: Pharmaceutical Products Press)

These journals are only a few of the thousands of scientific journals published worldwide. Finding articles on one particular area of interest requires more effort than scanning the issues of a few journal titles regularly.

Not long ago, someone researching a topic would be urged to begin with a standard bibliography, and to follow this by using printed indexes and abstracts that could be consulted only in a library. Advances in computer technology have made most printed finding tools obsolete. Printed sources are outdated the day they are published and, in the opinion of most, are much less convenient to use than online tools. Most online indexes can be accessed from desktop computers using the Internet. Many indexes link to the full text articles themselves, thus obviating many steps (both logically and geographically).

Researchers may also subscribe to table-of-contents alerting services, whereby the tables of content of selected journals are e-mailed to the researcher at the time of the publication of the issue. Some are services that must be purchased, such as those through companies like Ingenta. Or, publishers may offer the service as part of an individual or institutional subscription.

Finally, there are "packaged" medical collections that allow users to search across collections of textbooks, databases, and other materials. Collections such as Stat!Ref, MDConsult, and UpToDate are discussed under "textbooks."

Databases

Online databases, because of their convenience and ubiquity, are now the first choice to consult for locating pharmaceutical literature. For clinical literature, the databases of choice are *MEDLINE*, *EMBASE*, evidence-based medicine databases, the *Iowa Drug Information Service* (*IDIS*), and *International Pharmaceutical Abstracts*. For drug development, *Chemical Abstracts* and *BIOSIS Previews* are the most comprehensive. Each of these is available in print, through the World Wide Web ("the web"), on magnetic tape to be loaded on a local mainframe, or through commercial vendors such as Dialog or Ovid. Educational institutions and corporations often provide access for their researchers to one or more of these databases. An individual also can purchase access through a subscription or per-search arrangement with database providers or vendors.

Searching online databases appears to be easy—deceptively so—but doing a successful search can require a great deal of skill and prior experience. Novice searchers are often too impatient to learn proper searching techniques and may either miss many relevant items or retrieve a large number of irrelevant ones. Attending a class, consulting a manual, or working with a librarian can much improve a researcher's ability to do a comprehensive and highly relevant search.

MEDLINE

MEDLINE is produced by the US National Library of Medicine (Bethesda, MD). Its coverage of 4600 highly regarded clinical journals makes it the preeminent biomedical database. It is subsidized by the US government, with one search engine, PubMed, available at no cost all over the world. The resulting low or no cost to its users means that it is often the first and only choice of those seeking medical information. Its coverage is strongest in clinical and therapeutic topics.

The National Library of Medicine produces *MEDLINE* and makes it available directly to the public, but a number of other vendors make the database available as well. Each of these vendors has its own set of searching protocols, usually called *search engines*; each is a little different from the others, and each has a somewhat different way of indexing the files. The same search done with different *MEDLINE* search engines may yield different results.

PubMed (http://pubmed.gov), the *MEDLINE* search engine provided free to the world over the Internet by the National Library of Medicine, is a very easy to use and powerful search engine. Included as part of its website are excellent tutorials. Those who learn to use PubMed well get excellent results, but it is very easy to do a bad search in PubMed. The commercial vendor Ovid provides a search engine that forces its users to do better searches, so many institutions and corporations purchase access to it. Finally, there are several other free Internet-accessible versions of *MEDLINE*. Their search engines are considered to be less powerful than PubMed or Ovid and they should not be used.

PubMed also provides links to the articles it cites that are available in fulltext on the Internet. However, the articles must be free or part of their library's subscription in order for users to access them. Another feature of PubMed, Loansome Doc, lets unaffiliated searchers set up accounts with a medical library and order articles directly from them (at a cost). Institutions with subscriptions to Ovid may also choose to subscribe to electronic journals so that their users can connect directly to the articles they find in *MEDLINE*.

EMBASE

Another highly regarded medical database is *EMBASE*, produced and provided by Elsevier, a commercial publisher based in Amsterdam, Netherlands. Although its coverage of 4000 journals is comparable to *MEDLINE*, there is surprisingly little overlap between the two. In one 2000 study[1], a search for controlled clinical trials for 3 medical conditions, done in both *MEDLINE* and *EMBASE*, yielded a total of 4111 citations, but only 30% of these citations appeared in both databases.

EMBASE covers European literature in much more depth than does *MEDLINE*. It also is considered to be somewhat stronger in drug information and in areas of biological science related to human medicine. Because of its European focus and its high cost as compared to *MEDLINE*, *EMBASE* is searched less often in the US than perhaps it should be.

EMBASE is available through online vendors such as Dialog and Ovid, and through the web. A recent product, EMBASE.com, includes not only *EMBASE*, but also unique *MEDLINE* records so that both databases are searched simultaneously. EMBASE.com also includes links to articles from some major medical journals. Subsets on specific topics such as drug information or cardiology are available separately.

Evidence-Based Medicine (EBM) Databases

Increasingly health professionals are asked to base their decisions on evidence as demonstrated in randomized controlled trials (RCT's). In both PubMed and Ovid, *MEDLINE* searches can be limited to RCT's. However, strong proponents of EBM feel that only RCT's that meet vigorous standards of methodology should be used. They prefer "systematic reviews": reviews in which all RCT's on a particular topic are collected and analyzed, a meta-analysis is performed (if possible), and that evidence is then used to come to a clinical decision.

PubMed allows the searcher to limit his or her results to systematic reviews. There are also several efforts to collect and make available systematic reviews.

The *Cochrane Library*, the best-known such collection, is a volunteer effort begun in Great Britain. International teams donate their time to identify all published and nonpublished RCT's on a particular topic and then to prepare a systematic review with implications for practice. Abstracts of the systematic reviews are available free on the Internet. The reviews themselves may be purchased from the *Cochrane Library* organization or searched through subscription to Ovid, Dialog, and other vendors.

A major drawback to the *Cochrane Library* is the amount of time it takes for volunteers to complete their projects. Similar commercial products finish their reviews somewhat faster. These include *Clinical Evidence* (*BMJ*), PIER (American College of Physicians), and Infopoems (Infopoems). Also, the American College of Physicians, through its *ACP Journal Club*, monitors major internal medicine journals and selects for review those articles with the most significance for therapeutic practice.

IOWA DRUG INFORMATION SYSTEM

Iowa Drug Information System (IDIS) is produced by the College of Pharmacy of the University of Iowa. *IDIS* is a handy self-contained product that allows the user to search for drug therapy articles selected from 200 clinical journals and to access the fulltext of the articles. Access is provided on the web,

by CD-ROM, or on microfiche. This product is especially useful for drug information centers and HMO's that may not otherwise be able to access a large collection of electronic journals.

INTERNATIONAL PHARMACEUTICAL ABSTRACTS

The scope of the *International Pharmaceutical Abstracts* (*IPA*) is different from either *MEDLINE* or *EMBASE*. *IPA* is produced by the American Society of Health-System Pharmacists (ASHP) and covers 850 pharmacy periodicals. It is a small database, but it covers publications not indexed elsewhere, including pharmacy trade magazines, state pharmacy journals, and the meeting abstracts of pharmacy-related associations.

Some drug therapy journals that are indexed in *MEDLINE* also are indexed by *IPA*. However, because *IPA*'s indexing rules are somewhat different from *MEDLINE*'s, a researcher may sometimes turn up materials in *IPA* that were missed in *MEDLINE* searches.

Many pharmacy and pharmaceutical science topics are much better searched in *IPA* than in any other database. This is the best database to use to find large numbers of articles on pharmacy administration, drug laws and legislation, and pharmacy ethics. Pharmaceutical manufacturing is covered as well. Ovid, Dialog, and the American Society of Health-System Pharmacists make *IPA* available through the web and on CD-ROM. Links from *IPA* to the indexed fulltext articles are not available as of this writing.

CHEMICAL ABSTRACTS

Chemical Abstracts (sometimes called *CAplus* or *CA Search*) covers areas of interest to pharmaceutical scientists. Perhaps the world's largest scientific database, *Chemical Abstracts* is produced by the American Chemical Society's Chemical Abstracts Service (CAS) in Columbus, Ohio. It contains 17 million abstracts from journals, patents, technical reports, books, conference proceedings, and dissertations. It is the most important database for those interested in drug development.

An important adjunct to *Chemical Abstracts* is the CAS Registry System that assigns code numbers to chemical substances, providing a unique identifier for each substance no matter how many names the chemical may have worldwide. This CAS registry number is so valuable that other databases use it to make sure that searchers can find all literature relating to a particular chemical. The CAS Registry System may be searched separately in some database systems.

A special type of searching that can be done in *Chemical Abstracts* is structure searching. It allows the user to draw the chemical structure of a substance and to search from that.

There are links from a *Chemical Abstracts* search to full-text articles available on the web, but to access them the searcher or the searcher's institution must subscribe to the journal that contains the article.

Vendors of *Chemical Abstracts* include Ovid, Dialog, and STN. Some subsets of the database are available on CD-ROM. Some institutions and corporations subscribe to SciFinder (or its academic equivalent, SciFinder Scholar), a user-friendly web interface that allows unlimited searching. Otherwise, *Chemical Abstracts* is very expensive to search and should be accessed only by those trained to do so. Classes are offered around the country by CAS. Academic chemistry or science librarians can often direct a researcher to an experienced freelance literature researcher.

BIOSIS PREVIEWS

Another important scientific database is *BIOSIS Previews*, the online version of *Biological Abstracts* and the *BioResearch Index*. It is produced by BIOSIS (Philadelphia, PA). *BIOSIS Previews* covers the literature of the life sciences, including preclinical toxicity and carcinogenicity studies. Among the many ways it can be searched are by keywords, broad subject areas, and codes representing taxonomic groups. Vendors include BIOSIS, Ovid, Dialog, and STN. Ovid provides links to fulltext articles.

Other Databases

In addition to the major online databases described above, there are many specialized databases that might be of use in the study of pharmacy. Some of these are available on standalone CD-ROMs, but most are accessible only through one of the two major database vendors, Dialog and Ovid.

ADIS LMS Drug Alerts (Langhorne, PA, ADIS International): Evaluates key articles from 2300 journals. Includes an evaluation score for clinical trials.

Adis Newsletters (Langhorne, PA: Adis International): Contains articles from the publications *Inpharma, Reactions*, and *Pharmacoeconomics*.

Adis Clinical Trials (Langhorne, PA: Adis International). Evaluates "key papers"from 1600 international clinical journals.

Adis R&D Insight (Langhorne, PA: Adis International). Reports on drugs under development, including clinical and marketing information.

ESPICom Pharmaceutical and Medical Device News (Chichester, UK: ESPICOM Business Intelligence). Fulltext of articles from *PharmaCompany Insight* and *Medical Industry Week*.

AMED: Allied and Complementary Medicine Database (London: British Library). Index to 596 journals, mostly European, Its coverage of complementary medicine is the most useful aspect for pharmacists. Document delivery system available.

Derwent Drug File (London: Derwent Information): Covers 1150 pharmaceutical journals on drug development and manufacture. Much more highly focused on drugs than is *Chemical Abstracts*.

Derwent Drug Registry File (London: Derwent Information): Retrieves groups of drugs with common structural features.

DIOGENES FDA Regulatory Updates (Gaithersburg, MD: Diogenes): News stories and unpublished documents relating to US regulation.

Drug Data Report (Barcelona: Prous Science): Continuously updated information on more than 65,000 bioactive compounds.

F-D-C Reports (Chevy Chase, MD: F-D-C Reports): Complete text of F-D-C Reports' industry newsletters including *Prescription Pharmaceuticals & Biotechnology* (*Pink Sheet*) and *Nonprescription Pharmaceuticals and Nutritionals* (*Tan Sheet*).

IMSWorld (London: IMS Global Services): Collection of databases that profile pharmaceutical companies, the pharmaceutical industry by country, and new drug launches.

NDA Pipeline: New Drugs (Chevy Chase, MD: F-D-C Reports): Tracks drugs through discovery, clinical trials, New Drug Application, and approval or disapproval by the FDA.

Pharmaceutical and Healthcare Industry News (Richmond, Surrey, England: PJB Publications): Complete text of PJB's industry newsletters: *SCRIP: World Pharmaceutical News*; *Clinica: World Medical Device and Diagnostic News*; *Animal Pharm* and others.

Pharmaceutical News Index (*PNI*) (Ann Arbor, MI: ProQuest): Indexes a number of major pharmaceutical industry newsletters.

Pharmaprojects (Richmond, Surrey, England: PJB Publications): Reports on worldwide progress of new pharmaceutical products.

SciSearch (Philadelphia: Institute for Scientific Information): If one knows of a pertinent article, one can locate subsequent articles that have cited the original publication.

SEDBASE: Side Effects of Drugs (Amsterdam, Netherlands: Elsevier Science): Analysis of published drug side-effects literature.

Toxfile (Bethesda, MD: National Library of Medicine): Compiles toxicity information from several online databases.

Searching of these databases can be expensive and require skill and experience. Science librarians and freelance literature researchers have the requisite abilities to get the best and most cost-effective results.

Secondary Literature

Compilations, commentaries, and digests of the primary scientific literature are referred to as *secondary literature.* A *review article* summarizes the research that has been done on a particular topic. While EBM supporters downplay the traditional

review article, it is still a useful secondary source. Usually written by invitation, the review article can serve as an excellent introduction to an area of research. Review articles are found in scholarly journals and also in special book collections with titles that begin *Annual Review of . . .* , *Progress in . . .* or something similar. Review articles in both journals and books can be found by using online or print indexes.

Other secondary sources include drug monographs, treatises, and various books written for a professional audience. They can be identified by using standard bibliographies, such as those found in a textbook, or in such compilations as the *AACP Basic Resources List for Pharmaceutical Education* (see "Sources for Further Reference" below). Once titles of interest are identified, a researcher should use library catalogs to locate the works themselves.

Almost all library catalogs are accessible from the web. From a desktop computer, a researcher can consult the catalog of the National Library of Medicine or large pharmacy school collections, such as that of the Philadelphia College of Pharmacy at the University of the Sciences in Philadelphia. Books unavailable in a local library usually can be obtained through interlibrary loan.

Textbooks

Textbooks are usually thought of as being written for students, but they can also serve as a state-of-the-art summation for a particular area. In medicine, certain textbooks are held in such high regard that editions continue to be produced long after the original authors are gone. *Remington: The Science and Practice of Pharmacy* (21st ed., Baltimore: Lippincott Williams & Wilkins, 2005) and *Goodman and Gilman's The Pharmacologic Basis of Therapeutics* (Hardman JG, Limbird LL, Gilman, AG, eds, 10th ed., New York: McGraw-Hill, 2001) are examples of works known by the names of those who first wrote them and which are considered to be the standard of practice. Textbooks can serve as an introduction to a new area, and reading new editions is a way to keep up to date.

Textbook Collections

Increasingly, standard textbooks are being made available online, primarily as part of packages. Stat!Ref (Jackson, WY: Teton Data Systems) and MDConsult (Amsterdam: Elsevier Science) are examples of products that allow the researcher to search across a number of textbooks and other materials at once. In addition to textbooks, MDConsult includes the fulltext of 50 journals and a thousand clinical practice guidelines. UpToDate (Wellesley, MA: UpToDate) is still yet another way of packaging online information. It includes topic reviews on hundreds of topics with links to *MEDLINE* abstracts. These packages can be purchased as web subscriptions, CD-ROMs or DVDs.

Trade Literature

In addition to scholarly literature, both pharmacists and pharmaceutical scientists can benefit from accounts of good practice and expressions of opinion. Periodicals such as *Journal of the American Pharmaceutical Association* (Washington, DC: APhA), *Drug Topics* (Montvale, NJ: Medical Economics), or *Pharmaceutical Executive* (Eugene, OR: Advanstar Communications) contain this kind of information. Articles on a particular topic can be found by using the *IPA* database.

SPECIAL INFORMATION SOURCES IN PHARMACY AND THE PHARMACEUTICAL SCIENCES

A variety of reference works are published on drugs and their uses. Many people call all such sources *pharmacopeias,* but a modern pharmacopeia is a very specialized reference work used mostly by pharmaceutical scientists and manufacturers. Reference works containing information on the therapeutic use of drugs such as the well-known *Physicians' Desk Reference* (*PDR*) are more properly called *drug compendia.* Pharmacists and other professionals in the pharmaceutical and health-care professions need to know the different types of drug reference works, what types of information can be found in them, and examples of each.

We will outline some of the major types of pharmacy and pharmaceutical science reference works available and give brief descriptions of important titles in each category. This is not a comprehensive bibliography but it does include references to bibliographies at the end. Almost all of the works described are available in print format. Notable exceptions are the *DRUGDEX System*, the *IDENTIDEX System*, and the *POISINDEX System*. These three titles are all produced by MICROMEDEX, and are available only in electronic formats.

Many of the other titles mentioned below are also available online or in other electronic formats. Since information about the various formats and their availability changes so rapidly, it is not included here. However, publishers' Internet addresses (URLs) have been included for the reader's convenience in obtaining information on the availability of other versions.

Numbers in brackets in the following text refer to references at the end of each section.

Pharmacopeias

In the past, pharmacopeias included information on the therapeutic uses of drugs, but modern pharmacopeias present official standards for purity, strength, quality, and analysis of drugs. Pharmacopeias are issued or authorized by governments or by international agencies. Most pharmacopeias are kept up-to-date through regular supplements.

The Federal Food, Drug, and Cosmetic (FDC) Act recognizes the *United States Pharmacopeia/National Formulary* (*USP/NF*) [1] as the official pharmacopeia of the United States. The *USP/NF* actually consists of two separate titles published in one volume. It does not include all the drugs approved for use in the United States (see *Approved Drug Products with Therapeutic Equivalence Evaluations* below); rather, it includes only those drugs and excipients for which standards have been developed and accepted by the members of the United States Pharmacopeial Convention, a representative organization of physicians, pharmacists, and others in the pharmaceutical and health-care communities. The *USP* is the larger of the two titles in the *USP/NF* and contains monographs on drugs and other substances with therapeutic uses. Standards for many dietary supplements, including some from botanical sources, are included in the *USP*. The *NF* includes monographs for excipients, the nontherapeutic additives used in pharmaceuticals (see Chapter 45 for more information about excipients).

After the *USP/NF*, the best-known national pharmacopeia is probably the *British Pharmacopoeia* (*BP*) [2], authorized by the government of the United Kingdom. The *European Pharmacopoeia* [3], published by the Council of Europe, sets standards for the use of the Council's members. The standards in the World Health Organization's (WHO) *International Pharmacopoeia* [4] are recommendations for the consideration of individual countries rather than requirements.

1. *United States Pharmacopeia/National Formulary.* Rockville, MD: United States Pharmacopeial Convention (http://www.usp.org), annual.
2. *British Pharmacopoeia 2003.* London: Her Majesty's Stationery Office (http://www.hmso.gov.uk). 6 volumes.
3. *European Pharmacopoeia,* 4th ed. Strasbourg, France: Council of Europe (http://www.coe.int), 2002.
4. *International Pharmacopoeia,* 3rd ed. Geneva: WHO (http://www.who.int/en), 1979–2003. 5 volumes.

Formularies and Related Lists

In the past, formularies were recipe books for making drugs, but now they are usually lists of drugs approved for use by a particular hospital, health plan, or government. Many hospitals and health plans have committees to consider which drugs should be included in the institution's formulary. In the United States, these committees are usually called pharmacy and therapeutics committees (P&T committees). Most P&T committees are composed of members of the institution's medical staff and include one or more representatives from the pharmacy. Chapter 127 discusses P&T committees and their roles.

In the United States, the Food and Drug Administration (FDA) has the responsibility to determine that marketed drugs are safe and effective. The FDA produces *Approved Drug Products with Therapeutic Equivalence Evaluations* [5], an annual publication that is popularly called the *Orange Book* after the color of its cover. The *Orange Book* lists both the drugs that have been approved by the FDA, and the FDA's evaluations of the therapeutic equivalence of different manufacturers' preparations of approved drugs. The *Orange Book* does not include drugs that were on the market prior to 1938, nor does it list drugs approved only on the basis of safety. Lists of products on the market before 1938 along with the complete *Orange Book* may be found in *USP DI, Volume III, Approved Drug Products and Legal Requirements* [6]. The *National Formulary* published with the *USP* is not a true formulary (see "Pharmacopeias" above).

5. *Approved Drug Products with Therapeutic Equivalence Evaluations.* Rockville, MD: Food and Drug Administration, US Department of Health and Human Services (www.fda.gov), annual.
6. *USP DI, Volume III, Approved Drug Products and Legal Requirements.* Englewood, CO: Thomson MICROMEDEX (http://www.micromedex.com), annual.

Nomenclature

Every drug has at least two names, its full chemical name and its generic drug name. A drug may also have other names including variant chemical names, proprietary trade names, and variant generic names. Additionally, drug names sometimes differ between countries. Table 8-1 lists some of the names used for the drug acetaminophen. For more information on drug names, see Chapter 27.

The *USP Dictionary of USAN and International Drug Names* [7] is the authoritative list of the United States adopted names (USANs) for drugs. As the title indicates, this work is published by the publisher of the *USP*, the United States Pharmacopeial Convention, as part of its standards-setting responsibilities. The World Health Organization establishes international nonproprietary names (INNs) and publishes them in *International Nonproprietary Names (INN) for Pharmaceutical Substances* [8].

Two other important sources for verifying drug names, especially those used outside of the United States, are *Index Nominum* [9] and the *Merck Index* [10].

Index Nominum is edited by the Swiss Pharmaceutical Society and includes drug names from around the world. Most *Index Nominum* monographs include chemical names and structures, generic names, proprietary names, therapeutic uses, and manufacturers.

The Merck Index has over 10,000 monographs on drugs, common organic chemicals, and a variety of other substances used in the pharmaceutical and chemical industries. Each *Merck Index* monograph includes the substance's various names (including chemical, generic, and proprietary), physical constants, chemical formula and structure, patent information, therapeutic category, and literature citations.

7. *USP Dictionary of USAN and International Drug Names.* Rockville, MD: US Pharmacopeial Convention (http://www.usp.org), annual.
8. *International Nonproprietary Names (INN) for Pharmaceutical Substances,* Cumulative List No. 10. Geneva: WHO (http://www.who.int/en), 2002. Available as CD-ROM only.
9. Swiss Pharmaceutical Society, ed. *Index Nominum: International Drug Directory,* 18th ed. Stuttgart, Germany: Medpharm (distributed in the US by CRC Press, http://www.crcpress.com), 2004.
10. O'Neil MJ, Smith A, Heckelman PE, eds. *Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals,* 13th ed. Whitehouse Station, NJ: Merck (http://www.merck.com), 2001.

US Drug Compendia: Prescription Products

For concise information on the therapeutic use of drugs (including dosage, contraindications, adverse effects, and pharmacokinetics), there are a variety of drug compendia. Probably the best-known one is the *Physicians' Desk Reference* [11], commonly referred to as the *PDR*. Other titles often found in pharmacies and pharmacy libraries in the United States are *AHFS Drug Information* [12] (sometimes called the *American Hospital Formulary Service*); *Drug Facts and Comparisons* [13]; *Mosby's Drug Consult* [14]; and *USP DI, Volume I, Drug Information for the Health Care Professional* [15]. Each of these works is arranged slightly differently with its own criteria for inclusion, but all include monographs for drugs with details on their therapeutic use.

The *PDR* lists only those drugs sold under a trade name, and the monographs it publishes are the FDA-approved labeling for those drugs. All of the other compendia contain information from the FDA-approved labeling as well as additional data from other sources, such as journal articles and textbooks. They also include descriptions of so-called *off-label uses,* therapeutic uses of a drug that do not appear on the FDA-approved labeling. Except for the *PDR*, these compendia are written or edited by pharmacists or other health-care professionals. The criteria for inclusion in these compendia vary from title to title; for example, *Drug Facts and Comparisons* includes some nonprescription products. All of these titles, including the *PDR*, are issued annually and most are updated by supplements throughout the year. A notable exception is *Drug Facts and Comparisons,* which is published both as a loose-leaf service updated monthly and as an annual volume.

By virtue of its electronic format, the *DRUGDEX System* [16] contains much more information than can fit into any one-volume printed compendium. *DRUGDEX*'s drug monographs are longer and more detailed than those found in the above compendia, and each monograph includes extensive references to the medical literature. In addition to monographs about individual drug products, *DRUGDEX* includes Drug Consults,

Table 8-1. Selected Names of a Drug

TYPE OF NAME	NAME
United States Approved Name (USAN)	Acetaminophen
United States Pharmacopeia (USP)	Acetaminophen
Recommended International Nonproprietary Name (Rec.INN)	Paracetamol
European Pharmacopoiea	Paracetamol
Chemical names	*N*-(4-Hydroxyphenyl)acetamide 4′-Hydroxyacetanilide *p*-Acetaminophenol
Proprietary names (country)	Asomal (Turkey) Becetamol (Switzerland) Dristancito (Argentina) Progesic (Indonesia; Hong Kong) Tylenol (United States and others)

Data from O'Neil, MJ; Smith, A; Heckelman, PE, eds. *Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals,* 13th ed. Whitehouse Station, NJ: Merck, 2001, and Swiss Pharmaceutical Society, ed. *Index Nominum: International Drug Directory,* 18th ed. Stuttgart, Germany: Medpharm, 2004.

which answer questions about specific drugs and drug therapies. In addition to prescription drugs, the Drug Consults cover such topics as investigational drugs, herbal medications, and drugs of abuse. *DRUGDEX* monographs are written by drug information specialists. The *DRUGDEX* database is updated quarterly, but the individual monographs in it are not updated as frequently. Each monograph includes the date of its latest revision and its author's name.

11. *Physicians' Desk Reference.* Montvale, NJ: Thomson PDR (http://www.pdr.net), annual.
12. *AHFS Drug Information.* Bethesda, MD: ASHP (http://www.ashp.org), annual.
13. *Drug Facts and Comparisons.* St Louis, MO: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated monthly or annual bound volume.
14. *Mosby's Drug Consult.* St Louis, MO: Mosby (http://www.us.elsevierhealth.com), annual.
15. *USP DI, Volume I, Drug Information for the Health Care Professional.* Englewood, CO: Thomson MICROMEDEX (http://www.micromedex.com), annual.
16. *DRUGDEX System.* Englewood, CO: MICROMEDEX (http://www.micromedex.com), quarterly.

US Drug Compendia: Nonprescription Products

The number of nonprescription drugs and the market for them continues to grow. There are several drug compendia dedicated to these products and their proper use.

The *Handbook of Nonprescription Drugs* [17] is organized by symptom or disorder. Each chapter includes a description of the symptom/disorder and available treatments. The book includes tables of available drugs and their ingredients, and extensive decision trees to aid health professionals in consulting with patients about nonprescription therapies. Chapters include literature references.

Nonprescription Drug Therapy [18] is also arranged by symptom/disorder. While it covers the same topics as the *Handbook of Nonprescription Drugs*, it is much more concise. It is available as a loose-leaf service updated quarterly or as an annual bound volume.

The Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements [19] includes participating manufacturers' label information for nonprescription products.

17. Berardi, RR, ed. *Handbook of Nonprescription Drugs: An Interactive Approach to Self-Care,* 14th ed. Washington, DC: APhA (http://www.aphanet.org), 2004.
18. Covington, TR, ed. *Nonprescription Drug Therapy: Guiding Patient Self-Care.* St. Louis: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf service updated quarterly or annual volume.
19. *Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements.* Montvale, NJ: Thomson PDR (http://www.pdr.net), annual.

US Drug Compendia: Parenterals

Parenteral drugs are those that are injected directly into the body and not absorbed through the gastrointestinal system.

Trissel's *Handbook on Injectable Drugs* [20] has dosage, stability, and compatibility information. The *Handbook* also includes monographs for some investigational drugs and for some foreign drugs. The *King Guide to Parenteral Admixtures* [21] is a comprehensive reference on the compatibility of parenterals. This work is in tabular format and includes information on the compatibility of both drug-drug and drug-infusion fluid mixtures.

20. Trissel LA. *Handbook on Injectable Drugs,* 12th ed. Bethesda, MD: ASHP (http://www.ashp.org), 2003.
21. Catania PA, ed. *King Guide to Parenteral Admixtures.* St Louis, MO: King Guide Publications (http://www.kingguide.com), loose-leaf updated quarterly or annual bound volume.

US Drug Compendia: Catalogs

The major catalog of products commonly found in US drugstores and pharmacies is the *Drug Topics Red Book* [22]. This catalog lists average wholesale prices and manufacturers for both prescription and nonprescription products, including a variety of health and beauty aids. It includes generic drug information that is often difficult to find elsewhere. The *Red Book* also includes other information of use to a practicing pharmacist, such as lists of the top-selling prescription drugs, and directories of poison control centers and state boards of pharmacy.

22. *Drug Topics Red Book.* Montvale, NJ: Thomson PDR (http://www.pdr.net), annual.

US Drug Compendia: Physical Identification

Several of the drug compendia described above include color photographs of tablets, capsules, and other dosage forms to aid in their identification. However, the most useful sources for the physical identification of drugs are ones that include an index of the codes imprinted on the dosage forms. Both *Ident-A-Drug Reference for Drug Tablet and Capsule Identification* [23] and the *IDENTIDEX System* [24] include such an index. The *IDENTIDEX System* also indexes the physical description (color and shape) of the dosage form and includes street drugs. In addition, the *IDENTIDEX System* includes monographs on the toxicology of the substances indexed.

23. *Ident-A-Drug Reference for Drug Tablet and Capsule Identification.* Stockton, CA: Therapeutic Research Center (http://www.therapeuticresearch.com), annual.
24. *IDENTIDEX System.* Englewood, CO: MICROMEDEX (http://www.micromedex.com), quarterly.

US Drug Compendia: Consumer Drug Information

Drug information for consumers can be found in a variety of publications including books, newspapers, magazines, and pamphlets as well as at many websites on the Internet. This section will consider only two types of books: guides sold to consumers by trade publishers, and compendia sold to pharmacists and other health-care professionals by organizations better known for their professional publications.

Among the most popular of the consumer guides are: Griffith's *Complete Guide to Prescription and Nonprescription Drugs* [25]; Rybacki's *Essential Guide to Prescription Drugs* [26]; and *The Pill Book* [27]. All of these books include basic information about drugs including the conditions they are used to treat, their safe use and their possible adverse effects.

Patient Drug Facts [28] and *USP DI, Volume II, Advice for the Patient* [29] are both marketed to pharmacists and other health-care professionals to assist them in their patient counseling activities. *Patient Drug Facts* includes both a quarterly loose-leaf update service and computer software. The loose-leaf is for use by the pharmacist in patient counseling, and the software provides customized printouts for patients. *USP DI, Volume II, Advice for the Patient* is published annually with supplements issued during the year. Pharmacists are given permission to make copies of individual monographs for patients when filling prescriptions for the drugs. *USP DI, Volume II, Advice for the Patient* is also sold directly to consumers by Consumer Reports under the title *Consumer Drug Reference*. Its monographs are available free on the Internet at various sites including the National Library of Medicine's consumer health site, MedlinePlus <http://www.medlineplus.gov>.

25. Griffith HW. *Complete Guide to Prescription & Nonprescription Drugs.* New York: Perigee (http://penguinputnam.com), annual.
26. Rybacki JJ. *The Essential Guide to Prescription Drugs.* New York: HarperCollins (http://www.harpercollins.com), annual.

27. Silverman, HM, ed. *The Pill Book.* New York: Bantam (http://www.randomhouse.com), biennial.
28. *Patient Drug Facts.* St. Louis, MO: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated quarterly or bound volume.
29. *USP DI, Volume II, Advice for the Patient.* Englewood, CO: Thomson MICROMEDEX (http://www.micromedex.com), annual. Also published as *Complete Drug Reference.* Yonkers, NY: Consumer Reports, annual.

Foreign Drug Compendia

Martindale: The Complete Drug Reference [30] is one of the preeminent international drug compendia. It is a compendium of therapeutic and other information on drugs and medicines from around the world. Its monographs include synopses and citations of published literature. *Martindale* also includes lists of proprietary products and manufacturers, making it an invaluable reference for identifying foreign drugs.

Most developed countries have at least one drug compendium with information about the drugs available there. Examples include the *CPS: Compendium of Pharmaceutical Specialties* [31] (Canada), *Diccionario de Especialidades Farmaceuticas* [32] (Mexico), *Rote Liste* [33] (Germany), and *Vidal* [34] (France).

30. Sweetman SC, ed. *Martindale: The Complete Drug Reference,* 33rd ed. London; Chicago: Pharmaceutical Press (http://www.pharmpress.com), 2002.
31. *CPS: Compendium of Pharmaceutical Specialties.* Ottawa, Canada: Canadian Pharmacists Association (http://www.pharmacists.ca), annual.
32. *Diccionario de Especialidades Farmaceuticas.* Mexico City: Ediciones PLM (distributed in the US by Thomson PDR, http://www.pdr.net), annual.
33. *Rote Liste.* Aulendorf, Germany: Editio Cantor Verlag (http://www.ecv.de/), annual.
34. *Vidal: Le Dictionnaire.* Paris: Vidal (http://www.vidal.fr), annual.

Herbal Medicines and Natural Products

In recent years, interest in herbal medicines and medicines from other natural products has grown among health-care professionals, scientists, and the general public.

The Review of Natural Products [35] is a monthly loose-leaf service that covers both herbal and other natural products (for example, charcoal and shark derivatives). Its monographs are written for health-care professionals, and each includes a brief overview of the chemistry, pharmacology, and toxicology of the product. Because it is updated every month, the *Review* often has information on products of current popular interest. *Herbal Medicines* [36] is written for health-care professionals, particularly those in the United Kingdom. Each of the monographs includes a 'Pharmaceutical Comment' with a recommendation on whether the herbal medicine should be used.

Pharmacognosy, Phytochemistry, Medicinal Plants [37] by Jean Bruneton is written for scientists working in the areas of pharmacognosy and phytochemistry. Each chapter describes a class of phytochemicals and the plants from which the chemicals may be isolated.

Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies [38] is written for the layperson. Each monograph includes a review of the literature and recommendations from the author.

35. *The Review of Natural Products.* St Louis, MO: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated monthly or annual bound volume.
36. Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Healthcare Professionals,* 2nd ed. London: Pharmaceutical Press (http://www.pharmpress.com), 2002.
37. Bruneton J. *Pharmacognosy, Phytochemistry, Medicinal Plants,* 2nd ed. Paris: Lavoisier (distributed in the US by Springer, http://www.springeronline.com), 1999.
38. Foster S, Tyler VE. *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies.* 4th ed. Binghamton, NY: Haworth Herbal (http://www.haworthpressinc.com), 1999.

Drug Interactions and Adverse Drug Reactions

Three loose-leaf titles monitor and report on the clinical literature about drug interactions: Hansten and Horn's *Drug Interactions: Analysis and Management* [39]; *Drug Interaction Facts* [40]; and *Evaluations of Drug Interactions* [41]. Each of these is updated several times a year. All include information on the drugs (or drug classes) involved in an interaction, the clinical significance of the interaction, the mechanism of the interaction, and the published evidence of the interaction.

As herbal medicines have become more popular with consumers, there has been increasing concern about the interactions they may have with other medications. *Drug Interaction Facts: Herbal Supplements and Food* [42] reviews the literature on these interactions and those between medications and food. It is updated quarterly.

Meyler's Side Effects of Drugs: an Encyclopedia of Adverse Reactions and Interactions [43] is a comprehensive review of the literature on adverse drug reactions and interactions. Between editions, it is supplemented by the *Side Effects of Drugs Annual* [44]. Both of these titles make extensive references to their own earlier editions and volumes as well as to the clinical literature.

In addition, all of the titles that were listed above in the section "US Drug Compendia: Prescription Products" contain information on possible drug interactions and adverse drug reactions.

39. Hansten PD, Horn JR. *Drug Interactions: Analysis and Management.* St. Louis: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated quarterly.
40. *Drug Interaction Facts.* St Louis, MO: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated quarterly or annual bound volume.
41. *Evaluations of Drug Interactions.* St Louis, MO: First DataBank (http://www.firstdatabank.com), loose-leaf updated 6 times per year.
42. *Drug Interaction Facts: Herbal Supplements and Food.* St Louis, MO: Facts and Comparisons (http://www.factsandcomparisons.com), loose-leaf updated quarterly.
43. Dukes MNG, ed. *Meyler's Side Effects of Drugs: an Encyclopedia of Adverse Reactions and Interactions,* 14th ed. Amsterdam, Netherlands: Elsevier (http://www.elsevier.com), 2000.
44. *Side Effects of Drugs Annual.* Amsterdam, Netherlands: Elsevier (http://www.elsevier.com), annual.

Poisoning and Toxicology

The field of toxicology is a large and diverse one that encompasses the laboratory research specialty as well as the clinical management of poisoning, including forensics and occupational (and home) health and safety issues.

One of the most comprehensive works on poisons and poisoning is the *POISINDEX System* [45] from MICROMEDEX. The *POISINDEX System* database includes product and substance information for household and industrial chemicals, pharmaceuticals, plants, and animals. It includes protocols for treating poisoning from all the listed substances.

The Poisoning & Toxicology Handbook [46] provides its user with a quick guide to toxicology, poisons, and poisoning. In *Sax's Dangerous Properties of Industrial Materials* [47], the emphasis is on the substances themselves. Each monograph includes chemical and physical data on the substance as well as toxicological data and literature citations.

Clarke's Analysis of Drugs and Poisons [48] provides methods of analysis used to determine the presence of specific drugs in biological samples. In addition, its drug monographs include ultraviolet and infrared spectra, and information on the fate of the drug and its metabolites in the body.

45. *POISINDEX System*. Englewood, CO: MICROMEDEX (http://www.micromedex.com); quarterly.
46. Leikin, JB; Paloucek, FP. *Poisoning & Toxicology Handbook,* 3rd ed. Hudson, OH: Lexi-Comp (http://www.lexi.com), 2002.
47. Lewis RJ. *Sax's Dangerous Properties of Industrial Materials*, 10th ed. New York, Wiley (http://www.wiley.com), 2000. 3 volumes.
48. Moffat, HC. *Clarke's Analysis of Drugs and Poisons: in Pharmaceuticals, Body Fluids and Post-Mortem Material.* 3rd ed. London: Pharmaceutical Press (http://www.pharmpress.com), 2003. 2 volumes.

Cosmetics and Toiletries

The International Cosmetic Ingredient Dictionary and Handbook [49] contains information on the chemical class, composition, function, and label requirements of ingredients used in cosmetics manufactured in the US, the European Union, and elsewhere. The series *Cosmetic and Toiletry Formulations* [50] contains industrial recipes for making a variety of cosmetics and toiletries. Each formulation includes the raw materials needed and the amount of each, suggestions of how to formulate the product, and the source of the formulation.

49. *International Cosmetic Ingredient Dictionary and Handbook,* 8th ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association (http://www.ctfa.org), 2000. 3 volumes.
50. Flick EW. *Cosmetic and Toiletry Formulations,* 2nd ed. Park Ridge, NJ: Noyes (http://www.williamandrew.com/), 1989– Multiple volumes.

Other Sources for Pharmaceutical Scientists

In addition to the above sources, pharmaceutical scientists often need information sources on the development and manufacture of pharmaceutical products including the excipients used in them.

The *Pharmaceutical Dictionary* [51] provides translations to and from English, French, German and Spanish for terms commonly used by pharmaceutical scientists and those employed in pharmaceutical manufacturing. *The Encyclopedia of Pharmaceutical Technology* [52] contains signed articles about the materials, methods, and processes used in producing drugs and dosage forms. It also includes articles on the development and regulation of pharmaceuticals.

The series *Profiles of Drug Substances, Excipients and Related Methodology* [53] began as *Analytical Profiles of Drug Substances* [54] in 1972. Its purpose was to supplement the monographs published in various compendia by providing information on the physical and chemical properties, methods of synthesis, and other biochemical data of drug substances. Twenty years later, the series increased its coverage to include excipients and changed its title to *Analytical Profiles of Drug Substances and Excipients* [55]. In 2003, the series changed its title once again to the current one, *Profiles of Drug Substances, Excipients and Related Methodology.* The volumes are not cumulative but each volume includes a cumulative index.

The Handbook of Pharmaceutical Excipients [56] describes the uses and the chemical and physical properties of excipients used in the manufacture of pharmaceutical dosage forms. Most of its monographs include illustrations. The monographs in the *Fiedler Encyclopedia of Excipients* [57] are much briefer than those of the *Handbook of Pharmaceutical Excipients*, but it includes many more entries and is a particularly good source for tradenames.

51. Maas A, Brawley J. *Pharmaceutical Dictionary: English, Deutsch, Français, Español*. 4th ed., rev. and expanded. Aulendorf, Germany: Editio Cantor Verlag (http://www.ecv.de/), 2002.
52. Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology,* 2nd ed. New York: Dekker (http://www.dekker.com), 2003. 3 volumes.
53. *Profiles of Drug Substances, Excipients and Related Methodology,* volume 30. Amsterdam, Boston: Elsevier (http://www.elsevier.com), 2003.
54. Florey K, ed. *Analytical Profiles of Drug Substances,* volumes 1–20. New York: Academic Press (http://us.elsevierhealth.com), 1972–1991.
55. *Analytical Profiles of Drug Substances and Excipients,* volumes 21–29. San Diego, CA: Academic Press (http://us.elsevierhealth.com), 1992–2002.
56. Rowe, RC, Sheskey, PJ, Weller PJ, eds. *Handbook of Pharmaceutical Excipients,* 4th ed. Washington, DC: APhA (http://www.aphanet.org), 2003.
57. Hoepfner E-MH, Reng A, Schmidt PC, eds. *Fiedler Encyclopedia of Excipients: for Pharmaceuticals, Cosmetics and Related Areas,* 5th ed. Aulendorf, Germany: Editio Cantor Verlag (http://www.ecv.de/), 2002. 2 volumes.

Sources For Further Reference

This chapter has presented some of the major pharmacy and pharmaceutical science reference works in brief. Bonnie Snow, in her book *Drug Information: A Guide to Current Resources* [58], considers the universe of such works in greater depth. The Library/Educational Resources Section of the American Association of Colleges of Pharmacy (AACP) maintains the *AACP Basic Resources List for Pharmaceutical Education* [59]. This list is arranged by subject and includes current textbooks and treatises as well as reference works recommended for inclusion in pharmacy college libraries. The list is available at the AACP's website.

58. Snow B. *Drug Information: A Guide to Current Resources,* 2nd ed. Lanham, MD: Medical Library Association and Scarecrow Press (http://www.scarecrowpress.com/), 1999.
59. *AACP Basic Resources List for Pharmaceutical Education.* Alexandria, VA: AACP, irregular. Accessible via http://www.aacp.org/

RESOURCES ON THE INTERNET

The Internet has revolutionized information and communications for all professions. Internet resources are available 24 hours a day, worldwide, to virtually anyone with a computer and telecommunications capability. Pharmacists and pharmaceutical scientists are well represented on the Internet. Resources are available to help these professionals communicate with each other, address patient needs, and keep informed about drug developments. We will discuss the types of pharmacy-related resources available on the Internet, giving special emphasis to resources available through the web.

Electronic Mail and Discussion Groups

Electronic mail, or *e-mail,* was one of the first Internet resources available to pharmacists and is used daily by many professionals. E-mail allows the pharmacist to communicate quickly with patients, physicians, and colleagues around the world. The sender posts a message to a specific Internet e-mail address. The message is delivered via the Internet and stored in the receiver's inbox until it is read. The receiver of the message may reply to the message, forward it to another e-mail user, print the message, delete it, or store it for future reference. Electronic attachments such as document files, pictures, and sound or video clips may also be sent via e-mail.

Several e-mail discussion groups, or *mailing lists,* have developed for the pharmacist. These forums allow groups of pharmacists with common interests or specialties to share information and ideas. The mailing list's software allows a user to subscribe to a discussion group and post messages to a central address. These messages are then automatically distributed to all of the subscribers to the list. Mailing lists exist for students, members of professional organizations, and individuals interested in specific topics (eg, geriatric pharmacotherapy, immunology-transplants, or hypertension).

Some e-mail mailing lists are moderated, restricted in membership, or both. In a *moderated list,* messages are first routed to an individual who determines whether the message fits

within the scope of the discussion group. The message is then either forwarded on to the group or rejected. Some mailing lists, maintain an *archive* of past messages that is available on the web. Lists of pharmacy related mailing lists may be found on the web at the Virtual Pharmacy Library (http://www.pharmacy.org) and at PharmWeb (http://www.pharmweb.com).

Pharmacists also communicate via *Usenet newsgroups*. These discussion forums allow individuals to post a new message or to reply to a message. Newsgroups are accessed through an *Internet service provider* (ISP) using software called a *newsreader*. Common newreaders include Microsoft Outlook Express and Netscape Messenger. Newsgroups differ from mailing lists in that the messages are stored centrally, not redistributed to individual subscribers. At any time, an individual may access newsgroup files to read the accumulation of recent newsgroup messages or the archive of older messages. Groups.google.com offers a web interface to newsgroups and other Internet discussion groups. Sci.med.pharmacy is a pharmacy-related newsgroup for patients and professionals.

The World Wide Web

The World Wide Web is the fastest growing and best-known component of the Internet. Information is presented in pages that contain *hyperlinks,* electronic links to other web pages. Every web page has an individual URL (uniform resource locator), which is the page's address for retrieval. The pages are retrieved and displayed by *browser* software such as Netscape Navigator and Microsoft Internet Explorer. When a *web page* is displayed, the viewer can click on the links, usually represented by underlined or highlighted words or images. This instructs the computer to retrieve and display the linked web page.

Search Engines and Directories

There are several ways to find pharmacy and pharmaceutical information on the web. *Search engines* and *directories* allow users to search for websites, e-mail addresses, messages posted to newsgroups or mailing lists, and images or sound files. They may also allow access by browsing categories such as drug information, clinical resources, pharmaceutical companies, employment opportunities, societies and associations, consumer-oriented sites, and research sites.

The *engine* portion of these services employ *natural language searching*—users simply ask their question in a search box: "What are the adverse effects of alcohol consumption?" Users may enter words or phrases such as "fetal alcohol syndrome" or use Boolean operators (*and*, *or*, and *not*) in their query. Power track interfaces are available on most search engines for the experienced searcher. Advanced query forms allow users to refine their searches (ie, specify the language of the web site or a date range, use Boolean operators, or search specific fields including URLs). Popular search engines include Google (http://www.google.com), All the Web (http://www.alltheweb.com) and MSN Search (http://www.search.msn.com).

Meta-search engines such as MetaCrawler.com, Dogpile.com, and Search.com afford the opportunity to query multiple search engines simultaneously. Search results are organized in a uniform format, listing the search engines in which the query terms were found.

The *directory* portions of these services are maintained by human indexers who organize links to websites into categories. The best services are selective in their listings and organize, annotate, and evaluate the included sites. Yahoo! (http://www.yahoo.com/) includes a search directory that allows browsing by clicking on various categories organized in a hierarchical structure. For example, online pharmacy journals may be found by navigating first to the health menu, then to pharmacy and finally to the journals category. This navigation scheme is useful when the searcher does not know the title of a particular website. Users may also search Yahoo! by entering a word or phrase into a search box that appears on every page. Many users combine the two strategies by first browsing to a section and then searching that category for more specific information.

Major Pharmacy Websites

The web offers a wealth of information for the pharmacist and pharmaceutical scientist. Sites have evolved that allow professionals to gain immediate drug information. Commercial, government, and educational sites provide access to a variety of information. Two major pharmacy-related web sites are PharmWeb and the Virtual Pharmacy Library.

PharmWeb (http://www.pharmweb.net/) is a structured website providing worldwide pharmaceutical and health-related information. This site provides a wide range of services including computer space where pharmaceutical and health-related organizations may house their own web pages. PharmWeb provides pharmacists with several communication mechanisms. The site sponsors moderated discussion groups and mailing lists. Users may link to real-time chat forums or arrange a virtual meeting with colleagues in a discussion room. PharmWeb maintains a searchable directory of people working in the health-care professions. The PharmWeb Yellow Pages is a directory of pharmaceutical information on the Internet. It lists and links to companies, pharmacies, hospitals, and other organizations. This resource also links to pharmacy schools, government and regulatory bodies around the world.

The Virtual Pharmacy Library (http://www.pharmacy.org) is part of the broader World Wide Web Virtual Library (http://www.vlib.org/) that has been in existence since 1994. The Virtual Pharmacy Library is updated and maintained by David W.A. Bourne, of the University of Oklahoma College of Pharmacy. It is a comprehensive directory providing organized lists of links to pharmacy related databases, government web sites, pharmaceutical company, community pharmacy and hospital pages, and job information.

Professional Development

Several major pharmacy-related professional organizations have a presence on the web. These sites allow the pharmacist to learn about the benefits of membership, register online for conferences, and order publications and materials. Members can easily communicate with organization staff. Some organizations provide table of contents listings or limited full text access to their journals and news publications.

The ASHP's website (http://www.ashp.org/) has a drug product shortages management resource center, provides job listings and online continuing education, and online updates to the publication *AHFS Drug Information*. The professional advocacy section reports on ASHP actions in legislative and regulatory affairs, and the site provides the ASHP practice standards online.

The American Pharmacists Association (APhA) also provides a wealth of information through the Internet (http://www.aphanet.org). In addition to member services, this site provides science and research news, government affairs and consumer information.

The American Association of Colleges of Pharmacy (AACP) website (http://www.aacp.org/) is a very good source of information for pharmacy educators and students. It also includes the AACP *Basic Resources List for Pharmaceutical Education,* described above.

The web supports continuing education for practicing pharmacists. The source for finding accredited programs is the American Council on Pharmaceutical Education (http://www.acpe-accredit.org). Their web site contains a comprehensive list with links to web sites of providers.

Libraries and Educational Organizations

Librarians and information professionals have been active in selecting and organizing links to resources on the Internet. Librarians at several academic medical centers in the Midwest have cooperatively developed HealthWeb (http://www.healthweb.org), which provides access to evaluated health-related Internet resources, including sections for pharmacy and pharmacology resources. Emory University's Robert W Woodruff Health Sciences Center Library supports MedWeb (http://www.medweb.emory.edu/MedWeb/. This site organizes health science resources into over 100 categories. The Pharmacy and Pharmacology section contains approximately eight subcategories. This organized hierarchy helps a user to find needed resources.

Pharmacy schools and colleges are also good sources for links to web-based information. The University of Oklahoma College of Pharmacy (http://www.pharmacy.ouhsc.edu/) maintains a comprehensive website providing information about the college's programs and links to appropriate Internet resources, including links to instructional, multimedia, pharmacokinetics, and toxicology resources.

David J. Temple, with the support of the Welsh School of Pharmacy at Cardiff University in Wales, edits a complete world list of schools of pharmacy (http://www.fip.org/education/). This listing includes Doctorate of Pharmacy programs and nontraditional educational programs.

Government Websites

A wealth of government information on the Internet is available to the pharmacist. The FDA home page (http://www.fda.gov/) is an umbrella site linking to the units of the agency, including the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). The CDER site contains the full text of several publications, including the *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as the *Orange Book*), *National Drug Code Directory,* and the latest new and generic drug approval information in the *FDA Drug Approvals List.* MedWatch is the FDA's safety information and adverse event reporting program, and can be accessed from their site. The site contains drug shortage information, a searchable database of inactive ingredients, and major drug information pages. Regulatory guidance information, top drug news, consumer health information, and public health advisories are also provided.

Electronic Publications

Electronic publishing has boomed on the web. The literature of pharmacy and pharmaceutical sciences is becoming available online. The full text of many publications is available only to paid subscribers, but many publishers allow individuals to view tables of contents or abstracts at no fee. For example, viewers may browse the table of contents of *Pharmaceutical Research,* published for the American Association of Pharmaceutical Scientists by Kluwer/Plenum Press. The *Medical Letter on Drugs and Therapeutics,* a newsletter specializing in new drug evaluations, maintains a website with a table of contents archive and sample issues (http://www.medletter.com/). *Drugtopics.com* is an online publication associated with the trade magazine, *Drug Topics.* Emory University's MedWeb site maintains a comprehensive list of pharmacy-related electronic publications.

On-Line Community Pharmacies

Many community pharmacies have expanded their services to Internet customers. These online pharmacies allow consumers to fill prescriptions and purchase over-the-counter products online. These services usually require the patient to mail in a written prescription, or provide the name and phone number of the prescribing physician. Most of these services will bill third-party insurance. The National Association of Boards of Pharmacy developed the Verified Internet Pharmacy Practice Sites (VIPPS) program (http://www.nabp.net/vipps) in response to a growing concern of the safety of Internet pharmacies. VIPPS-certified pharmacies comply with criteria such as overall quality control, security and authorization of prescriptions, privacy rights of patients and adequate patient/pharmacist consultation. These pharmacies also must comply with the licensing requirements of their state and other states that they do business in.

Health Information for the Consumer

In addition to resources for the professional pharmacist, the web is a source for health information for the consumer. Several pharmacy organizations provide unbiased drug and health-related information to consumers. The University of Maryland Drug Information Service maintains such a website (http://www.pharmacy.umaryland.edu/UMDI/). Consumers may ask questions concerning pharmaceuticals or health-related topics. Visitors also may browse an archive of frequently asked questions. The FDA maintains a Consumer Drug Information web site (http://www.consumerdruginformation.com) providing information sheets about newly approved prescription drugs. DrugDigest (http://www.drugdigest.org) is a noncommercial, evidence-based, consumer health and drug information site. PDRHealth (http://www.pdrhealth.com/) from the publishers of the PDR provides disease overviews, health and wellness information, drug information and information about clinical trials.

Site Evaluations

The pharmacist must evaluate health information found on the Internet as thoroughly as any other type of medical information. Websites should identify sources, present unbiased and complete information, clearly state the authors' names and credentials, and keep information up to date. Good health-related websites present a mission statement and a disclaimer that encourages individuals to seek the advice of their own physicians. The Health on the Net Foundation (http://www.hon.ch/) is a nonprofit organization dedicated to building and supporting the international health and medical community on the Internet. The foundation's HONcode Principles provide a recommended code of conduct for medical and health websites.

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REFERENCE

1. Suarez-Almazor ME, Belseck E, Homik J, et al. *Control Clin Trials* 2000; 21:476.

CHAPTER 9

Clinical Drug Literature

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Accessing, reviewing, analyzing, evaluating, and interpreting the clinical drug literature are important responsibilities of health-care practitioners; this is particularly true for pharmacists, who are the "drug experts." Pharmacists have been using and providing drug information for years, focusing initially on drug product compounding and dispensing information; however, the need for drug information has continued to expand along with the expansion of pharmacists' roles. The 1975 report of the Study Commission on Pharmacy concluded that the pharmacy profession was not effective in developing, organizing, and distributing knowledge and information about drugs. In fact, they felt that pharmacy's greatest deficiency was its inadequacy as an information transmitting system to patients, physicians, and other health-care practitioners.[1]

Although more work needs to be done to fully realize the pharmacist's potential in all practice settings, the profession has certainly made great strides forward since the Study Commission's report with regard to providing enhanced drug information to patients, physicians, and other health-care professionals. This is evidenced by the continual growth and development of patient-oriented pharmacy services across practice settings. Also, the establishment of the entry-level Doctor of Pharmacy degree program will better prepare future practitioners to assume their proper role as information specialists on the health-care team.

The types of drug information needed by practicing pharmacists and other health-care professionals are varied and include, but are not limited to, information about side/adverse effects, drug interactions, uses, teratogenicity, stability, and compatibility; product identification and availability; dosages and administration; toxicity, pharmacokinetics, pharmacodynamics, pharmacogenomics, health-related quality of life, and pharmacoeconomics; and efficacy, including the comparative efficacy among drugs in the same chemical or pharmacological class as well as among drugs from different classes. Health professionals must be knowledgeable about not only the variety of information resources available and how and why to use them, but importantly, must be able to critically analyze, evaluate, and interpret the information they retrieve.

The advances in computer technology, the continual growth of the Internet, and the widespread availability of free MEDLINE and other database-searching capabilities have placed unprecedented amounts of information readily within an individual's grasp. In particular, patients and health-care providers are increasingly turning to the Internet as an information resource, despite the unregulated and variable quality of information provided there.[2] It has been estimated that about 100 million Americans seek online health-related information. Key responsibilities of pharmacists and other health professionals include differentiating good from poor quality information, identifying the strengths and limitations of the available information, appropriately applying the information they obtain to patient care, and recommending to patients high quality web sites.

This chapter provides introductory information about the roles of the pharmacist in the area of drug information, and defines tertiary and secondary information resources and their uses. The discussion then focuses on the primary literature and its evaluation. The quality of pharmaceutical manufacturers' and Internet information are also discussed.

THE PHARMACIST AND DRUG INFORMATION

Pharmacists are involved with many aspects of drug related information, including literature retrieval and analysis, adverse drug events, drug use decisions, educational activities, and clinical research. A primary role of the pharmacist as a pharmaceutical care provider is to respond to drug information questions from other health-care professionals and patients and to help resolve drug therapy related problems. Thus, a key activity of modern pharmacy practitioners is conducting literature searches to locate complete, up-to-date information upon which patient-care decisions can be made. Selecting the proper database and search strategy is an important consideration when searching for information. Medical *informatics* has been defined as the rapidly developing science that deals with the storage, retrieval, and optimal use of biomedical information, data, and knowledge for problem-solving and decision-making.[3] Once acceptable sources of information are identified and retrieved, the pharmacist must analyze and evaluate the published literature and develop recommendations based on the best available data. An understanding of searching techniques, research design, and biostatistics is important to the critical evaluation of literature. Once evidence from published clinical research is obtained, pharmacists should also apply evidence-based medicine (EBM) principles to their drug therapy related decisions. Two fundamental principles of EBM involve: (1) using consideration of benefits/risks, inconvenience, costs, and patient values together with evidence in making clinical recommendations, and 2) considering the hierarchy of evidence (eg, observations, strength of published study designs) when making clinical decisions.[4] Since EBM is being increasingly taught to and applied by health care practitioners, pharmacists should be knowledgeable about this process. The Evidence-Based Medicine Working Group has published a book that reviews the essentials for applying EBM to clinical practice, and this resource is recommended to readers wishing to learn more about this area.[4] Many of the principles discussed are included in the "Primary Literature and its Evaluation" section later in this chapter.

Adverse drug events/experiences/reactions not only result in patient morbidity and mortality, but also increase health-care costs by millions of dollars annually. Pharmacists play an active role in preventing, detecting, and reporting adverse events. Pharmacists are one of the major groups of health-care professionals who report adverse drug events to the Food and Drug Administration (FDA) via MedWatch (phone 800-FDA-1088; online at www.accessdata.fda.gov/scripts/medwatch; fax 800-FDA-0178). Pharmacists can also implement systems to prevent drug misadventures (such as errors in the prescribing, dispensing, and administration of medications) and to enhance patient compliance. Pharmacists can report medication errors to the US Pharmacopoeia (USP) via the Medication Errors Reporting (MER) Program (800-23-ERROR; via the web at www.usp.org/mer).

Another important role that pharmacists perform is actively participating in pharmacy and therapeutics committees that make decisions concerning rational drug use within health-care institutions. Through the design and conduct of drug utilization reviews and drug usage evaluations, pharmacists can contribute to continual improvement in the manner in which drugs are used.

Pharmacists are involved in many different drug information educational activities that are conducted for other health-care professionals and patients. Since the practice of medicine and pharmacy involves lifelong learning about the ongoing advances in pharmacotherapeutics, pharmacists can contribute to the continuing education of health-care professionals through the preparation and dissemination of newsletters and by providing seminars and lectures. Pharmacists also can provide verbal and written information to patients about their medications.

Participation in clinical research trials is another application of the drug information skills of pharmacists, allowing them to improve their understanding of how drugs work and ultimately enhance patient care. Their familiarity with the research process also makes them especially well suited to serve on institutional review boards, which are established to protect the rights of study subjects.

Drug information centers were established in the mid-1960s,[5,6] and they are staffed by pharmacists who review, collect, organize, and analyze drug information and disseminate it to health-care professionals and consumers.[7,8] Drug information centers or services often exist as functioning departments within health-care institutions, within the pharmaceutical industry, in academic settings, or as independent centers serving health-care professionals and the public.[9–12] The activities of drug information centers or services have increased dramatically since they were first established. Drug information centers or services are an excellent resource for health-care practitioners when assistance is required in handling a difficult clinical problem or when significant time or resource constraints exist.

TYPES OF LITERATURE

The types of literature can be divided into tertiary, secondary, and primary sources. *Tertiary sources* consist of general reference works and textbooks. When basic information on topics such as pharmacotherapeutics, toxicology, or drug interactions is required, a tertiary literature source may be the best means of starting the learning process and often provide references to more in-depth information if needed.

Secondary sources, literature used to identify and locate primary and other resources, consist of bibliographies, abstracting services, and indexing services. Pharmacists should use a secondary literature source when extensive or detailed information is needed, when a topic is new enough that it is not likely to be included in standard reference sources, when newly published data are needed to augment older information, when the most recent information concerning a topic is required, or whenever primary literature is needed.

The advantages of secondary literature sources are that several are now available to anyone with a computer and Internet access, they are generally current and up-to-date, and they are the best method for identifying primary literature sources. Some secondary literature sources contain a full text version of articles, making it possible to review the information available without going to a library or requesting copies from literature retrieval services or libraries. The disadvantages of secondary literature sources include that several are costly, they can require specific training on their use, and accessing the articles they retrieve can be difficult or time-consuming if one is not located near a medical library. When selecting a specific secondary resource, one must also consider the scope of primary literature and topics covered and the lag time from the date of publication of articles until they appear in the secondary source, which can be considerable in some cases.

Primary sources consist of original studies and reports in journals, monographs, and published conference proceedings and symposia. The primary literature should be consulted when making recommendations concerning the optimal therapy for disease states, when searching for recent reports of adverse events or drug interactions, when looking for information about new or investigational drugs or uses, or any time the tertiary literature does not provide needed information.

PRIMARY LITERATURE AND ITS EVALUATION

An understanding of basic study designs is important when assessing the validity of the results from clinical trials. Researchers may use the wrong study design, use the right methods incorrectly, misinterpret their results, report their results selectively, reference other studies selectively or incorrectly, or draw unjustified conclusions from their research.[13] Health-care professionals must critically evaluate study methods and results to ensure they are sufficiently valid to produce useful information. Pharmacists should be familiar with the methodologies employed in safety and efficacy trials as well as trials designed to evaluate pharmacokinetics, pharmacodynamics, pharmacoeconomics, patient outcomes, and quality of life. Special care must be exercised when reviewing promotional literature and using pharmaceutical sales representatives as sources of drug and drug-related information.[14,15]

Recent efforts on the part of biomedical journal editors, researchers, statisticians, and authors to improve the quality of reports of clinical trials resulted in the development and subsequent revision of the Consolidated Standards of Reporting Trials (CONSORT) statement.[16] The standards proposed by the CONSORT group have resulted in content suggestions and checklists for authors to use when submitting manuscripts of randomized controlled trials to medical journals. These standards have been adopted by such prestigious journals as the *British Medical Journal, JAMA,* the *Lancet,* and *Annals of Internal Medicine.* An initiative to improve the quality of reporting of diagnostic accuracy studies, the Standards for Reporting of Diagnostic Accuracy (STARD) is also underway.[17] A checklist of the types of information that should be provided in such studies has been prepared. However, the reader must realize that the CONSORT and similar processes have limitations, and thus should not assume that the articles published following these processes are automatically free of bias.[18] For example, the CONSORT recommendations cannot prevent authors from misrepresenting their research. The successful pharmacy practitioner must have the skills necessary to critically evaluate primary literature and to draw their own conclusions based on a study's merits, rather than simply relying upon the authors' conclusions.

In general, medical studies can be divided into two broad general types, descriptive and explanatory. *Descriptive studies* simply record data from observations, whereas *explanatory studies* use comparisons as a basis for deriving conclusions about cause and effect.

Table 9-1. Strength of Design of Clinical Trials

STRENGTH	STUDY TYPE
Strongest	Randomized experimental
↓	Cohort
	Case-control
	Case series
Weakest	Case report

Each study type has advantages and disadvantages, and these should be considered by researchers when selecting the design to use. Factors such as the number of patients required to obtain meaningful results, the study's complexity, the amount of time required to conduct the study, and the cost of study completion are important considerations when selecting a design. The critical reader should be aware of these factors when deciding how much credence to give to the findings from trials employing a given study type. The relative strength and weakness of each of these study types is shown in Table 9-1.

Descriptive Studies

A descriptive study can be used to document and communicate experiences that the author feels are important to bring to the attention of the medical community. The investigator simply records data from observations made and draws conclusions as to possible reasons for the events witnessed. Alternatively, descriptive studies may describe unusual or new events, such as the occurrence of sudden infant death syndrome (SIDS) in several siblings within a single family.

Descriptive studies fall into two main types: (1) case reports or (2) case series. *Case reports* are based on the observations of individual patients. They are often used to describe an adverse event following the use of a particular drug or group of drugs, or to report a possible drug interaction. Case reports frequently generate hypotheses to serve as the basis for more rigorous studies to examine the relationship between drug administration and the outcomes observed.

Case series document observations from a group or series of patients, all of whom have been exposed to a particular drug or group of drugs. The outcomes are observed and recorded. Case series are also used to examine the prior histories of patients with the same outcome in hopes of identifying a possible cause and effect relationship. Case series are useful for estimating the incidence of an adverse event of a newly marketed drug when there is limited information available about that particular event. Conversely, case series can be employed to help ensure that a certain adverse event is not associated with the use of a drug, for example, suicidal ideation following haloperidol use.

A major limitation of descriptive studies is that they do not provide definitive explanations, determine causes, or supply evidence that one drug is superior to another. Indeed, the outcome observed might not even be related to the drug. For these reasons, readers must exercise a great deal of caution when interpreting the results of case reports or case series and should not draw conclusions about causality from them.

Explanatory Studies

Explanatory studies use a more rigorous design to identify answers to questions that arise in clinical medicine. Investigators employ these designs to determine the efficacy of medications or identify whether there is a true relationship between the use of a drug and the occurrence of an outcome (eg, whether oral contraceptives cause an increased incidence of breast cancer, or what role the eradication of *Helicobacter pylori* plays in the prevention of peptic ulcer disease recurrence). Explanatory studies can be divided into two main designs: (1) observational and (2) experimental.

OBSERVATIONAL STUDIES: CASE-CONTROL, COHORT, CROSS-SECTIONAL

When conducting *observational studies,* the investigators are bystanders to the events under study. They examine the natural course of health events, gather data about the subjects included, and then classify and sort the data. The investigators employ comparisons to provide insights into the cause of diseases or the risk factors associated with disease occurrence.

When evaluating the relationship between drugs and the occurrence of specific outcomes, there are two basic approaches an investigator can take: work from the effect or outcome back to the cause or exposure (case-control studies), or proceed from the cause or exposure to the effect or outcome (cohort studies). Cross-sectional studies collect data simultaneously from the comparison groups.

Case-Control Studies

In *case-control studies,* one group of patients with a target condition or disease (the cases) are selected and compared with another group of individuals without the condition or disease (the controls). Cases and controls are compared with respect to existing or past characteristics or exposures that are thought to be relevant to the development of the disease or condition under evaluation.

A case-control study design has several advantages. Case-control studies take little time to design, initiate, and conduct because the outcomes have already been experienced. They are useful for the study of rare diseases or conditions that take many years to develop because they require fewer patients than other study designs. Additionally, since case-control studies use patients who have already developed the disease of interest, there is no need to wait for time to elapse between an exposure and the manifestation of diseases with long latency periods.

From an ethical perspective, case-control studies have an advantage in areas of investigation where neither experimental nor follow-up observational studies can be sanctioned (eg, the incidence of HIV-positive tests following injuries with needles contaminated with HIV-positive blood, drug teratogenicity). Further, case-control studies are ideal for initiating exploratory studies (so-called "fishing expeditions") of disease etiology so that a specific hypothesis can be formulated and sufficiently supported to justify a detailed investigation. There is no risk to the patients involved in case-control studies because they have already experienced the outcome under evaluation. Finally, when compared to other types of explanatory study designs, case-control studies are inexpensive, since existing records can often be used to collect the necessary data.

There are several disadvantages associated with the case-control study design. A detailed study of mechanism is rarely possible with this design. The case-control method is not suited to the evaluation of therapy because there is no comparison to other drugs, nor is it suited to study disease prophylaxis. In these situations, experimental trials should be used.

A major problem with the case-control design is the reliance on patient recall or on existing medical records for information. Sufficiently accurate information may not be available from medical records. Likewise, information concerning the dose, duration, or drug administration in relation to the event under evaluation may be inadequately recorded and imperfectly remembered. Validation of information collected is difficult or sometimes impossible to accomplish.

The case-control design has incomplete control of extraneous variables that may affect the cause and effect relationship. Case-control studies are subject to antecedent-consequent relationships (the chicken-and-egg phenomenon)—one cannot be sure whether the characteristic really led to the effect or disease, or if the outcome in some way predisposed people to acquire factors or characteristics that appear to be predictive of the disease.

Case-control studies are also subject to numerous types of bias. An exhaustive discussion of biases associated with case-control trials is beyond the scope of this chapter, but several types can be highlighted. Case-control study design may be affected by *recall bias* (selective recall). Patients who have unpleasant experiences or diseases may recall the past quite differently from those in a comparison, nondiseased group. Other important biases to consider when evaluating case-control studies include *reporting bias,* which occurs when publicity concerning a disease results in an increase in the disease's reporting; and *surveillance bias,* which can occur when a disease or condition under study is asymptomatic, mild, or otherwise liable to escape routine attention. With surveillance bias, the condition is likely to go unreported in the control group and is more likely to be detected in the patients under frequent medical surveillance in the case group.

The appropriate selection of cases is important to the reporting of valid results in case-control studies. Who patients are, where they come from, and what spectrum of disease they represent are important considerations. However, selection of an appropriate control group is difficult when conducting case-control studies because it is almost impossible to find a comparison group identical to the cases. A sampling procedure is intended to avoid over- or under-representation of exposed cases and exposed controls in the study, thus avoiding biased selection. Each eligible case in the target population, irrespective of exposure, should ideally have an equal chance of appearing in the study. Methods have been developed to help manage the problems associated with the proper selection of a control group in case-control studies, although they cannot eliminate the problems. One such method is through the selection of *multiple controls,* wherein more than one control group is selected for comparison. Another method employed is *matching,* which uses the selection of control subjects who share particular characteristics with the cases.

Cohort Studies (Follow-up Studies)

Cohort studies begin with patients who have not yet experienced the outcome; these patients are then followed over time, looking for differences in the outcome's development. The characteristics that are thought to influence the development of the disease of interest are catalogued and measured, and comparisons of patient groups with (exposed) or without (nonexposed) the various characteristics are made to identify the causes of the outcome of interest. The cohort study represents the best observational study design strategy when there are no time or financial limitations.

Historical (or retrospective) cohort studies can be conducted using data contained in large medical databases. The cohorts (those with characteristics/exposed and those without characteristics/nonexposed) are established and their experience is assessed from existing records. The main feature of a historical cohort study is that all outcomes have occurred before the start of the investigation. The key element is that individuals are identified for inclusion in either the study or control group without knowledge by the investigators of whether the disease has later developed.

A cohort study design has several advantages over the case-control study. This design allows for the complete description of experience subsequent to exposure, including rates of progression, staging of disease, and natural history. The cohort design offers greater assurance that the characteristics under study preceded the outcome under study. It also permits the study of multiple potential effects of a given exposure, thereby obtaining information on potential benefits as well as risks. The cohort design allows for the calculation of rates of disease in exposed and unexposed individuals after the cohorts are established and their experience is assessed. In addition, this design permits flexibility in choosing the variables to be systematically recorded. Cohort studies can delineate various types of consequences that may be produced by a single risk factor.

In contrast to the case-control design, the cohort design (with the exception of the historical cohort) has few problems associated with incomplete medical records, and there is no recall bias. Another advantage of the cohort study design over the case-control design is that the cohort design is not associated with antecedent-consequent relationship problems.

Cohort studies do have disadvantages. Cohort studies are subject to patient selection problems. Every effort must be made to identify independently each characteristic affecting the disease or outcome under study and to ensure an even distribution of these factors. The external validity (discussed later in this chapter) of cohort studies may be difficult to determine, because clinicians may not know how closely the subjects described in the cohort study mirror their patients.

The major problem of the cohort study design is maintaining patient follow-up over time. As time goes on, patients move, fail to respond to questionnaires, or decide to quit the study, which can result in an uneven distribution of patients between groups. Reports of cohort studies should identify the attempts made by the investigators to track down subjects and minimize the number lost to follow-up. The investigators should identify the rate of follow-up losses and explore for the possibility of biased attrition. By examining the characteristics of dropouts, the investigator may identify reasons for subject loss that are related to the outcomes under study, and compensate for any differences identified. The more similar the dropouts are to those in the study group, the less chance there is for attrition bias. Finally, if possible, investigators should contact a representative sample of the dropouts to identify the reasons for discontinuation and take any differences into account when analyzing the study results.

Another disadvantage associated with cohort studies is that current practice, usage, or exposure to study factors may change over time, making the findings of the study irrelevant. Cohort studies are also subject to surveillance bias due to an unequal examination or scrutiny of the subjects under evaluation. Since cohort studies follow patients over time, they may require a potentially long duration of follow-up when a long lag time exists between cause and effect. Cohort studies are relatively expensive to conduct because they require an expenditure of resources over long time periods. Finally, like case-control studies, a detailed study of mechanism is rarely possible with cohort studies.

Cross-Sectional Studies (Prevalence Studies)

The *cross-sectional study* also gathers data from both study and control groups, but it makes simultaneous assessments of both the outcome and potential predictors at the same (ie, present) time. The cross-sectional design is suited for studies designed to evaluate a new laboratory test or a new application of an existing test, to evaluate the receiver-operator characteristics of diagnostic procedures, to identify risk factors and etiological agents of a disease or condition, and to determine the prevalence of a disease or condition at a specific point in time.

Advantages of the cross-sectional design include the efficiencies and time-savings that result from all of the information being collected at the same time. Investigators do not have to wait for outcomes to develop when conducting cross-sectional studies.

As cross-sectional studies compare a desired study group with a control group, they are subject to selection problems. The type of patients selected for the study group has a major influence on the results. External validity is a concern, since the findings can only be applied to other patients to the extent that they exhibit similar characteristics to the study subjects. Selection methods must define the characteristics of subjects who will be included in the analysis. Sampling rules must be formulated to avoid bias in the study results. Methods such as *systematic sampling* (selecting the *n*th individual who is eligible for the study), *random sampling* (where each possible

individual has a fixed and determinate probability of selection), and *matched sampling* (the pairing of one or more controls to each study subject on the basis of specified variables to eliminate their effects on the comparison) are frequently employed in the cross-sectional design.

An additional disadvantage of this design is the existence of antecedent-consequent relationships (the chicken-and-egg phenomenon), as described earlier.

EXPERIMENTAL STUDIES

Experimental studies are prospective trials in which *intervention,* an attempt to regulate the variables in a study, occurs on the part of the investigators.[19] There are two types of experimental studies, controlled and noncontrolled. *Controlled studies,* in contrast to noncontrolled studies, use a comparison group(s) in addition to the group receiving the drug being investigated. This allows the investigator to help account for the possible influence that other outside factors (eg, environmental) could have on a study's outcomes independent of the drug being evaluated.

Since the controlled study is the strongest type of experimental study, the remainder of the discussion will focus on the controlled design. Several guides and checklists have been published to assist readers in evaluating the quality of experimental clinical studies.[20] Table 9-2 lists the criteria usually included in such checklists, and can be used as a guide for the evaluation of published clinical drug studies.

Journals/Authors

The quality of the journal an article is published in can be used as a preliminary, indirect measure of the potential quality of the article itself. An *editorial board* is one method that helps to ensure the quality of the information that a particular journal publishes. *Peer review* is another method employed for helping ensure the quality of articles published. This is a process in which a journal sends out a received manuscript to

Table 9-2. Criteria for the Evaluation of Published Experimental Drug Studies

AREA/STUDY SECTION	CRITERIA
I. Journal/authors	Editorial board present.
	Peer review used.
	Author(s) has/have expertise in subject.
	Potential conflicts of interest absent.
II. Introduction/background	Background and rationale clear.
	Relevant previous work cited.
	Objective(s) clearly stated.
	Objective(s) described in sufficient detail.
III. Methods	
A. Patients/subjects	Inclusion and exclusion criteria clearly defined.
	Inclusion and exclusion criteria appropriate for objective(s).
	Inclusion and exclusion criteria complete.
	Number of patients/subjects adequate.
	Source and selection of patients/subjects described.
	Appropriate study setting.
B. Study design	Type(s) of control(s) used appropriate.
	Design appropriate to address study objective(s).
	Randomization process described and followed.
	Type of blinding used adequate and employed successfully.
C. Treatment considerations	Dosages of study and control drugs adequate and comparable.
	Dosage frequency appropriate.
	Route(s) of administration and dosage forms appropriate.
	Duration of therapy adequate.
	If measured, plasma/serum/blood concentrations adequate.
	Any concurrent medications accounted for.
D. Outcome measures	Efficacy and safety measures included.
	End points defined clearly.
	Measurements valid, reliable.
	Known confounders accounted for.
	Measure(s) clinically important.
	Compliance measured.
E. Data analysis	Power analysis performed and power adequate.
	Types of statistical tests and analyses described clearly and appropriate.
IV. Results	Statistical tests and analyses used for key outcome measures.
	Measures of variability provided with measures of central tendency.
	P values or confidence intervals reported.
	Size of treatment effect important clinically.
	Actual numbers included with percentages.
	Side/adverse effects reported.
	Text/tables/graphs clear and consistent.
	Reason(s) for patient/subject dropout provided; handling of dropout data described.
V. Discussion	Data obtained consistent with conclusions.
	Study limitations addressed.
	Significance of findings discussed.
	Extrapolation of findings consistent with study design.

"peers," other individuals with expertise in the area, who review and comment on the quality of the manuscript and the work undertaken in addition to providing suggestions for revision, prior to a decision being made regarding publishability. Based upon the peer reviewers' comments and the editors' opinions, a decision is made to return the manuscript to the author(s) for revision, reject the manuscript, or publish the manuscript. Although the best approach for the peer review process has been debated and peer review does not guarantee the quality of work described,[21] it is another important method for providing the reader with some measure of confidence in the information published.

Many journals ask authors to describe any potential *conflicts of interest* when they submit their manuscript for publication consideration. According to the International Committee of Medical Journal Editors, "Conflict of interest for a given manuscript exists when a participant in the peer review and publication process-author, reviewer, and editor-has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected."[22] These potential conflicts of interest include serving as a consultant for or an employee of the manufacturer of one or more of the drugs being investigated, obtaining a grant from the manufacturer to fund the study undertaken, or holding stock in a company that manufacturers one or more of the study drugs. The problem faced is how to perform research studies that might be translated into marketable products in a way that will hold all sponsors, investigators, authors, and journals involved in the publication of clinical trials to objective, honest, scientific, and ethical behavior uninfluenced by financial considerations. The existence of a potential conflict of interest does not automatically invalidate the findings reported; rather, the reader should keep this possible conflict in mind when analyzing the study's results and the author's interpretation and discussion of the findings, particularly if biased or unsupported statements appear to exist.[23]

Introduction/Background

Several points should be covered by the author in the introduction or background portion of a published study. The rationale for the study should be clearly described and pertinent previous work in the area, with both positive and negative findings if they exist, should be summarized and cited. The specific study objective or hypothesis should be described in sufficient detail to enable the reader to determine if it actually addresses the problem explored and whether it can be reasonably accomplished by the study.

METHODS

The methods or methodology section includes several important areas to review and analyze in order to assess the overall quality of a study: patients/subjects, study design, treatments used, outcome measures, and the data analyses used. Particular attention should be devoted to the methods employed by the investigators in conducting the study. Flawed methods produce results that yield incorrect conclusions, and patients may suffer harm from either ineffective or toxic therapy.

Patients/Subjects

It is important to examine the types of patients or subjects included in a clinical study to determine whether the study sample is representative of the desired study population and the extent to which the study's results can be extrapolated to others outside the study sample. The study's inclusion and exclusion criteria are key to making these determinations.

The *inclusion criteria* define the characteristics a patient or subject must have to be included in a specific study. The *exclusion criteria* include those characteristics that, if present, would prevent a patient or subject from being enrolled. The inclusion and exclusion criteria should be defined clearly. This is crucial for determining the extent to which a study's results can be applied or extrapolated to patients outside the study. For example, if patients with "renal dysfunction" are excluded from study participation, then its meaning should be clear to the reader (eg, what the exact creatinine clearance values are that constituted "renal dysfunction").

The study sample should also be representative of the population that the authors are interested in examining as part of their study objective; that is, the characteristics of the patients enrolled in the study should be similar to other patients likely to be found in the population of interest, and this population should be appropriate for the study's objective.

Finally, whether any other inclusion or exclusion criteria should have been incorporated to strengthen the study must be considered. For example, it might be appropriate to exclude concurrent medications known to increase blood pressure in a study of a new antihypertensive medication.

An important consideration when analyzing a study's results is the *sample size,* or number of subjects included. Sample size is one of the factors affecting a study's power, the extent to which a statistical test can detect a significant difference among treatments if such a difference really exists (ie, appropriately rejecting the *null hypothesis,* no difference among treatments, when it is false).

As sample size increases, *power* increases as well. Thus, the smaller the number of patients enrolled in a study and the lower the power, the greater the likelihood of a type II error, also referred to as beta. A *type II error* is, by definition, failing to reject the null hypothesis when it is actually false—that is, concluding that there is no statistically significant difference among treatments when there actually is. Ideally, power should be calculated by the investigators prior to study initiation and reported for the reader.[24] By convention, an acceptable degree of power in a study is considered to be at least 0.8 or 80%.

When reading a study that concludes there was no significant difference present among treatments, consider whether the power was adequate. If the power was not reported, consider the number of patients involved (the larger the better) and the actual magnitude of the difference found.[24] For example, a difference in mean serum cholesterol concentrations of only 1.5 mg/100 mL between two antilipidemic drug groups is unlikely to be clinically relevant even if a large number of patients were enrolled; a difference of 1.5 mg/100 mL might be found to be statistically significant if a very large number of patients were studied.

More information regarding sample size and how to determine an appropriate number of subjects to enroll is beyond the scope of this chapter and can be found in other articles.[25,26]

The *source* of the patients/subjects enrolled in a study should be considered with regard to the potential ability to extrapolate the results, as well as the manner in which they were selected for inclusion. For example, if a study examined subjects who were selected from among nursing home residents, the results might not be applicable to relatively healthy, active elderly persons.

The *setting* of the study should also be appropriate for the study's objective; if the objective is geared toward active outpatients, then the study should best be conducted in the outpatient setting. If the subjects were randomly selected from the population of interest, as opposed to nonrandom techniques such as convenience or consecutive sampling, the method used should be described.

Investigators conducting randomized clinical trials are required to follow Good Clinical Practices (GCPs) in the design, conduct, analysis, and reporting of studies.[27] Good clinical practice sets ethical and scientific standards for all research involving human participants. The FDA in conjunction with the European Union and Japan has developed a series of guidances to

facilitate the mutual acceptance of clinical data by the regulatory authorities of all countries involved (see http://www.fda.gov/cder/guidance/959fnl.pdf). Compliance with GCP ensures that the rights, safety, and well being of study participants are protected, consistent with the principles that have their origin in the *Declaration of Helsinki*. A primary tenet of GCP is the submission of research protocols to an Ethics Committee (EC) or Institutional Review Board (IRB). Research is generally not accepted for publication without assurance that the study was reviewed by an IRB and that informed consent was obtained from research participants prior to their participation in the clinical study.

Study Design

Several design aspects warrant consideration when analyzing the quality of a published experimental study. The first involves the type of control employed. An *active control* uses a drug with proven efficacy for the treatment of a condition as a comparison to the drug being evaluated. For example, in a study of a new nonsteroidal anti-inflammatory agent that compares its efficacy to a group of patients receiving naproxen, the naproxen group would constitute the active control. A *placebo control* incorporates a group of subjects receiving placebo as the comparison group. A *no treatment control* incorporates a group of subjects receiving no therapy as the comparison group. A *historical control* uses as the comparison group individuals who received the intervention previously as part of a different study or as part of a different evaluation.

An active control can only provide information about the relative efficacy of drugs—whether one was more efficacious, less efficacious, or the same as another. However, it is possible that neither the active control nor the drug being evaluated were truly efficacious for the patient groups being studied. In contrast, a placebo control allows one to determine the true efficacy of a drug for treatment of a certain condition.

Placebo controls are preferable to no treatment controls because they minimize possible bias introduced by the patient as a result of knowing what they are receiving. Either placebo or no treatment controls can pose an ethical dilemma, however, for studies involving serious illnesses in which patients should receive active therapy.

Historical controls should only be used in special circumstances, such as when the disease being treated has known high mortality and it would be easy to identify a new efficacious therapy. In many studies, both active and placebo controls are employed to allow for determinations of both the actual and comparable efficacies of a given agent.

Another consideration involves the type of design used in a controlled experimental study. The controlled experimental designs include concurrent control (parallel treatment), crossover, and time series (before and after). Of these, the concurrent control design is generally preferred.

In the *concurrent control design*, patients are divided into at least two groups: control versus experimental. They only receive the intervention of the one group they were assigned to. Results obtained from the experimental group(s) are then compared with those from the control group. With this design, it is important that the experimental and control group patients are as similar as possible to help ensure comparability of the results.

In a *crossover design*, the patients are initially assigned to either the control or experimental groups; after completion, they are then placed in the other group(s) so that each patient eventually receives each intervention. The crossover design generally includes a *washout* period between each intervention to allow the treatment and its effects to be eliminated from the body prior to beginning the next study phase. Since the patients are the same in the control and experimental groups in a crossover design, it is easier to eliminate differences in patient characteristics as being responsible for any differences identified between groups. A smaller sample size can also be used for the crossover design as compared to the concurrent control. Disadvantages of the crossover as compared to the concurrent control design include a longer study duration, the effects of time itself on the results, and the possibility of carryover effects occurring (ie, effects from the previous intervention persisting and affecting the results from the subsequent intervention, such as when an inadequate or no washout period was employed). More complex analyses are required because differences might be identified among groups depending on the order in which they received the interventions. For example, patients who received the control first might be found to respond differently than patients who received the control last.

In the *time series design*, each patient also receives each study intervention except, in contrast to the crossover design, they receive each intervention at the same time. This makes analyses of the results easier compared to the crossover design, but the time series design cannot control for the effects that time itself might have on the outcomes.

Randomization is the process of randomly assigning the enrolled patients/subjects to study groups (eg, control versus treatment groups) using a technique such as random numbers. This is a very important procedure for ensuring a study's quality. It helps to eliminate subjective factors and bias when assigning subjects to treatment groups, and reduces the likelihood that differences in subject characteristics (either identified or unidentified) are actually responsible for the outcomes observed rather than the treatment itself.[28] It is important to recognize that randomization does not guarantee that a study's groups will be identical; through chance alone the groups could be different with regard to one or more important criteria.

Studies will usually compare the study groups after randomization with regard to characteristics that might influence outcomes (eg, age, sex, race, number of years with a certain condition) to ensure that they are indeed comparable. If baseline differences exist, these can often be accounted for later using statistical methods.[29] When a study refers to itself as a "randomized controlled" trial, the word "randomized" is referring to assignment, not selection. The actual process used for randomization to study groups should be reported in a study. A reader should consider whether the process was indeed truly random and whether the investigators adhered to the process they described.

Blinding, or *masking,* is a process in which the identity of the control and experimental groups in a study is not known to the subjects and/or investigators; that is, the subjects and observers do not know who is receiving the control or experimental treatments.

In an *unblinded study,* also referred to as *open label,* both the subjects and investigators are aware of the group assignments. There is a risk of bias introduction by either the subjects or investigators with this type of design.

In a *single-blind study,* the subjects are unaware of the intervention they are receiving but the investigators know. This type of blinding might be acceptable when the measures employed in the study are all objective (eg, blood concentrations). In the *double-blind study,* neither the subjects nor investigators are aware of the intervention each subject is receiving. This type of blinding is preferred for studies to minimize the likelihood of bias introduced by the subjects or investigators and is an important part of the "gold standard" study design–controlled, randomized, double-blind. The term *triple-blind* has been used for studies in which an individual other than the investigator analyzes the data, and the subjects, investigators, and data analyzers are unaware of the group assignments.

When blinding is used in a study, it is important for the investigators to describe the means by which this was accomplished (eg, identical appearing/smelling/tasting capsules, tablets, or liquids) as well as any evidence as to whether the blinding was successful.[16]

There is always a danger of *unblinding* (unmasking) occurring in a blinded study. This is when the subjects or investigators can successfully guess or identify the intervention given. Unblinding is more likely when the drug involved has an odor

or taste that is difficult to disguise, or when characteristic side effects or laboratory test alterations occur that would alert the subjects or investigators to the true identify of the treatment. For example, the headache from nitroglycerin or the red-orange urine discoloration from rifampin could likely lead to unblinding, even in a double-blind study. The investigators should provide evidence either supporting or negating the success of the blinding employed.

Treatment Considerations

When evaluating the quality of clinical studies, pharmacists in particular should pay close attention to the appropriateness of the treatment regimens employed. Characteristics of the treatment regimens to examine include the dosage, dosing frequency, route of administration, dosage form, and duration of therapy for each drug used, any drug concentrations obtained, and the use of any concurrent medications.

With regard to the *dosages* of the experimental drug and any active controls, they should be appropriate and comparable. For example, if the active control is being dosed at the high end of its usual dosage range, the experimental drug should generally be dosed comparably. Also, if the dosage of a drug is usually adjusted based on an individual's response in clinical practice, it might be inappropriate to employ a fixed dose of that drug for all the patients in a study.

The dosing *frequency* should be consistent with the pharmacokinetics and pharmacodynamics of the drug. If a drug has an established therapeutic serum, plasma, or blood concentration range, then the study should measure drug *concentrations* in the patients and ensure that they are appropriate. Likewise, the concentrations should be taken at the correct times in relation to the doses and at steady state for efficacy studies.

Some studies allow patients to take other nonexperimental medications concurrently with the drug in the study. For example, a study of the effects of zinc capsules on flu symptoms might allow patients to also take acetaminophen as needed. If *concurrent medications* are allowed in a study, it is important for the reader to consider whether these medications could interact with the study drug or affect the disease state or symptoms being studied. If the concurrent medication could affect the study outcomes, it is important that the study record and quantitate the amounts taken in both the control and experimental groups and analyze whether these quantities were comparable or could have otherwise influenced the study's findings.

Outcome Measures

The outcomes of interest to be measured in a clinical study should be derived from the study's objective. In an efficacy study, the outcome measures should include not only determinations of efficacy but of safety as well. For example, in a study of a new antihypertensive medication, determining the systolic and diastolic blood pressures would be important, as would recording the drug's adverse effects or effects on blood lipids or glucose.

The *desired end point(s)* of the study, the key measures that will support or refute the study's hypothesis,[30] should be clearly specified to the reader and should be identified by the investigators at the beginning of the study. In the antihypertensive example mentioned earlier, the main or primary end point might be the ability of the drug to decrease systolic and diastolic blood pressures to the normal ranges.

A study might also have *secondary end points,* meaning other measures of interest but not of primary concern. For example, the effect of an antihypertensive drug on serum triglycerides might be an important secondary end point but not the major reason for performing the specific trial. The investigators should specify the minimum differences between the control and experimental groups that they feel are of importance.[16] As the reader, you should also ensure that these differences are of clinical importance.

The techniques or methods used to measure or determine whether the study's outcome was achieved should be valid. *Validity* refers to whether the measurement is really measuring what the investigators would like to measure or think they are measuring.[31] Types of validity include, but are not limited to, internal, external, and construct validity:

Internal validity refers to the extent that, within the study, the tests, measurements, results, and interpretation were appropriate and accurate.[32]

External validity is generalizability, the extent to which the results can be extrapolated or applied to other nonstudy individuals and across settings or times.[31,32] External validity is important to clinicians who are interested in the degree to which they can apply the results from an individual study to their patients. Readers should examine factors such as the study's inclusion and exclusion criteria, how subjects were selected, and the study setting to assist them in determining the generalizability of its results.

Construct validity refers to the extent to which a measure actually reflects what it purports to measure. This can be determined by the extent to which it agrees or converges with other methods established to measure the same variable, and the extent to which it disagrees with or diverges from other methods used to measure different effects.[31]

In addition to being valid, measures in a study should also be reliable, specific, and sensitive.

Reliability refers to the extent to which a measure provides similar results when used on different occasions—that is, its reproducibility.[33]

Specificity refers to the degree to which a measure can accurately detect only the disease or effect of interest. Stated another way, it refers to the degree to which a measure can accurately classify as negative those people who lack the disease or effect.

Sensitivity indicates the extent to which a measure can identify the presence of the effect or disease.[34]

Confounding variables, or confounders, are factors that could affect the outcome being measured (in addition to the characteristic of interest), thereby confusing the interpretation of the results.[35,36] For example, if a study was examining the effect of age on ulcer relapse rate and several of the ulcer subjects also smoked (a known factor influencing relapse), smoking could be a confounder when analyzing the results. If a study has known confounding variables present, the investigators should account for their presence either in the study design (methods section) or in the analysis of the results.[37]

Finally, it is important that clinical drug studies assess the degree of patient *compliance* with their therapy, as noncompliance with one of the drug regimens in a study could make that drug erroneously appear less efficacious than another.[37] Studies should make an effort to determine the extent of patient compliance by using a variety of methods (eg, pill counts, patient self-report, diaries, or drug concentrations) and report this information for the reader.

Data Analysis

The methods section of a study should generally include a discussion of power (sometimes found in the results section) and the type of statistical tests or analyses performed on the data collected. (Power was referred to earlier in the discussion of sample size.) A common reason for the failure to detect significant differences among treatment groups in a study is a lack of statistical power, often a result of too small a number of patients enrolled or actually completing the study. As a reader, check to see whether the investigators performed a power analysis and reported this information. If so, determine whether the power was appropriate. If not, consider whether a lack of power might have been responsible for any negative finding reported.

As a reader, determine whether the statistical tests or analyses employed are described in sufficient detail to allow for their replication.[38] The tests or analyses used should also be appropriate for the variables of interest.

Results

The results section of a published study is of obvious importance to the reader. There are several areas to focus on within this section and key questions to ask. These areas include the statistical tests and analyses performed and the specific findings reported, side or adverse effects, the presentation of the data, and patient dropouts. The topic of statistics is covered in more detail in Chapter 12. However, important statistics-related points that the reader should consider when critically analyzing studies will be discussed here.

The first consideration is that statistical tests and analyses should have been performed on all the key outcome measures. There are primarily two types of statistics involved: descriptive statistics and inferential statistics.

Descriptive statistics, numerical or graphical summaries of data, include measures of central tendency (eg, mean, median, mode), measures of variability (eg, range, standard deviation, variance, standard error), and measures of precision for effect estimates (eg, confidence intervals).

Most *inferential statistics,* methods to generalize from the data obtained from the study sample to the entire population of interest, involve the tests and analyses (eg, parametric tests, nonparametric tests) performed to test hypotheses and determine whether statistically significant differences exist among study groups. Other statistical procedures include correlation and regression analyses (to describe and quantify the association among study variables) and estimates of risk associated with developing a disease, condition, or adverse event (eg, relative risk, odds ratio).

Next, readers should consider whether the statistical method employed in a study is appropriate for the type of variable being examined. For example, parametric tests (such as *t* tests or ANOVA, analysis of variance) should be used only when certain criteria are met, such as normally or near-normally distributed data, continuous level data, or variances of the populations from which the samples are drawn being nearly equal. If these criteria do not apply, then nonparametric tests (eg, Chi-square test, Fisher's exact test, or Mann-Whitney *U* test) should be employed, taking into account whether the data are *nominal* (data without numerical qualities that can be placed into mutually exclusive categories) or *ordinal* (data that can be rank ordered on a scale, but differences between rankings cannot be precisely measured).

It is also important that information about the variability of study data be provided in addition to information about the central tendency of that data. For example, the mean is commonly used to illustrate the "average" or representative value in a group of data. However, the mean can be affected significantly by a small number of outlying data points (extreme high or low values) and therefore might not represent accurately where most of the individual data values lie. Also, the mean might have the same value regardless of whether all the individual data points cluster very closely or widely around it.

Because clinicians are interested in applying the results from studies to their individual patients, an indication of the variability of the individual data points in a study is valuable. For example, suppose two studies report the same mean plasma concentrations of 50 mg/mL in response to drug administration. However, the individual patients' drug levels in the two different studies are as follows (in mg/mL): 48, 49, 50, 51, 52 and 1, 5, 50, 95, 99. Although the mean values are identical, the patients in the latter study exhibit much more variability in response to the drug. Thus, studies that report values such as means for their outcome measures should also include corresponding ranges or standard deviations.[38]

Further, the results from statistical analyses performed should include exact *P* values or confidence intervals.[37,38] The *P* value indicates the *probability* of a type I error (ie, rejecting the null hypothesis when it is in fact true). Stated another way, it means concluding that a statistically significant difference exists among treatments when there actually isn't one and the results are due to chance. The probability of a type I error is also referred to as the alpha level. The smaller the *P* value, the less the likelihood that a type I error was responsible for the difference observed (or the less the likelihood that chance was responsible for the difference observed). Thus, a *P* value of 0.001 indicates that the likelihood of a type I error, or that chance alone was responsible for the difference observed, is only 1 out of 1000. By convention, $P < 0.05$ is generally considered statistically significant.

However, since *P* values only indicate the risk of type I error and do not provide information about the magnitude of the clinical effect, the *confidence interval* (CI) is increasingly being reported. The CI is calculated using the study sample data and provides the likelihood or confidence that the true population value is included within the range of values reported.[29] For example, if a study reports a difference in the response rates between two treatments of 35% with a 95% CI of 30–40%, this means that there is a 95% likelihood that the true difference in the response rates if the population as a whole were studied would fall between 30% and 40%. Although the 95% CI is generally calculated, the reader may also see 90% or 99% CIs reported in studies. The CI provides health practitioners with useful data for predicting how their patients would likely respond to the same treatment (assuming that their patients had similar characteristics as those in the study sample, ie, are part of the population the study sample represented).

The size of the actual treatment effects reported in studies should be clinically useful.[29] Further, when reporting results in studies, actual numbers should be included with any percentage change data.[38] For example, large percentages can be misleading when small numbers are involved, and the reader should be aware of this.

It is difficult to determine the clinical utility of a treatment without considering safety as well as efficacy. This includes not only the risk of adverse reactions from the drug regimen employed, but also the risk to the patient of an adverse event if he or she is not treated. The reader should assess the side or adverse effects reported in a study when determining how to incorporate the results into clinical practice. A "number needed to harm" can be calculated, representing the number of patients that need to be treated to cause one adverse effect, in a manner similar to the "number needed to treat" approach.[39]

When presenting data in a study, any tables or graphs used should be clear and not misleading. Also, the text description should be consistent with the information illustrated in the tables or graphs. Finally, the reason for any patient/subject losses (dropouts) should be provided as they could influence the interpretation of the clinical usefulness of the treatment employed. For example, patients could drop out of a study because the therapy was ineffective or intolerable side effects developed. Two approaches used for handling the data from dropouts include the intent-to-treat (or intention-to-treat) and exclusion of subjects (or per protocol) methods.

With the *intention-to-treat analysis,* the data from all patients are analyzed together with the rest of the data from the group they were originally assigned to, regardless of whether they completed the entire treatment (ie, it evaluates the treatment as originally offered to the patients). The advantage of this method is that it better reflects normal clinical practice with regard to drug therapy; however, if large numbers of subjects dropout from non–drug-related causes (eg, subjects move away or simply don't want to bother with follow-up study visits), the true efficacy of a drug can be obscured. For example, suppose 10 patients are enrolled in a study and only 5 complete it, with the remainder dropping out for non–therapy-related reasons. If the drug is efficacious in four of the five patients, the

efficacy with the intention-to-treat method would be reported as only 40% (4 of the 10 patients originally assigned to treatment).

The *exclusion of subjects* or *per protocol method* excludes the data from subjects who do not complete the therapy as assigned (ie, it evaluates the treatment as actually taken by the patients). This method does not underestimate the efficacy of treatment, but it also does not take into account those reasons for dropout that affect the clinical usefulness of a drug (eg, side effects or lack of efficacy).

In some studies, the reader will see the data reported by using both methods. This provides the best way in which to evaluate the results of a study.

Discussion

Considerations when evaluating the final discussion section of a published study include whether the conclusions of the investigators are consistent with the data obtained and reported; whether the investigators explored the potential limitations of their study and its design (eg, small study size, the occurrence of "unblinding," or large dropout rate); and whether any extrapolation of their findings, or discussion of the study's external validity, was consistent with the study's original objectives and design, particularly the inclusion/exclusion criteria employed. The discussion should provide an honest synopsis of the significance of the findings in light of all other available evidence.

The significance of the findings should include a statement about the clinical relevance of the results, not simply the statistical significance. It is possible for very small differences between study groups to obtain statistical significance (ie, low risk of type I error), but the differences could be too small to be of clinical usefulness. Also, the significance of the findings should include an assessment of the benefit versus risk from the therapy employed. The "number needed to treat" provides an estimate of the number of patients that would need to receive the treatment in order to prevent one adverse event. Finally, published studies should also relate their findings to previous work in that area. For example, an analysis of 26 published randomized controlled trials found that only two of the studies discussed their results in the context of a systematic review of earlier work, and four additional articles referred to relevant systematic reviews but did not update these reviews with the addition of their results.[40]

Electronic communications are dramatically impacting the way study information is exchanged among the healthcare community. The World Wide Web offers researchers the opportunity to present data that support their published findings, describe their methods in greater detail, illustrate their recent presentations, allow others to comment on work in preliminary stages and to have those comments available to be viewed by other readers, and the web also provides important sources of specialized information and links to other Web sites and citations. The Internet provides a means to publish scientific work and to distribute it widely without major barriers to access; however, it is important that quality assurance (eg, peer review) is still maintained. Many medical journals have already instituted the dissemination of important studies by presenting the data at their web sites prior to publication in their journal. Other journals provide access to their issues via the Internet at no charge. Electronic biomedical publishing is beginning to change the face of the medical literature and how it is accessed.

REFERENCES

One of the International Committee of Medical Journal Editors' requirements for publishing manuscripts is that the references cited in the article must be verified by the author. Whenever possible, authors should cite results obtained from a clinical trial rather than relying on the accuracy of another author's reporting of the results in a review article. Readers should be cautious when references cited are over-represented by papers authored by one of the study authors.

SUMMARIES OF THE LITERATURE

Clinicians are often interested in obtaining a comprehensive summary of the available information on a specific topic instead of individual studies. *Review articles* constitute one type of publication, a systematic overview, used for summarizing the medical literature on a certain subject. These reviews generally compile published information on broad aspects of a topic and offer recommendations or conclusions based upon the author's opinions. Authors of review articles should specify the methods they used to identify the relevant literature (eg, databases and search terms used) as well as how they selected the articles included in order to avoid a biased sampling (ie, selection of only articles that support a given hypothesis). One advantage of a review article is that it provides a healthcare practitioner who might know little about a specific subject with a summary of much of the published information on that topic. This can allow the practitioner to become fairly up-to-date on a topic relatively quickly. A review article's bibliography can also be used as a source for clinical studies of interest on a subject.

Unlike a qualitative review article, a meta-analysis (another type of systematic overview) is a summary article that provides quantitative data. A *meta-analysis* uses formal statistical techniques to sum a body of separate, but similar, original research studies in order to formulate a conclusion.[28] Meta-analyses have been reported to an increasing extent in the medical literature. Meta-analyses can be used to increase statistical power for end points and subgroup analyses, to improve estimates of effect size, to address questions not posed at the start of individual trials, to provide preliminary data regarding sample sizes and hypotheses needed for large definitive clinical studies, to help resolve uncertainties when individual trials disagree, and to generalize conclusions to a more varied range of patients and treatment protocols.[28,41–44]

Despite the convenience and proposed advantages of review articles and meta-analyses, several problems or pitfalls exist. Review articles often are not based upon a focused clinical question, might not include the criteria used by the authors in locating relevant material or in selecting the articles to include, might not assess the validity of the studies included, and can reflect subjective and inaccurate opinions of the authors.[45] Potential problems with meta-analyses are summarized in Table 9-3 and should be kept in mind when reading them. A published

Table 9-3. Issues and Problems with Meta-Analyses

Which studies should be included in the analysis?
Could selection bias be present in the studies included?
What should be done with poorly designed trials?
Should the studies included be weighted using predetermined criteria?
Have all the relevant studies been retrieved? Publication bias (the tendency of journals to publish studies with positive findings) could influence the results if only published studies are sought; however, obtaining all the relevant published and unpublished literature could be difficult.
Were tests of homogeneity done to minimize the likelihood that significant heterogeneous trials were combined?
Were the adverse effects in each study that were included in the analysis appropriately considered?
Were differences in the treatment interventions present? Differences in the treatment interventions (eg, drug dosages, dosing intervals or duration of administration) could make it difficult to combine study results.

users' guide for how to use review articles includes several important questions to ask about these articles, such as are the results valid, what are the results, and how can the results apply to patient care?[45]

Studies have reported that discrepancies can exist between meta-analyses and subsequent large well-controlled trials.[44,47,48] The results of meta-analyses were found to disagree 10–35% of the time with subsequent large clinical trials.[47,48] It has been suggested that meta-analyses should be used primarily to generate hypotheses for further study in large controlled trials rather than to test hypotheses, and to help understand and predict discrepancies in the findings of different trials.[44,48] However, in the absence of definitive studies, a well-performed meta-analysis can provide valuable guidance with regard to therapeutic recommendations.

When searching the secondary information source MEDLINE, it is easy to identify and retrieve literature summaries by limiting the search to publication types such as review article or meta-analysis. Once these types of articles are retrieved, however, the reader should also conduct a critical analysis of them.

PHARMACEUTICAL INDUSTRY AND PUBLISHED INFORMATION

The pharmaceutical industry represents a rich source of information concerning the medicines it produces. By some accounts, the pharmaceutical industry spends more time and resources on generating, analyzing, and disseminating medical information than it does on manufacturing its medications.[49] Most of the data generated during the discovery phase of new drugs remains confidential. In order to obtain approval to market a drug, drug manufacturers must compile an application containing results from clinical trials conducted for the indications sought. Pharmaceutical marketing is aimed mainly at physicians, although it has been increasingly targeting consumers as well, and has been criticized because it may lead to inappropriate physician prescribing and thereby potentially increase costs while leading to a worsening in health. Drug companies realize the value of publications of studies of their drugs as a means of influencing medical practice. There is a preponderance of positive studies sponsored by pharmaceutical manufacturers that are published in the medical literature. Reasons for this include the use of protocols that employ inappropriate doses of comparator drugs, selective publication of studies that have significant findings, selective reporting of studies using the more favorable per protocol analysis, and multiple publications from the same studies.[50,51] The income for the medical journals themselves from the publication of clinical trials may also play a role in the overrepresentation of positive studies in the medical literature.

Promotional Information

Although the main reason that journals publish drug advertisements is to earn money, advertisements may have educational value as well. The Federal Food, Drug, and Cosmetic Act requires that all drug advertisements contain (among other things) information in brief summary relating to side effects, contraindications, and effectiveness. Typically, print advertisements include a reprinting of the risk-related sections of the product's approved labeling (also called full prescribing information or the package insert). The FDA encourages sponsors to write this risk information in language appropriate for the targeted audience. In addition to the specific disclosure requirements, advertisements cannot be false or misleading or omit material facts. They also must present a fair balance between effectiveness and risk information.

Pharmacists, health care professionals and consumers alike should be cautious when assessing information concerning efficacy, safety, convenience, or economics that is contained in pharmaceutical advertisements. The FDA through the Division of Drug Marketing Advertising and Communications (DDMAC) has authority over the publication of promotional information. However, it lacks the resources to ensure that all promotional information is accurate, truthful and well balanced. Journal editors likewise lack the appropriate resources to carefully review all advertisements submitted for publication in their journal. One thing editors can do is to ensure that advertisements are easily distinguishable from other articles by the use of color and placement within the journal.[52] Advertisers have been criticized for their use of false or misleading claims, extension of the indications, making exaggerated claims, and application of one standard for developed countries and another for the developing countries.[14] Use of terms such as "Drug of Choice" or "New" carry connotations that can be misleading and the FDA has prescribed definitions of such terms to help ensure that promotional language is not misleading.

INTERNET MEDICAL INFORMATION

There are estimated to be over 167 million US Internet users, a figure that has increased steadily. Over 63% of adults were reported to have online access, with more than 100 million Americans looking online at least once for health/medical information.[53] The Health On the Net Foundation conducted an Internet survey in 2001 to characterize Internet use for medical and health related purposes. Of 3,325 respondents, 70% were ≥ 40 years of age. Ninety-two percent browsed web sites; the majority searched for medical literature (83%), drug information (81%), or disease descriptions (67%). Only about 63% of persons discussed the search results with their care provider(s).[54] The more recent 2002 survey reported similar findings, with about 28% of patients indicating that accuracy was the most critical issue facing medical information on the Internet (the highest percentage for any issue).[55]

Web sites have been found to provide incomplete or incorrect information on various health topics such as complementary medicine for inflammatory bowel disease or emergency contraception. Only a minority (20%) of Internet information from traditional medical sites discussing childhood diarrhea treatment were found to actually conform to American Academy of Pediatrics guidelines.[56] Of 19 web pages providing information about the home management of cough in children, their quality scores ranged from −5 to 5 (maximum of 6 points), with only three sites scoring 3 or above. Ten of the 19 received negative scores, indicating they provided more incorrect than correct information.[57] In one study, the investigators developed a rating scale, based upon clinical practice guidelines published by the Agency for Health Care Research and Quality, for determining the quality of web-based information on depression treatment. Of 21 web sites evaluated, the mean quality score was only 4.7 out of a maximum of 43 points.[58] In another study, of 10 sites providing English language depression information, only 44% supplied more than minimal coverage and completely accurate information. For childhood asthma and obesity, only 36% and 37% of sites, respectively, provided more than minimal coverage and completely correct information.[59] Internet information about St. John's Wort, an herbal product, was found to be of predominantly poor quality.[60] Additional analysis found that citing professional sources and a lack of financial interest were significantly associated with providing correct information, although content quality was still found to be fairly low in such sites. A recent review of studies examining web site quality found that most concluded that quality was a problem, although the methodology employed by the individual studies was variable.[61] Given widespread, increasing public use of the Internet, it is critical that its medical information be accurate and reliable. This is particularly true since most people do not appear to

actually use rigorous criteria when determining a web site's accuracy and credibility, even when claiming to do so.[62]

Pharmacists and other health care professionals should be knowledgeable about key points to look for and criteria to use to help determine the quality of Internet information, and they should assist patients in locating reputable web sites that will meet the patients' medical information needs.

A wide range of organizations have developed or are in the process of developing methods or tools for evaluating and rating web site quality that can be used by web site developers or consumers. These methods/tools include codes of conduct, quality labels, user guides, filters, and third party certification.[63] Codes of conduct consist of quality criteria for the content of Internet sites for use by developers and consumers. However, the extent to which oversight is provided with regard to implementation of the code is variable and can be nonexistent. A quality label or award is included on a web site to indicate the developer's commitment to adhere to a code of conduct. The degree to which this is enforced and the criteria upon which the label is assigned can be unclear. While user guides can help consumers perform their own evaluation of a web site, the time, effort, and expertise required on the part of consumers to rate web sites can make these of limited benefit. Filters are used to accept or reject web sites based on preestablished criteria, and serve a "gateway" function. These can be very useful to consumers although high in cost to maintain due to the expertise required to review web sites. Third party accreditation labels are awarded to web sites that meet the criteria established by a third party organization or accrediting body. These are not yet in existence on a large-scale basis.

One study reviewed rating instruments that have been used to assess web site quality and provide site awards, with 98 instruments identified from 1997 to 2002.[64] Of these, many were not functioning at the end of that 5-year period. Many more were not eligible for review in the study because they did not provide a description of their rating criteria used. A total of 11 rating instruments were ultimately reviewed. Of these, none appeared to have been validated. A number of initiatives have been underway to identify or to help consumers identify high quality Internet health information sites.[64,65] These include government organizations such as Medline Plus from the National Library of Medicine, Healthfinder from the US Department of Health and Human Services, and HealthInsite from the Australia Department of Health and Aging,[64,65] as well as two initiatives from the United Kingdom, the Electronic Quality Information for Patients (EQUIP) and the Organising Medical Networked Information (OMNI),[65] among several others. Readers are urged to refer to these latter two references for additional information and the web site addresses for these initiatives.

REFERENCES

1. *Pharmacists for the Future: The Report of the Study Commission on Pharmacy*. Ann Arbor, MI: Health Administration Press, 1975, p 48.
2. Karp S, Monroe AF. *Manag Care Quart* 2002; 10(2):3–8.
3. Blois MS, Shortliffe EH. The computer meets medicine: emergence of a discipline. In Shortliffe EH, Perreault LE, Wiederhold G, et al, eds. *Medical Informatics: Computer Applications in Health Care.* Reading, MA: Addison-Wesley, 1990, p 20.
4. The Evidence-Based Medicine Working Group. *Users' guides to the medical literature. Essentials of evidence-based clinical practice*. Guyatt G, Rennie D, eds. Chicago, IL: AMA Press, 2002, pp 8–14.
5. Grace M, Wertheimer AI. *Am J Hosp Pharm* 1975; 32:903–904.
6. Pearson RE, Lauper RD, Davis LJ. *Am J Hosp Pharm* 1975; 32:31–34.
7. Price KO, Goldwire MA. *Am Pharm* 1994; NS34:30–39.
8. Gong SD, Millares M, VanRiper KB. *Am J Hosp Pharm* 1992; 49:1121–1130.
9. Russello CM, Peterson AM. *Am Pharm* 1993; NS33(11):49–52.
10. Martin S. *Am Pharm* 1991; NS31(2):25–26.
11. Justice J. *Am Pharm* 1993; NS33(11):53–57
12. Colvin C. *Am J Hosp Pharm* 1990; 47:1989–1990.
13. Altman DG. *BMJ* 1994; 308:283–284.
14. Villaneuva P, Peiro S, Libero J, et al. *Lancet* 2003; 361:27–32.
15. Ziegler MG, Lew P, Singer BC. *JAMA* 1995; 273:1296–1298.
16. Moher D, Schulz KF, Altman D for the CONSORT Group. *JAMA* 2001;285:1987–1991 http://www.consort-statement.org/revised-statement.htm, Accessed July 28, 2003.
17. Bossuyt PM, Reitsma JB, Gatsonis CA, et al. *BMJ* 2003; 326:41–44.
18. Moher D. *JAMA* 1998; 279:1489–1491.
19. Gehlbach SH, ed. *Interpreting the Medical Literature.* New York: McGraw-Hill, 2002, p 17.
20. Moher D, Jadad AR, Nichol G, et al. *Control Clin Trials* 1995; 16:62–73.
21. Altman LK. *Lancet* 1996; 347:1382–1386.
22. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Available at http://www.icmje.org/index.html#conflict. Accessed July 28, 2003.
23. Alpert JS, Furman S, Smaha L. *Arch Intern Med* 2002; 162:635–637.
24. Gehlbach, *Interpreting the Medical Literature,* p 156.
25. Young MJ, Bresnitz EA, Strom BL. *Ann Intern Med* 1983; 99:248–251.
26. Stolley PD, Strom BL. *Clin Pharmacol Ther* 1986; 39:489–490.
27. Expert Working Group (Efficacy) of the International Conference on Harmonisation. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance. April 1996. http://www.fda.gov/cder/guidance/959fnl.pdf. Accessed July 28, 2003.
28. Berger VW, Bears JD. *Vaccine* 2003; 21:468–472.
29. Guyatt GH, Sackett DL, Cook DJ. *JAMA* 1993; 270:2598–2601.
30. Adam A, Posner J, eds. *A Guide to Clinical Drug Research.* Dordrecht: Kluwer Academic, 1995, p 7.
31. Motheral BR. *J Managed Care Pharm* 1998; 4:382–390.
32. Gehlbach, *Interpreting the Medical Literature,* p 84.
33. Gehlbach, *Interpreting the Medical Literature,* p 130.
34. Gehlbach, *Interpreting the Medical Literature,* p 181.
35. Gehlbach, *Interpreting the Medical Literature,* p 226.
36. Basskin L. *Formulary* 1997; 32: 279–280,283–286.
37. Cho MK, Bero LA. *JAMA* 1994; 272:101–104.
38. The Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature. *Ann Intern Med* 1996; 124:741–743.
39. Guyatt et al. *Users' Guides to the Medical Literature*, pp 378–380.
40. Clarke M, Chalmers I. *JAMA* 1998; 280:280–282.
41. Egger M, Smith GD. *BMJ* 1998; 316:61–66.
42. Egger M, Smith GD. *BMJ* 1997; 315:1371–1374.
43. Egger M, Smith GD, Phillips AN. *BMJ* 1997; 315:1533–1537.
44. Borzak S, Ridker PM. *Ann Intern Med* 1995; 123:873–877.
45. Guyatt et al. *Users' Guides to the Medical Literature*, pp 243–266.
46. Gibaldi M. *Drugs* 1993; 46:805–815.
47. LeLorier J, Gregoire G, Benhaddad A, et al. *N Engl J Med* 1997; 337:536–542.
48. Ioannidis JP, Cappelleri JC, Lau J. *JAMA* 1998; 279:1089–1093.
49. Collier J, Iheanacho I. *Lancet* 2002; 360:1405–1409.
50. Melander H, Ahlqvist-Rastad J, Meijer G, et al. *BMJ* 2003; 326:1171–1175.
51. Lexchin J, Bero LA, Djulbegovic B, et al. *BMJ* 2003; 326:1167–1176.
52. Fletcher RH, Fletcher SW. *Ann Intern Med* 1992; 116:951–952.
53. Harris Interactive. 100 million U.S. net users are 'cyberchondriacs' (April 25, 2001). http://www.nua.ie/surveys. Accessed October 2003.
54. Health on the Net Foundation. Evolution of Internet use for health purposes. www.hon.ch/Survey/FebMar2001/survey.html. Accessed October 2003.
55. Health on the Net Foundation. Excerpt of the 8th HON's survey of health and medical internet users. www.hon.ch/Survey/8thHONresults.html. Accessed October 2003.
56. McClung HJ, Murray RD, Heitlinger LA. *Pediatrics* 1998; 101(6):1–4. (Pediatrics online) http://www.pediatrics.org/cgi/content/full/101/6/e2
57. Pandolfini C, Impicciatore P, Bonati M. *Pediatrics* 2000;105(1): 1–8. (Pediatrics online) http://www.pediatrics.org/cgi/content/full/105/1/e1.
58. Griffiths KM, Christensen H. *BMJ* 2000; 321:1511–1515.
59. Berland GK, Elliott MN, Morales LS, et al. *JAMA* 2001; 285:2612–2621.
60. Martin-Facklam M, Kostrzewa M, Schubert F, et al. *Am J Med* 2002; 113:740–745.
61. Eysenbach G, Powell P, Kuss O, et al. *JAMA* 2002; 287:2691–2700.
62. Eysenbach G, Kohler C. *BMJ* 2002; 324:573–577.
63. Wilson P. *BMJ* 2002;324:598–602.
64. Gagliardi A, Jadad AR. *BMJ* 2002; 324:569–573.
65. Huang QR. *Aust Fam Physician* 2003; 32:335–341.

APPENDIX Selected Journals of Interest to Pharmacy

ACP Journal Club (American College of Physicians)
AJHP: American Journal of Health-System Pharmacy
American Family Physician
American Heart Journal
American Journal of Cardiology
American Journal of Clinical Nutrition
American Journal of Emergency Medicine
American Journal of Medicine
American Journal of Obstetrics and Gynecology
American Journal of Psychiatry
American Journal of Respiratory and Critical Care Medicine
Anesthesiology
Annals of Allergy, Asthma, and Immunology
Annals of Emergency Medicine
Annals of Internal Medicine
Annals of Neurology
Annals of Pharmacotherapy
Archives of Dermatology
Archives of General Psychiatry
Archives of Internal Medicine
Archives of Neurology
Archives of Pediatrics and Adolescent Medicine
Arthritis and Rheumatism
BMJ: British Medical Journal
Cancer
Chest
Circulation
Clinical Infectious Diseases
Clinical Obstetrics and Gynecology
Clinical Orthopaedics and Related Research
Clinical Pediatrics
Clinical Pharmacokinetics
Clinical Pharmacology and Therapeutics
Clinics in Sports Medicine
CMAJ/Canadian Medical Association Journal
Critical Care Medicine
Diabetes
Diabetes Care
Digestive Diseases and Sciences
Disease-a-Month
Diseases of the Colon & Rectum
Drugs
Endocrinology
Emergency Medicine Clinics of North America
Fertility and Sterility
Gastroenterology
Geriatrics
Gut
JAMA: The Journal of the American Medical Association
Journal of Allergy and Clinical Immunology
Journal of Alternative and Complementary Medicine
Journal of Clinical Endocrinology and Metabolism
Journal of Family Practice
Journal of Infectious Diseases
Journal of Pediatrics
Journal of Substance Abuse Treatment
Journal of the American Academy of Dermatology
Journal of the American College of Cardiology
Journal of the American Dietetic Association
Journal of the American Geriatrics Society
Journal of the National Cancer Institute
Lancet
Medical Clinics of North America
Medical Letter on Drugs and Therapeutics
Medicine
Neurology
New England Journal of Medicine
Obstetrics and Gynecology
Pediatric Clinics of North America
Pediatrics
PharmacoEconomics
Pharmacotherapy
Postgraduate Medicine
Rheumatology
Sports Medicine
Therapeutic Drug Monitoring

Data from Hill DR, Stickell H, Crow SJ. Brandon/Hill selected list of print books and journals for the small medical library. http://www.mssm.edu/library/brandon-hill/small_medical/pdf/brandon4.pdf. Accessed January 2004.

CHAPTER 10

Research

Maria L Webb, PhD

Medical and pharmaceutical research provide a basis for the development of new therapeutic approaches to human and animal disease. This process of drug discovery research can be basic (seeking an understanding of biological phenomena that are unknown) or applied (using principals that are known to produce a desired new product or effect). In either case, drug discovery research results from an unmet clinical need, a recognized deficit in treatment options. The outcome of a successful drug discovery program is the generation of a therapeutic where none previously existed, or the replacement of established therapies in favor of a newer modality that is safer and more efficacious.[1]

The main function of the pharmaceutical industry is to create products (ie, drugs, that have an impact on health care). Products of this type can be foreseen to some extent through knowledge and study and thus are amenable to planned research and development (R&D). For example, if the cause of a disease has been identified as an infection by a microorganism, a search can be undertaken for an agent that will prevent or cure the infection. However, in some instances, the etiology of a disease is unknown despite intensive investigation. In the latter situation, the pathway to a satisfactory cure or method of prevention cannot be foreseen or forecast. In such cases, products may only be developed after application of careful investigations, from a revolutionary new approach, or perhaps from a serendipitous finding.

Although much of the drug discovery research in the United States is carried out by major pharmaceutical manufacturers and biotechnology companies, this research is dependent on a vast and growing background of scientific knowledge generated by diverse organizations. Universities, private institutes, governmental laboratories, and industrial research all play significant roles in developing new technologies and knowledge that provides the basis for discovery and the ultimate generation of a new product. This new knowledge may involve development of a new technology, improved scientific methodology and instrumentation, or increased understanding of the basic molecular or cell biology underlying a disease.

The major objective of research in the pharmaceutical industry is to produce safe drugs that prevent, cure, or ameliorate disease. Interim research goals that lead to this major objective are to:

- Understand the molecular basis of biological mechanisms in health and disease.
- Develop new biological testing procedures relevant to human medicine.
- Develop a quantitative understanding of the interaction of drugs with key biological systems, leading to the more rational design of drugs.
- Understand the absorption, transport, and mode of action of drugs.
- Develop drugs of low toxicity, reproducible delivery, and high specificity for a given pathological state.

This chapter will touch on the above points to illustrate how drug discovery research is used to develop new products that fulfill clinical needs.

EVOLUTION OF 20TH CENTURY PHARMACEUTICAL RESEARCH

The search for medicines to treat disease began with natural products. Up to the early part of the 20th century, pharmaceuticals derived almost entirely from natural products such as menthol, which was derived from peppermint and used for treating coughs and colds. The practice of gathering and preparing dried herbs was commonplace. Boneset tea reduced fevers, peppermint relieved an aching tooth or a colicky baby, and foxglove could revive a failing heart. Early challenges were to develop and manufacture drugs of uniform strength and quality, as the quality often varied with the raw materials or the skill of the pharmacist. Current challenges for natural products relate more to mining natural biodiversity[2] and meeting the synthetic challenges.[3]

Until World War I, most synthetic drugs and chemicals used in the United States were discovered and produced in Europe. When supplies were curtailed by the war, the impetus was provided for the establishment of an independent US chemical and pharmaceutical industry. Accordingly, production of chemicals and drugs was undertaken and was the stimulus for the development of industrial research. In the following years, the US pharmaceutical industry made major contributions through discovery and development of new drugs, and it assumed a place of leadership in the world.

Toward the mid-20th century, chemical research on the isolation, identification, and synthesis of drugs began to yield many important drug substances. During this time the synthesis and manufacture of vitamins was a major focus of companies such as Roche and Merck. Discovery and development of the sulfonamides, antibiotics, and other anti-infective agents dramatically reduced the death rates from a number of infectious diseases. Among the major drugs discovered and/or developed in the United States during this period were insulin, sulfonamides, penicillin and broad-spectrum antibiotics, cortisone and other steroid compounds, isoniazid for the treatment of tuberculosis, diuretics, and the tranquilizers. Principally through the use of drugs like isoniazid, the tuberculosis death rate between 1945 and 1978 declined from 39 per 100,000 people to 1 per 100,000 people. As a large proportion of the deaths from these diseases had occurred prior to adulthood, these drugs al-

lowed more individuals than ever before to mature and assume productive roles in society.

Since the 1980s, new classes of drugs that impact hypertension and lipidemias have emerged and made inroads to morbidity and mortality from cardiovascular disease. These are now some of the world's most efficacious, safe, and profitable drugs. Cancer medicines are moving from cytotoxic agents to cytostatic agents, but there is much to learn and do to progress this complex area of cell signaling and rampant proliferation. New challenges have emerged in areas of dementia given our improved life span and our awareness.

Of increasing importance as longevity improves and the world population grows are the classes of drugs that have marked effects on quality of life without significantly affecting longevity. For example, compounds that control pain have always been necessary. The development of reliable oral contraceptive therapy made intelligent family planning possible. Tranquilizers and other central nervous system drugs made an important contribution to the treatment of mental illness and restoration to normal activities. Newer life style drugs as we head into the 21st century are those that impact addictive behaviors such as smoking, weight control, sexual dysfunction.

PHARMACEUTICAL RESEARCH ORGANIZATIONS

The pharmaceutical and biotechnology industries are leaders among all US industries in the support of R&D. The industry finances almost all of its R&D with its own funds; no other industry spends as high a percentage of R&D funds for basic and applied research. A significant portion of every sales dollar is devoted to drug research activities (Table 10-1). For instance, in 2001, US pharmaceutical companies devoted 12–20% of their sales revenues to R&D.[4] The average R&D spending for the top 20 pharma companies was US 1.9 billion or 16.3% of sales. This expenditure in part underlies the cost of prescription drugs.[5]

Technological advances have led to an explosion of small biotechnology companies that specialize in one or more steps in the preclinical and clinical processes. Often large pharmaceutical companies contract to the smaller outside companies as a way of extending their internal resources. The trend toward outsourcing among large pharmaceuticals companies has led to the growth of many companies such as Covance that contract production of biopharmaceuticals.[6]

The academic community plays a vital role in the development of new drugs. Its role includes, but is not limited to, research on a basic understanding of disease states, development of biochemical or physiological rationale for drug targets, the initial evaluation of new drugs, consultantships with companies to use their academic and scientific expertise to guide pharmaceutical research, and certainly not least, the training of scientists. During the late 1980s and early 1990s, scientists at universities made many basic discoveries toward identification of enabling technologies, which led to the founding of many biotechnology companies. Over time, the platform technologies were used to enable the biotech technology-focused company to become a product-focused company, the true endpoint of pharmaceutical research. Examples of a platform technology to product conversion are: (1) Ligand Pharmaceuticals, founded by Dr Ron Evans of the Salk Institute, was based on the discovery of novel intracellular receptors and their role in gene transcription, focusing on the identification of agonists and antagonists primarily of steroid hormone receptors. Ligand and its sister company X-ceptor continue today to work on these important drug target families. Ligand markets four products—ONTAK, Targretin capsules, Targretin gel, and Panretin gel. Ligand's fifth and newest product, AVINZA, is a treatment for chronic, moderate-to-severe pain. In addition, Ligand's pharmaceutical partners develop products for men's and women's hormone-related diseases, osteoporosis, metabolic disorders, and cardiovascular and inflammatory diseases. (2) Vertex was founded by Dr Joshua Boger, using the structure-based design that relies on the high-resolution molecular image of the active site of a disease molecule. Vertex has several major pharmaceutical partnerships including with GlaxoSmithKline for the development and marketing of Agenerase (amprenavir) for HIV, and with Kissei for p38 MAP Kinase inhibitors for use in inflammatory disease. (3) In contrast to the target-family focus brought by Ligand and X-ceptor or the structure-based desing brought by Vertex, Pharmacopeia, founded by Drs Michael Wigler and Clark Still, a combinatorial chemistry company employs chemical and biological diversity and high-throughput screening approaches to lead and drug discovery. Pharmacopeia has a drug pipeline based on its collaborations with key pharmaceutical partners such as Schering-Plough, Bristol-Myers Squibb, Daiichi, and Berlex Laboratories. Thus, partnerships between academia and biotechnology, as well as between biotechnology and large pharma, have propelled both the genesis and evolution of biotech. It is likely that change will continue to occur at a faster pace in the smaller and more opportunistic biotech area than in its large pharma partners.

Table 10-1. Leading Pharmaceutical Companies Ranked by R&D Spending (US$ in millions) in 2001

COMPANY	R&D SPENDING	PHARMA SALES	R&D AS % OF SALES
Pfizer	4,847	25,518	19
GlaxoSmithKline	3,694	24,791	14.9
AstraZeneca	2,687	16,183	16.6
Aventis	2,574	14,879	17.3
Johnson & Johnson	2,465	14,851	16.6
Merck & Co	2,456	19,732	12.4
Eli Lilly	2,235	10,856	20.6
Pharmacia	2,085	11,970	17.4
Bristol-Myers Squibb	2,066	15,300	13.5
Novartis	2,046	11,963	17.1

From Charish P. *Scrip Magazine* 2003; (February):41.

Clinicians and clinical scientists often lead the discovery of new uses for drugs and new directions for research based on observations made in the clinical setting. Chlorpromazine was originally synthesized as an antihistamine but found to be useful as a tranquilizer. The clinical use of this compound, and of other central nervous system drugs, has resulted in a marked reduction in the number of the mentally ill needing hospitalization.

Research in the academic community has been supported to a major extent by agencies of the US government, such as the Public Health Service (PHS), the National Institutes of Health (NIH), the Center for Disease Control (CDC), and the National Science Foundation (NSF). The pharmaceutical industry also contributes financial support to academic laboratories where research of general or specific interest to the industry is conducted. Institutes established by private endowment such as the Sloan-Kettering Institute, Shriner Children's Hospitals, the Institute for the Study of Aging, and the Gates Foundation all pursue basic and applied research in many fields related to the public health. Many hospitals also maintain research clinics and/or privately or publicly endowed foundations to pursue causes and treatment of specific diseases, a related group of diseases, diseases endemic to a certain geographical area, or groups of diseases affecting a certain organ of the body. Because research does not depend on the vending of items or services, it is not immediately self-supportive and necessarily must be supported by public as well as private funds.

Interest in pharmaco-epidemiological research has prompted the development and need for review criteria in this area. The Hartzema guide[7] makes use of case-controlled and cohort studies as major methodologies in this field. Generally, the evaluation criteria for case-controlled and cohort studies address proper sample-frame definition, compatibility of cases and controls, drug-exposure validations, unintended-effect ascertainment procedures, and related considerations. Although these

can be confusing, Hartzema provides interpretation of the statistics used in reporting case-controlled and cohort studies and gives review criteria for meta-analysis, an approach to integrating the pharmaco-epidemiological literature.

THE SEARCH FOR NEW DRUGS

Until the early 20th century, most useful drugs, such as morphine, quinine, digitalis, ergot, and atropine to name a few, were derived from plant sources, and their therapeutic uses were based on serendipitous discoveries. As the science of medicinal chemistry evolved, screening of natural products has become more methodical. Screening of natural products is based on the concept that evolution favors molecular conservation. However, the future of natural products screening for drug discovery is presently limited by speed and compound diversity.

In the mid-20th century, useful drugs were derived from natural products, chemical syntheses, or combinations of both sources. The approaches used to identify lead molecules that evolved to drugs covered the spectrum between molecular diversity to rational design. Rational, or structure-based, drug design refers to a process that begins with a high-resolution map to the active site of a disease target. With an x-ray crystal structure or a nuclear magnetic resonance image, medicinal and protein chemists can engineer molecules to fit, or better fit, the active site. This approach is appealing, has been applied by biotechnology companies in a more high-throughput fashion, and has been successful in the field of human immunodeficiency virus (HIV) protease inhibitors, and many protein kinases.

Structure-based design is not currently applicable to all classes of drug targets, however. Guanine nucleotide-coupled receptors (GPCRs), which have proven to be one of the most feasible classes of drug targets, intertwine between the extra- and intracellular surface seven times. Because of their architecture in the lipid bilayer of the cell membrane, the structure of these "heptahelical receptors" has not been solved. However, using processes described below, many successful drugs have been found that work through GPCRs.

The advent of combinatorial chemistry in the 1980s and 1990s greatly impacted drug discovery. This technology refers to the generation of compounds in sets, or libraries, that are typically chemically related and made by combining sets of reactions such that the chemical steps are efficiently conducted. Combinatorial chemistry was initially applied to amino acids and nucleotides by Affymax and NeXagen, respectively. Since then, several companies predominantly Pharmacopeia and Arqule, have applied this technology to small molecules. Having large numbers of compounds allows for increases in subtle alterations in chemical relatedness as well as chemical diversity. This point is critical since the biological target is the true measure of a successful chemical interaction and attempts to use descriptors to capture chemical diversity will not discriminate in the relevant ways that biology does. This point was well made by Jurgen Drewes[8] when he wrote that "It is, however, by no means certain to what extent molecular diversity as viewed by chemists and as calculated by structural descriptors resembles diversity as 'seen' by a biological target molecule."

Collections of compounds can be designed to be "drug-like" in that they have favorable physicochemical properties in common with known drugs. These properties were first elucidated by Dr Chris Lipinski of Pfizer and have become known as the "Lipinski Rule of 5". Based on his analysis of drugs developed predominantly at Pfizer, Dr. Lipinski described key traits for a molecule to have suitability as a drug.[9] These traits are less than 5 hydrogen-bonds, less that 10 hydrogen-bond acceptors, an octanol-water partition coefficient less than 5, and a molecular weight less than 5. It is important to note, however, that approximately 25% of the drugs in the Comprehensive Medical Chemistry (CMC) data base do not follow the "Rule of Five." Typically, these exceptions are antibacterials, antineoplastics, or CNS drugs. The large percentage of exceptions would advise against overly strict adherence to these guidelines as rules. Indeed, it is rare to identify a drug in a HTS and best to think of compound collections as sources of leads that can be optimized by medicinal chemists, biologists, and pharmacologists to drugs.

The testing of compound collections in high-throughput screens (HTS) is another area where key advancement has occurred in the last 25 years of the pharmaceutical industry. HTS allows scientists to devise biochemical assays around a molecular target using new technologies. With more sensitive high-throughput technologies focused on identification of activity at a precise molecular target, the likelihood that a compound will be identified in a high-throughput screen (HTS) also increases. One of the primary impacts of combinatorial chemistry and its HTS counterpart has been the identification of leads from chemical libraries more efficiently.

Chemical Libraries and Sample Collections

Prior to the advent of combinatorial chemistry, organic chemists in the pharmaceutical industry synthesized new compounds one at a time. The collection of these compounds was not particularly diverse but led to hundreds of thousands of compounds in a company's sample collection. Combinatorial chemistry has greatly increased the efficiency of compound synthesis leading to significantly larger compound collections. For example, at present Pharmacopeia has 7 million drug-like compounds. The explosion in synthesis of chemical libraries necessitated more efficient testing of biological activity.

Initial screening of thousands of compounds is accomplished rapidly by use of in vitro enzymatic or receptor screens. Typically, several unique active lead compounds emerge, which are studied in a variety of secondary assays, either confirming or refuting the original hypothesis.

The small molecular weight of compounds in a chemical library favors the chance of their oral availability. The Lipinski guideline that is applied for oral absorption across the gastrointestinal tract is that a compound should be about 500 daltons.[9] Other guidelines are polar surface area and hydrophobicity measures.[10] Orally available drugs are highly desirable, and that is why small molecule drug discovery remains the focus of pharmaceuticals over their biological counterparts.

Whether a molecular diversity or rational design approach was followed to identify the lead molecule, drug discovery tends to proceed thereafter through an iterative process of chemical modification and biological testing. Teams of scientists improve the characteristics of their lead compound in an optimization process. If successful in building the appropriate characteristics, this process results in a drug candidate.

Natural Product Sources

In addition to compound collections, organic chemists and biochemists derive leads from natural product sources. Natural products can derive from plant and animal sources; in the latter category microbial and marine organisms often are considered separately from ordinary domestic animals. Digitalis glycosides, such as digitalis and digoxin, derive from the foxglove plant and are powerful cardiac stimulants. The poppy plant has provided opium alkaloids (morphine, codeine) used in analgesia; and the belladonna plant provided the belladonna alkaloids (atropine and scopolamine) used as parasympathetic blockers. In addition to the plant alkaloids mentioned earlier, some important natural products include antibiotics, steroid and peptide hormones, vitamins, enzymes, prostaglandins, and pheromones.

Although serendipity plays a relatively large role in the search for natural products, rational biological inputs based on deficiency syndromes, replacement therapy, or known biologi-

cal effects clearly influence the development of these drugs. Nutritionists, endocrinologists, pharmacologists, microbiologists, biochemists, and physiologists all play a vital role in understanding the underlying biological mechanisms. Antibiotics, steroids, and prostaglandins provided fertile new fields for chemical modification, leading, in all three cases, to drugs that are more useful than the parent compounds. Much research is being undertaken by the NIH and private companies on unique natural products that have anticancer properties. For example, Taxol (paclitaxel), which derives from the bark of a Pacific yew tree (*Taxus brevifolia*), was developed for the treatment of ovarian cancer by Bristol-Myers Squibb. As mentioned earlier, current challenges for natural products research relate to mining natural biodiversity[2] and meeting the synthetic challenges.[3]

FUNCTIONS OF RESEARCH SCIENTISTS

The pharmaceutical industry is an outstanding example of successful collaboration between scientists of biological and physical sciences disciplines. Chemists and other physical scientists predominantly have been responsible for synthesis, isolation, and characterization of medicinal agents. However, biological scientists have played an equally essential role in originating meaningful screening and testing models and in the overall evaluation of new agents. Qualified specialists in many fields including pharmacy, physics, statistics, chemistry, biology, engineering, pharmacology, physiology, medicine, and many others take part in the tremendous research effort in pharmaceuticals. Cooperation is a major feature of today's scientific investigations. Multidisciplinary teams are essential in industrial research requiring collaboration and effective communication as frequently a hundred or more scientists may be involved in discovering and developing a compound into a useful drug.

Some industrial research laboratories are organized according to scientific disciplines, such as departments of organic chemistry or pharmacology. Other companies may use a project-team style wherein chemists, biologists, and pharmacologists are organized into a project unit for the purpose of discovering drugs useful for a particular disease state. Frequently the latter organizational approach is focused on therapeutic areas such as diseases of the cardiovascular, immunological, or central nervous systems. Irrespective of the organizational style, problems in drug discovery and development have become so complex that a multidisciplinary approach to research nearly always is used. For the sake of simplicity, this section will outline the functions of scientists with particular backgrounds who play leading roles in pharmaceutical research; however, the reader should understand that drug development is a cooperative venture among all scientists.

Organic Chemistry

As noted previously, organic chemists synthesize new drug candidates as well as isolate and characterize natural products, such as alkaloids. In each case, there is interest in the complex relationships between chemical structure and pharmacological action. These structure-activity-relationships (SARs) are fundamental to drug discovery. Once synthesized, compounds are evaluated for numerous types of biological and pharmacological action. Observation of interesting and repeatable biological activity opens pathways for additional chemical research effort in the expansion of the series and often leads to significant new medicinal products. Determination of the pharmacological activity of a compound is an involved process with very small changes in structure frequently yielding profound changes in the pharmacological effect. Many of the currently used antispasmodics, anticonvulsants, local anesthetics, non-narcotic analgesics, chemotherapeutic agents, and hypnotics have been products of this approach.

Another research approach is to identify, isolate, and purify compounds from biologically active mixtures. The determination of the structure of a biologically active molecule provides a twofold benefit to pharmacy and medicine. It makes possible research leading to synthesis and modification of the structure. Changes in structure usually are accompanied with changes in biological activity, and occasionally vast improvement is accomplished. For example, our present knowledge of adrenal corticosteroids began with the study of the various components in an extract of the adrenal cortex. The components were characterized structurally and biological activities were assessed. Eventually, cortisone was synthesized from bile acids. Today, some synthetic analogs of cortisone are available that are superior therapeutically to the naturally occurring steroids.

A second example comes from the tetracyclines, a clinically important group of antibiotics. The first of these, 7-chlorotetracycline, was isolated in 1948 from *Streptomyces aureofaciens*. Shortly thereafter, a group of scientists isolated 5-hydroxytetracycline from *Streptomyces rimosus,* and in 1953 its structure was established. Once the chemical structure of this antibiotic was known, the way was opened for systematic variation of the basic nucleus to obtain new drugs with improved properties. Specifically, the catalytic removal of chlorine from 7-chlorotetracycline gave tetracycline itself, which proved to be superior to either of the above-mentioned antibiotics, and has replaced them to a large extent. Although tetracycline subsequently has been isolated from a Streptomyces species, this useful antibiotic is prepared more readily by the semisynthetic method.

Studies on the structure and synthesis of penicillins led to the development of the semisynthetic penicillins and later to cephalosporins and monobactams. These new compounds have made possible major improvements in antibiotic therapy. Total synthesis is made possible by knowledge of chemical structures and, in many instances, is important economically in reducing the cost of the drug. Chloramphenicol, which can be obtained from cultures of *Streptomyces venezuelae*, combats bacteria-produced typhoid dysentery and Rocky Mountain spotted fever. A commercially feasible chemical synthesis has replaced the fermentation process for production of the antibiotic.

Microbiology

Since the discovery and development of penicillin during World War II, the search for new antibiotics among the metabolic products of microorganisms has constituted a major research effort in the pharmaceutical industry. The proven clinical usefulness of antibiotics in treating many bacterial infections has fully justified this effort. Microbiologists have searched among a wide variety of fungi and bacteria looking for antibiotic substances. In this search, microorganisms from plant tissues, animal sources, the sea, many types of soil, and from many other ecological niches have been examined. More than 1000 antibiotic substances have been detected and at least partially characterized. A combination of microbiological and chemical methods is required to distinguish the new antibiotics from the host of older ones that already have been discovered.

After a culture has been found to produce a new antibiotic, microbiologists then turn their attention to the biosynthesis of the compound, seeking to improve yields in order to produce quantities of the compound for testing and evaluation. An effort also is made to understand biosynthetic pathways, improve yields further, and facilitate the biosynthetic production of the isotope-labeled antibiotic for pharmacological and toxicological evaluation.

New antibiotics are being evaluated for application in an increasing number of disease conditions. Tests are conducted to determine activity of new antibiotics against a variety of yeasts, molds, and protozoa, as well as against normal and antibiotic-resistant bacterial pathogens. The antibacterial drugs have contributed to major advances in the control of bacterial and other microbial diseases. However, impetus for continued

research is provided by problems of drug resistance, patient sensitivity, and the inability to control certain infections.

Microbiologists are concerned not only with the microorganisms that produce antibiotics, but also with the microbial pathogens that the antibiotics are expected to control. The mode of transmission of disease and the pathogenicity, virulence, and invasiveness of the infectious microorganisms are under investigation. A serious problem in drug resistance involves the transfer of drug resistance among gram-negative bacteria by means of an episome bearing one or more antibiotic resistance factors. Agents that prevent the emergence of the resistance factor, or that prevent its transfer, have been sought. Current research is being directed toward agents that enhance host resistance.

Integration of microbiological research and organic chemical research resulted in the production of a series of semisynthetic penicillins and cephalosporins. These antibiotics are chemically modified derivatives of biosynthetically produced antibiotics, which possess improved spectra of action or other advantageous chemical and biological properties.

Biochemistry, Cell Biology, and Molecular Biology

Pharmaceutical research in biochemistry, cell biology and molecular biology has exploded in the past 20 years. These areas include investigations of specific action of substances affecting cellular processes such as the mode of action of biologically active compounds. Biochemistry and cell biology are focused on understanding the underlying biochemical and cellular processes that are involved in the wonderfully complex mechanism of living things: the signal transduction processes, the energy-yielding systems, and the synthetic systems for generation of proteins, nucleic acids, and other macromolecules. Normal cellular communication and metabolic patterns are determined, and efforts are made to define the abnormal conditions that occur in various disease states. Biochemists also are involved in the isolation, purification, and characterization of small and large biologically active molecules.

The increasing sophistication of research demands that an understanding of the molecular bases of diseases emerge as a primary goal. This knowledge has strongly influenced both the methodology of testing new drugs and the choice or design of compounds to be tested. Biological targets (ie, the molecular locations where drugs act) are identified, isolated, and characterized. Usually this involves the cloning and expression of the target from human tissue as well as from various other species that may serve as model systems in drug testing. Some of the receptor systems for which drugs have been developed include those for catecholamines, opiates and steroids, and various peptide hormones such as bradykinin, angiotensin II, and endothelin. The discovery of the enkephalins, natural brain polypeptides that bind the opiate receptor, has opened new horizons in CNS pharmacology. This information has been useful in acquiring new knowledge of the interaction between drugs and their receptor sites and in understanding the requirements for specific spatial orientation of essential structural features of drugs. Drug design also makes provision for those characteristics that will assure absorption, transport to the receptor site and elimination of the therapeutic agent.

Biochemists and cell biologists develop the biomedical rationale to guide medicinal chemists in the design of drugs that are more selective for specific aspects of disease. For example, knowledge of the structure and biochemical function of coenzymes stimulated chemists to synthesize a large number of analogs of coenzymes, some of which have proven to be useful compounds in the chemotherapy of cancer.

Increasing emphasis is being placed on studies of enzymatic processes such as those related to the biosynthesis of cholesterol, fatty acids, and triglycerides; regulation and control of protein and nucleic acid synthesis; absorption processes; and biochemical mechanisms in central nervous processes and ischemia. The significance of elevated blood levels of cholesterol and certain other lipids in atherosclerosis has focused attention on drugs affecting cholesterol metabolism. Several of these drugs, such as Pravachol, Lipitor, and Crestor are now available. These drugs have had a dramatic impact in reducing serum cholesterol, and more may be expected.

Acute problems associated with atherosclerosis often are caused by thrombi. Current antithrombolytic approaches are directed at inhibiting platelet aggregation through warfarin (Coumadin); heparins; aspirin; Integrilin (eptifibatide) or ReoPro (abciximab)—inhibitors of gpIIb/IIIa; or ticlopidine. The direct inhibition of the clotting enzyme, thrombin is also a drug target. This approach involves the investigation of thrombin receptor inhibition. Enzymes that are capable of dissolving a recently formed blood clot, such as streptokinase, tissue plasminogen activator (tPA), and urokinase, have been approved and are useful under specific primary care circumstances in the treatment of stroke.

Major advances have been made in the field of gastrointestinal physiology; many new gastrointestinal polypeptide hormones have been isolated and characterized, and their primary functions have been determined. Evidence for many years pointed to the existence of gastric receptors for histamine in addition to the vascular receptors. Recently, new drugs have been designed to block specifically the H2 receptor and have been very successful in the treatment of peptic ulcer.

Molecular biological research has impacted every area of drug discovery. Molecular biology provides insight into the organism's fundamental genetic composition.

Of note to pharmaceutical research is the use of recombinant expression as a source of scarce or valuable human proteins such as growth hormone, antibodies, interferon, and insulin. This science also allows dissection of cell pathways and the generation of reagents for better assays. A major objective of research is the design of satisfactory model systems in animals, cell culture, and other innovative means to give reliable predictions of the safety and efficacy of new drugs in humans. Molecular biology has advanced the reduction in the numbers of animals used in drug research. Tests for biological activity at the molecular level are done first, after which animal tests using standardized, controlled experiments are conducted.

Virology and Immunology

The search for antiviral agents, which has depended on the development of methodology for propagation and assaying of viruses in tissue culture, has led to more precise procedures of testing compounds for antiviral activity. Tissue-culture techniques have made possible the production of large quantities of viruses for vaccine manufacture. New and improved vaccines represent a major objective of biologic research. New separation methods developed in biochemistry and physical chemistry have been applied to the isolation and purification of viruses, and have led to preparation of highly purified and concentrated vaccines. Such vaccines are more effective and produce markedly fewer side effects.

The discovery of HIV and its epidemiological implications has opened new avenues of research to develop suitable therapies. In combinations with cocktails of other drugs, HIV protease inhibitors are the main avenue of therapeutic approach for controlling HIV today. The discovery that chemokines and chemokine receptors are involved as co-receptors for HIV defined new pharmaceutical strategies toward small-molecule drug discovery.

New viral threats will surely emerge. Currently, the world is working to understand a new corona virus which has led to the SARS threat. New viruses will threaten the world due to global travel and could be used in bioterrorism. Advances in virology will add new understanding, disease controls through treatement, and eventually cures.

Recent immunological research has focused attention on a number of important diseases with an autoimmune component such as arthritis, Lupus, IBD, and multiple sclerosis. These diseases continue to be poorly treated over time. Suppression of immune phenomena or induction of immune tolerance may be of great importance. A more detailed knowledge of the molecular basis of B and T differentiation, signal transduction, and leukocyte trafficking is needed to search for drugs that either enhance or inhibit these immune responses. In addition, a clearer picture of the molecular basis of immune disease is required to improve the probability that additional drugs will be found to alleviate allergic reactions.

Immunological research also has been directed toward cancer. The existence of tumor-specific antigens in both virus- and chemical-induced tumors, as well as new evidence for host reactions to the tumor, increase the possibility of useful immunological approaches to cancer. One of the most important developments in the past decade has been the isolation and production of monoclonal antibodies. These agents can be used to identify tumor-specific antigens and thus serve as powerful in vitro diagnostic and therapeutic tools. The technique can be applied to other antigens as well. These substances are being developed as carrier systems for drugs by virtue of their ability to deliver the antibody-drug complex directly to the antigen-producing cell or tissue.

Pharmacology

The role of pharmacological research in drug discovery continues to evolve. Initially, the pharmacologist was a whole animal biologist who developed animal models of disease to the extent possible, and tested compounds in animals to measure efficacy. Classical pharmacology contributed in two major areas[11]: (1) The design and operation of animal model for detecting and evaluating the activity of compounds, and (2) Determination of the dosage, toxicity, mode of action, metabolism, and fate of a drug candidate in the body. More recently, the molecular pharmacologist is involved in the discovery and validation of new targets for drug discovery, as well as the generation of new assays, both in vitro and in vivo. Classic pharmacological methods using intact animals, whole organs, and isolated tissues tended to be used 10 years ago. These have evolved to more automated and molecular oriented methods where purified or recombinant enzyme and receptor systems are used in initial phases of discovery pharmacology, with in vivo testing following as needed. Potential drug candidates are examined early on for specificity against other unrelated molecules, a means of reducing side effects in individuals. Safety assessments are done earlier in the discovery process and allow the physician and clinical pharmacologist to work together to set the starting points for dosing drugs with minimal side effects and to monitor what form of toxicity might appear, or what conditions in the patient would contraindicate use of the drug.

The study of drug absorption, distribution, metabolism, and excretion is frequently referred to as ADME. Drug therapy requires an elaborate and thorough knowledge of the kinetics of these processes after intravenous and/or oral administration of the drug. Initial studies are often conducted using in vitro experimental systems such as Caco cell permeability to determine the likelihood of oral absorption, or stability to human liver microsomes to determine the likelihood of metabolic stability. Common next steps are to test suitable compounds in animals to determine if the experimental systems are accurate for a particular chemical series and to extend the data set to a whole organism. Experiments are often performed with radioactive forms of the drug to determine the amounts of drug and its metabolites that appear in blood, urine, and tissues. Animals can be used to determine the manner in which a living organism assimilates a drug; however, human pharmacokinetic studies are essential to determine the fate of the compound in man: Is it accumulated in specific organs, is it excreted into bile or urine, and is it metabolized?

To determine the concentration of drugs in biological fluids or tissues requires special separation techniques as well as sensitive, accurate, and precise instrumental measurements. Accurate quantitation and identification of the drug and its metabolites usually requires the use of chromatographic techniques coupled with the mass spectrometry. These sensitive LC/MS methods provide powerful data on early drug candidate molecules that influence the direction of new chemical synthesis.

Toxicology

To be certain that a new drug is safe, detailed studies are made of the effects of varying doses and prolonged administration of that drug. The pharmacologist provides acute toxicity data; however, the toxicologist then must refine the acute toxicity measurement in laboratory animals and begin subacute and chronic studies. The latter are conducted in a variety of species, at several dosage levels of the drug and over periods of time ranging from 3 months up to 30 months. During the test period, animals are observed carefully for all adverse symptoms. At the end of this period, and occasionally during its progress, the animals are killed, and their vital tissues (such as liver, heart, kidney, intestine, or brain) are removed and studied grossly and microscopically by a pathologist.

In addition to gross and microscopic pathology, biochemical and physiological responses are measured as an indication of liver function, kidney function, or endocrine function. During recent years, metabolic investigations have become more sophisticated and have been brought to bear on the comparative effects of drugs on various animals and on humans. In some instances, the metabolism of drugs or the therapeutic effects of drugs vary from species to species. Such variability can be the basis for differences in toxicity as well as differences in efficacy. For these reasons, increasing emphasis is being given to studies of comparative metabolism in man and animals to determine which laboratory animal handles the drug in a manner similar to humans. Selection of that species for extensive toxicity testing increases confidence that the toxic reactions that may occur in man will have been predicted by the animal tests.

Reproductive studies to determine the potential effects of the new drug on the reproductive processes and on subsequent generations are performed. Teratological studies are done to determine whether the new drug affects the fetus. Special toxicity tests have been designed to detect specific toxic reactions, such as nerve damage resulting in hearing loss.

Carcinogenicity trials, which are lifelong studies in animals carried out at doses approximating the maximum (tolerated) human dose, provide evidence of a new drug's ability to potentially produce human cancer. Several newer methods of toxicity are evolving in the biotech industry using gene activation methodology whereby one can evaluate if a candidate drug is transcriptionally active at a number of genes involved in liver metabolism or stress responses. These methods are likely to transform toxicological testing in the future.

In 1992 a global effort aimed at establishing uniform standards for toxicology testing of new drugs began, under the auspices of the International Conference on Harmonization (ICH). Guidelines were published on toxicology testing in late 1992 for drugs. Biologicals were not covered by those guidelines. Product-specific toxicology programs normally are required for biologicals. Toxicological studies are assuming increasing importance in the world of pharmacy and medicine. As knowledge and skills increase, and ability to measure toxic reactions improves, the greater safety and efficacy of new drugs may be ensured.

During the 1990s significant progress has been achieved in the concept of replacing animals in toxicology/safety assessment with numerous in vitro systems. These are attempts to re-

duce the number of animals used and to refine the manner in which they are used. A review of annual reports of testing in the United States, United Kingdom, and Japan showed that the number of animals used was being reduced continuously for all species.[12] Overall, multiple in vitro systems have been developed for screening and testing and for eye and skin irritation, skin sensitization, teratology, and other endpoints; and a scientific consensus has been reached on requirements and processes for validation. However, the use of these newer test systems in place of existing in vivo tests is not yet a reality. Much progress and dialog has continued in the decade of the 1990s on modification of both US and international requirements and guidelines for testing, and for defining an approval process for alternatives and innovations.

Physical Chemistry

Modern research in pharmacy and medicine is supported and expedited by instrumentation. Modern instruments make possible the rapid and accurate measurement of physical and chemical properties of molecules. Separation and characterization of molecules are sometimes possible today in a matter of hours or days; only a decade or two ago, such work often required days, weeks, or even months. Examples of specialized physicochemical and computational methods that are applicable to structural research are electron microscopy, nuclear magnetic resonance (NMR) spectroscopy, and crystallography.

NMR spectra identify chemical groups and indicate the nature of neighboring chemical groups in the molecule. Mass spectrometry permits determination of the molecular weight and empiric formula of an organic molecule, and of the major fragments of the molecule. With this information, it is often possible to deduce the entire structure of a molecule rapidly and precisely. X-ray crystallographic analysis enables the physical chemist to determine the precise position of each atom of a molecule as it exists in the crystalline form. Structures of both the drug target and a potential drug in the active site of an enzyme have been critical to the discovery of HIV protease inhibitors.

Physicochemical studies are directed at the chemical groups and stereochemical configuration of biologically active molecules; these studies can describe molecules in terms of energy and electron distributions, and approximate the influence of the chemical environment on these distributions. The spatial and electronic conformation of drugs and the changes in conformation that occur in various environments govern the absorption, transport, distribution, and reaction with the receptor site. If description of molecules in these functional terms is achieved, correlation of electronic structure with function may be possible, and the design of safer, specific, and more effective drugs on a rational basis may occur.

Information Science

The information sciences (IS) have spearheaded a great amount of data generation, assimilation, and scientific communication. IS departments are now commonplace in academic, government, and industrial settings. The amount and sophistication of chemical and biological information has led to the critical role of bench-top and desktop computers in assimilating data. Computer-assisted chemistry, computer graphics, and relational databases have added a new dimension in structure and activity relationships. The computer-based monitoring and analysis of animal studies is routine. On-line signal processing allows investigators to interact more fully with their experiments. Computer-assisted automation permits collection of more data, with a resulting increase in accuracy; sophisticated software packages are available commercially or may be developed in-house.

Communication between scientists and the literature also has evolved with the explosion of IS technologies and access to the Internet. Attention and access to the scientific and patent literature has accelerated. Formerly, the individual scientist subscribed personally to a few journals and depended on a scientific library for coverage of additional new scientific findings. With the tremendous growth of the scientific and patent literature and the emergence of interdisciplinary investigations, desktop searches are conducted by individual scientists to stay abreast of the literature. Despite increasing use is being made of various kinds of alerting services and facilities, many of them computer-based, for retrieval or retrospective search of pertinent information, personal perusal of literature remains critical and ability to initiate desktop searches are fundamental to independent scientific research.

DRUG DEVELOPMENT

Before a new drug candidate can proceed to toxicological or clinical evaluation, considerable analytical chemical development is required to lay the groundwork for subsequent quality control and stability studies. Drug standards are established and analytical methods for the bulk drug and the proposed final product are devised. Tentative chemical, physical, and biological specifications of the candidate drug are established. Simultaneously with analytical development, pharmaceutical chemists begin formulation studies toward the goal of a stable, highly acceptable product that delivers the correct amount of drug in a reproducible, effective manner. Sometimes a new drug must be modified chemically via esterification to a prodrug in order to provide a form that is pharmaceutically acceptable and effective. Accelerated and long-term stability studies are started to estimate the conditions in which the product will be stable.

If a compound has desirable activity in an experimental testing system and appears to be safe upon toxicological examination, it becomes a candidate for clinical trial. Two additional tasks must be accomplished before a clinical trial can be undertaken. First, the drug candidate must be in a suitable, stable dosage form, and the candidate compound must be available for absorption and transport to the site of action. The stabilization of a drug candidate must preclude physical or chemical change (discoloration, precipitation, or decomposition). These components, or excipients, must often meet the standards outlined in the US Pharmacopeia/National Formulary (USP/NF), European pharmacopeias, or other national compendia. Because of the many physical forms in which pharmaceuticals are presented, the research necessary is broad in scope, and not only involves the principles of physical pharmacy but also requires the application of principles from the allied fields of chemistry and biology.

The second task at this stage is to file an Investigational New Drug (IND) application with the FDA. The IND is, in fact, a document that gives a full description of the new drug, where and how it is manufactured, all quality control information and standards, stability, analytical methods, pharmacology, toxicology, documentation of efficacy in animals, and the physicians (and their qualifications) who will be doing the clinical studies with complete protocols of the proposed clinical studies.

A new drug is administered to humans for the first time by a physician or clinical pharmacologist. These Phase I studies are carried out most often in healthy male volunteers in order to study the safety and pharmacokinetics of a new drug. The first trial of a drug in humans is done with great caution and on a very limited basis.

When dosing limits have been established and are found acceptable, the drug made is available to a larger number of practicing specialists for the Phase II study, which principally is concerned with the determination of safety and efficacy in patients having the primary disease for which the drug is to be tested. The minimum effective dose, the maximum tolerated

dose, and the dose response (intermediate doses) also must be determined.

If, after Phase II, the drug still looks promising, it is distributed more widely to selected practicing physicians in the Phase III study. The purpose of the Phase III stage is to secure data from a larger number of patients on efficacy and incidence of side effects.

Finally, before the new drug can be marketed, a New Drug Application (NDA) is filed with the FDA and approval obtained. The NDA contains most of the information included in the IND, revised and updated, as well as all the results of the clinical studies proving safety and efficacy. Most all clinical, laboratory, and patient history data are processed on computers. These medical data are updated in computerized retrieval systems and are designed to provide timely information during the FDA review. These systems also provide an additional information resource for premarketing and postmarketing queries. Only after FDA approval of the NDA can distribution and marketing of the new drug begin.

Depending on the nature of the disease, and the clinical endpoints that are monitored, some drugs require long-ranging and expensive clinical trials. Some trials by necessity monitor mortality rates. Clinical trials are carefully designed with the input of statisticians to determine numbers of patients and duration of the studies. Trials cost hundreds of million of dollars (Fig 10-1) over multi-year periods, and they demand careful monitoring throughout.

Figure 10-1 also depicts the clinical research effort on a new drug represents the culmination of many years of effort by large numbers of scientists of many disciplines and skills. It is the proving ground where the intelligence, creativity, and perseverance of laboratory researchers come to fruition. Of the candidate drugs that come to clinical research, only a few survive as safe and efficacious and are added to the portfolio of therapeutics. Indeed, the 2002 reports from the Pharmaceutical Manufacturers of America (PhRMA) titled Increased Length and Complexity of the Research and Development Process[13] and Incentives to Discover New Medicines: Pharmaceutical Patents[14] revealed the following information on the drug discovery research process:

- One in 5000 compounds screened is approved for patient use
- The average cost of one new medicine is $500 million
- It takes an average of 12–15 years to develop a new medicine.
- Only 3 in 10 prescription drugs generate revenue that meet or exceed the average R&D costs
- The time that companies have to recoup their investment is decreasing due to generic competition

Together with the cost of conducting R&D (Table 10-1), the above data explains the rising costs of prescription drugs. In National Institute for Health Care Management (NIHCM) Report of "Prescription Drug Expenditures in 2001", the top 50 selling drugs are listed.[15] The top 10 of these are "blockbusters" (ie, over $1 billion in sales(Table 10-2)[15] and account for $27 bil-

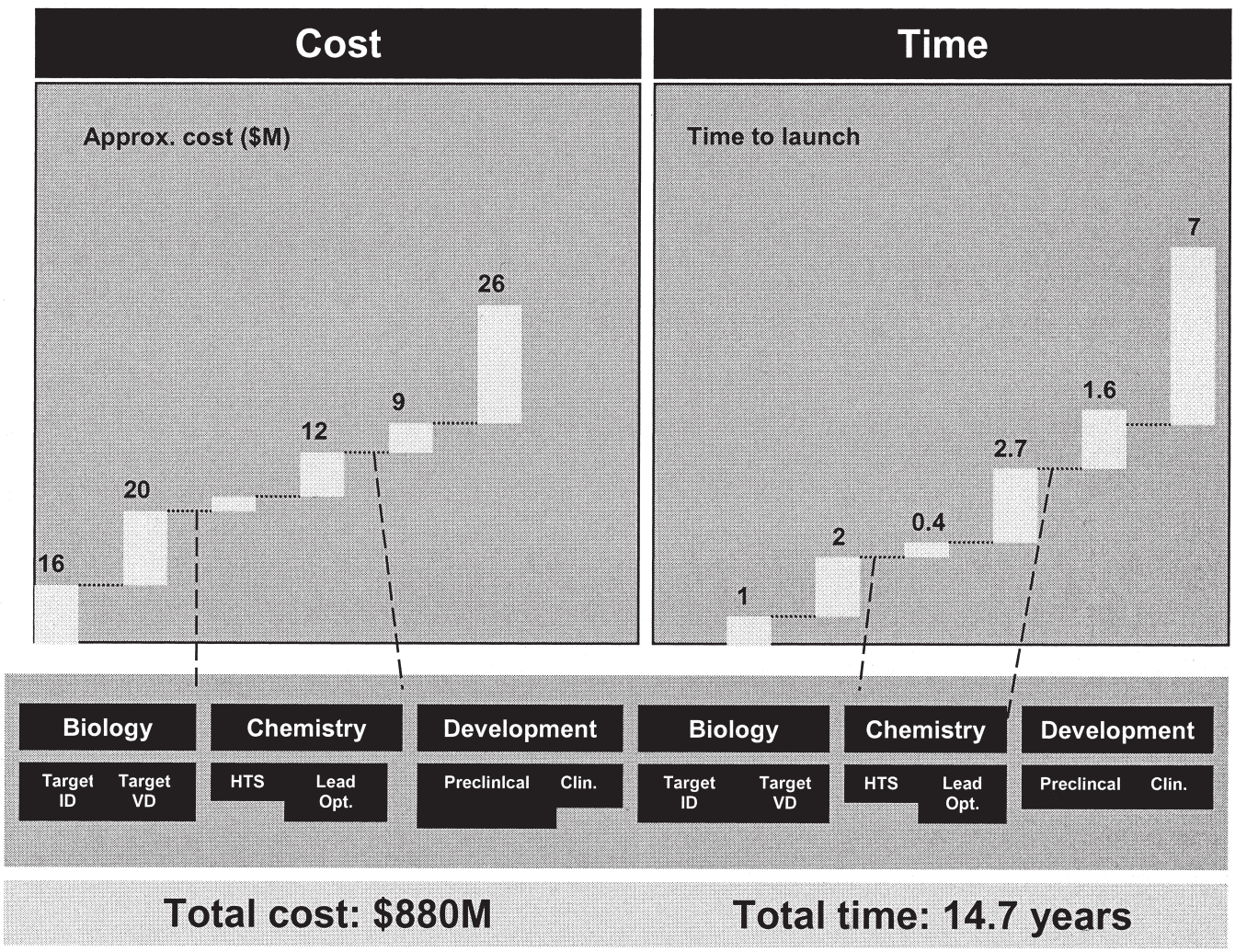

Figure 10-1. The cost and time from target identification to clinical trials. (From the Boston Consulting Group, 2001.)

Table 10-2. The Top-Selling Drugs in 2001

RANK	DRUG	COMPANY	TYPE OF DRUG	2001 SALES(BILLIONS)
1	Lipitor	Pfizer	Cholesterol reducer	4.5
2	Prilosec	AstraZeneca	Antiulcer	4.0
3	Prevacid	Takeda-Abbott Pharma	Antiulcer	3.2
4	Zocor	Merck	Cholesterol reducer	2.7
5	Celebrex	Pfizer	Anti-arthritic	2.4
6	Zoloft	Pfizer	Anti-depressant	2.2
7	Paxil	GlaxoSmithKline	Anti-depressant	2.1
8	Vioxx	Merck	Anti-arthritic	2.0
9	Prozac	Lilly	Anti-depressant	2.0
10	Augmentin	GlaxoSmithKline	Enhanced antibiotic	1.9

From the National Institute for Health Care Management Research and Educational Foundation. *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs.* Washington DC, 2002.

lion of sales in a $155 billion market, or 17% of the market). Another factor in rising costs that cannot be discounted is the view that overall research productivity and investment in innovative research for new approaches and new medicines in the large pharma tier of companies has declined.[16] This may in part be attributable to merger and acquisition (M&A) consolidation in the industry. Of the top 10 companies, all are the result of M&A (Table 10-3).[15,16]

The drug discovery research effort represents the culmination of, on average, 12 to 15 years of research and development by many scientists from multiple disciplines. It is the proving ground where the intelligence, creativity, and perseverance of researchers come to fruition. Of the candidate drugs that come to clinical research, only ~20% survive as safe and efficacious and are added to the portfolio of therapeutics. The great investment in pharmaceutical research in the early part of the 20th century that has led to advancements in pharmaceutical therapies needs to be remade in the 21st century.

Table 10-3. Top 10 Pharmaceutical Companies Worldwide in Prescription Sales (US$ in millions) for the First Six Months of 2002

RANK	COMPANY	PHARMA SALES	INCREASE (%)
1	Pfizer	13,131	9.1
2	GlaxoSmithKline	12,968	8.1
3	Merck & Co	10,053	−2.3
4	AstraZeneca	8,635	8.7
5	Johnson & Johnson	8,439	14.8
6	Aventis	7,910	9.8
7	Novartis	6,456	8.8
8	Bristol-Myers Squibb	6,408	−30.1
9	Hoffman-La Roche	5,807	1.3
10	Wyeth	5,803	11.2

From Charish P. *Scrip Magazine* 2003; (February):41.

REFERENCES

1. Spilker B, ed. *Multinational Pharmaceutical Companies: Principles and Practices*, 2nd ed. New York: Raven, 1994.
2. Tulp M, Bohlin L. *Trends Pharmacol Sci* 2002; 23:225.
3. Schreiber SL, Nicolaou KC, Davies K. *Chemistry & Biology* 2002; 9:1.
4. Charish P. *Scrip Magazine* 2003; (February):41.
5. Pharmaceutical Manufacturer's Association. 2002 Annual Report. *Why Prescription Drugs Cost So Much*. Washington, DC, 2002.
6. McCoy M. *Chem Eng News* 1998(July): 27.
7. Hartzema AG. *Ann Pharmacother* 1992; 26(1):96.
8. Drews J. *Science* 2000; 287:1960.
9. Lipinski CA. *Pharmaceutical News* 2002; 9:195.
10. Egan WJ Merz KM Jr, Baldwin JJ. *J Med Chem* 43:3867.
11. Frenkel JK. *Fed Proc* 1969; 28(1):160.
12. Gad SC. *Fundam Appl Toxicol* 1990; 15(1):8.
13. Pharmaceutical Manufacturer's Association. 2002 Report: *Increased Length and Complexity of the Research and Development Process.* Washington, DC, 2002.
14. Pharmaceutical Manufacturer's Association. 2002 Report: *Incentives to Discover New Medicines: Pharmaceutical Patents.* Washington, DC, 2002.
15. National Institute for Health Care Management Research and Educational Foundation. *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs.* Washington DC, 2002.
16. Drews J. *Drug Discovery Today* 8:411.