CHAPTER 101

The Prescription

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A *prescription* is an order for medication issued by a physician, dentist, or other properly licensed medical practitioner. Various states also have licensed other prescribers who have limited scopes of practice. For example, a veterinarian may prescribe only for animals; a podiatrist can prescribe only for conditions of the human foot; and optometrists have been given authority, in some states, to use drugs for diagnostic purposes, whereas in others they have received authority to use and prescribe drugs for disorders of the eye. In certain states, nurse practitioners, optometrists, psychologists, and even pharmacists, can issue prescriptions under protocol or with certain restrictions. Prescriptions designate a specific medication and dosage to be administered to a particular patient at a specified time. Commonly, the prescribed medication also is referred to as the *prescription* by the patient.

The prescription order is a part of the professional relationship among the prescriber, the pharmacist, and the patient. It is the pharmacist's responsibility in this relationship to provide quality pharmaceutical care that meets the medication needs of the patient. The pharmacist must be precise in the manual aspects of filling the prescription order and must provide the patient with the necessary information and guidance to assure the patient's compliance in taking the medication properly. It is also the pharmacist's responsibility to advise the prescriber of drug sensitivities the patient may have, previous adverse drug reactions (ADRs), and/or other medications that the patient may be taking that may alter the effectiveness or safety of the newly or previously prescribed medications. Pharmacists now find themselves frequently contacting physicians to suggest alternative drug products for individual patients as dictated by the formularies used by third-part prescription insurance plans. To meet these responsibilities, it is essential that the pharmacist maintains a high level of practice competence, keeps appropriate records on the health status and medication history of his/her patients and develops professional working relationships with other health professionals.

Pharmacists must establish and maintain the trust of the prescriber and the patient. Pharmaceutical care cannot optimally occur until the pharmacist has established a relationship with the patient. An important part of this relationship includes maintaining confidentiality. The medication being taken by a patient and the nature of his illness is a private matter that must be respected. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) mandated the development of standards and requirements to control the flow of health information throughout the healthcare system. The act, which went into effect in April 2003, places additional restrictions and safeguards on how medical information can be utilized and disclosed. Pharmacists must now take special care to avoid discussing patient information where others not directly involved in the care of the patient can overhear the conversation and must obtain written permission from the patient to disclose certain types of medical information.

There are two broad legal classifications of medications: those that can be obtained only by prescription and those that may be purchased without a prescription. The latter are termed *nonprescription* drugs or *over-the-counter* (OTC) drugs. Medications that may be dispensed legally only on prescription are referred to as *prescription* drugs or *legend* drugs. The latter term refers to the *legend* that must appear on the label of the product as it is provided to the pharmacist by the manufacturer—*Caution: Federal Law Prohibits Dispensing Without Prescription*. Occasionally, physicians may issue prescriptions for nonlegend drugs that they desire the patient to receive.

Prescriptions may be written by the prescriber and given to the patient for presentation at the pharmacy, may be telephoned or communicated directly to the pharmacist by means of a fax machine, or may be electronically sent from a physician's computer to a pharmacist's computer. Prescription orders received verbally should be reduced to proper written form immediately or entered directly into a prescription computer by the pharmacist.

In the future, electronic prescribing may become the dominate means by which pharmacists receive prescriptions. In an attempt to minimize medication errors and enforce the use of the institution's drug formulary, numerous large hospitals now require physicians to enter orders directly into at a computer terminal or through a PDA. These orders are screened for potential errors and sent directly to the pharmacy for processing. This practice has been implemented on a much smaller scale in retail pharmacies in some geographic areas. As systems that interface between physician offices and pharmacies are further developed and refined, the practice of electronic prescribing will likely to become widespread.

Potential advantages associated with electronic prescribing include: (1) reducing or eliminating the errors associated with illegible handwriting; (2) prescribers can receive on-screen prompts for drug-specific dosing information; (3) information from the patient's medical record can be linked with information from the patient's prescription records; (4) prescribers would be notified if a drug product is covered by the patient's insurance plan when the order is being generated rather than when it is presented at the pharmacy; (5) refill requests can be expedited; and (6) computers can facilitate data exchange between the physician and pharmacist allowing individuals to better manage their time and facilitate interactions with their patients.[1]

FORM OF THE PRESCRIPTION ORDER

Prescriptions usually are written on printed forms that contain blank spaces for the required information. These forms are called *prescription blanks* and are supplied in the form of a pad. Most prescription blanks are imprinted with the name, address, telephone number, and other pertinent information of the physician or his or her practice site (eg, hospital or clinic) (Fig 101-1). The printed information clarifies the prescriber's name when it is signed illegibly, and his address and telephone number facilitates additional professional communication, as may be required.

Certain health-care institutions or systems, such as the Veterans Health Administration, provide prescription forms for use only in their facilities; these forms are printed on security paper and sequentially numbered. The front of the Veterans Administration (VA) form, printed in gray tone, has checkoff blocks to indicate patient status (eg, inpatient) as well as checkoff blocks to override the general authority to allow drug substitution and require the product name, strength, and quantity to be placed on the label. The back of the form, in white, which must be completed before dispensing an original or refill prescription, provides space to enter the manufacturer and control number of the product, the date dispensed or mailed, the signature or initials of the dispensing pharmacist, and any calculations or written notations.

Prescription blanks that are used by the pharmacist in his/her transposition of verbally received prescriptions commonly are imprinted with the name, address, and telephone number of the pharmacy. These blanks also may be used by physicians to write prescriptions when visiting the pharmacy. Specially imprinted prescription blanks are not required legally for prescriptions; any paper or other writing material may be used. Most states allow prescription orders to be faxed to a pharmacy *directly from* the prescriber, and even allow direct computer transmission of a prescription order from the prescriber to the pharmacy's computer.

Some states require prescription blanks for controlled substances (especially *Schedule II*) to include certain security features. These include triplicate prescription forms, sequentially numbered forms, forms with special watermarks that can only be observed at a 45° angle, and forms that reveal a repetitive *void* pattern when the prescription is photocopied. Check-off boxes with specified quantities also may appear on the forms to confirm the actual number of dosage units authorized by the prescriber. For the purpose of study, the component parts of a prescription are described as follows and are identified in Figure 101-1.

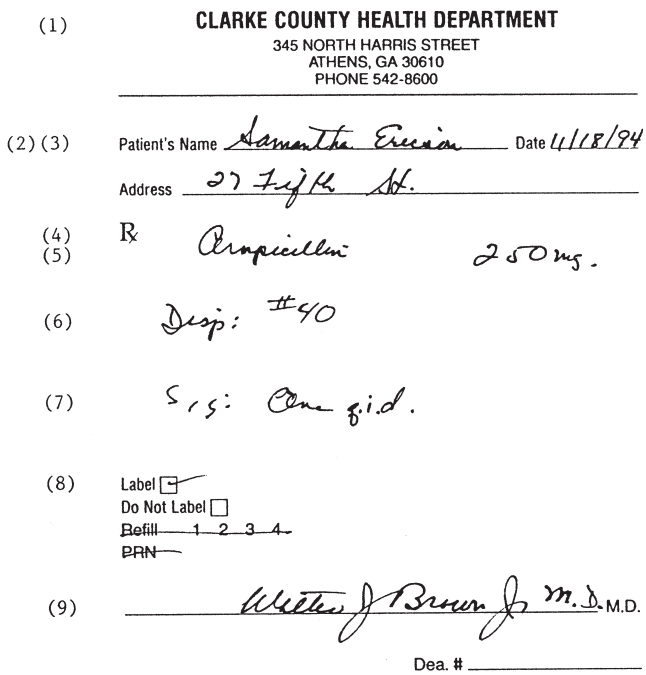

Figure 101-1. Example of a physician's prescription showing typical form and content.

1. Prescribers office information
2. Patient information
3. Date
4. ℞ symbol or *superscription*
5. Medication prescribed or *inscription*
6. Dispensing directions to pharmacist or *subscription*
7. Directions for patient or *signa* (to be placed on label)
8. Refill, special labeling, and/or other instructions
9. Prescriber's signature and license or Drug Enforcement Agency (DEA) number as required

In practice, some of the above information (such as the patient's address) may be absent when the prescription is received by the pharmacist. In these instances the pharmacist obtains the necessary information from the patient or physician, as is required.

PATIENT INFORMATION—The full name and address of the patient are necessary on the prescription for identification purposes. Names and addresses written illegibly should be clarified on acceptance of the prescription. Incorrect spelling of a patient's name on a prescription label might cause concern in the patient's mind as to the correctness of the medication and possibly would hamper the desired professional relationship between the pharmacist and patient.

Federal law requires that the full names and addresses of the prescriber and the patient be included on prescriptions for certain controlled substances. The physician's DEA registration number also is required on the prescription. Controlled substances are drugs that, because of their potential for abuse, are controlled under special regulations by the federal government. The address of the patient is useful for identification purposes as well as for delivery of medication to the patient's home.

Some prescription blanks used by medical specialists, particularly pediatricians, include a space for insertion of the patient's age, weight, or body surface area. This information is placed on the prescription by the physician when medication dosage is an important function of age or weight. This information assists the pharmacist in interpreting the prescription, checking the dose prescribed for the child and is particularly useful when a child has the same name as one of his/her parents.

DATE—Prescriptions are dated at the time they are written and also when they are received and filled in the pharmacy. The date is important in establishing the medication record of the patient. An unusual lapse of time between the date a prescription was written and the date it is brought to the pharmacy may be questioned by a pharmacist to determine if the intent of the physician and the needs of the patient can still be met. The date prescribed is also important to a pharmacist in filling prescriptions for controlled substances. The *Drug Abuse Control Amendments* specify that no prescription order for controlled substances may be dispensed or renewed more than 6 months after the date prescribed.

℞ SYMBOL OR SUPERSCRIPTION—The ℞ symbol generally is understood to be a contraction of the Latin verb *recipe*, meaning *take thou* or *you take*. Some historians believe this symbol originated from the sign of Jupiter, ♃, employed by the ancients in requesting aid in healing. Gradual distortion through the years has led to the symbol currently used. Today, the symbol is representative of both the prescription and the pharmacy itself.

MEDICATION PRESCRIBED OR INSCRIPTION—This is the body or principal part of the prescription order. It contains the names, dosages, and quantities of the prescribed ingredients.

Today, the majority of prescriptions are written for medications already prepared or prefabricated into dosage forms by industrial manufacturers. The medications may be prescribed

under their trademarked or manufacturer's proprietary name or by their nonproprietary or *generic* names.

Pharmacists are required to dispense the trademarked product when prescribed, unless substitution of an equivalent product is permitted by the prescribing physician or by state law. Most states have generic substitution laws that mandate the use of a generically equivalent product for certain patients. In some instances, the patient also must consent to the drug substitution. Some states require the prescriber to write specific instructions or sign a specific line on the prescription to allow or disallow product substitution. Many health maintenance organizations and prescription benefit plans have strict formularies for which only certain drug products within a therapeutic class may be dispensed. Thus, the pharmacists may be directed by the prescription plan to dispense a similar but different drug product than was prescribed for the patient.

Prescription orders requiring the pharmacist to mix ingredients are termed *compounded* prescriptions. Prescriptions requiring compounding contain the names and quantities of each ingredient required. The names of the ingredients generally are written using the nonproprietary names of the materials, although occasionally proprietary names may be employed. Quantities of ingredients to be used may be indicated in the metric or apothecary system of weights and measures; however, the use of the apothecary system is dramatically diminishing to becoming nonexistent. These systems are described in Chapter 11.

In the use of the metric system, the decimal is often replaced by a vertical line that may be imprinted on the prescription blank or drawn by the prescriber. The symbols *g* or *mL* often are eliminated, as it is understood that solids are dispensed by weight (in grams) and liquids by volume (in milliliters).

DISPENSING DIRECTIONS TO PHARMACIST OR SUBSCRIPTION—This part of the prescription consists of directions to the pharmacist for the preparation of the prescription. With diminished frequency of compounded prescriptions, such directions are likewise less frequent. In a majority of prescriptions, the subscription serves merely to designate the dosage form (eg, tablets, capsules, inhaler, transdermal patch) and the number of dosage units to be supplied. Examples of prescription directions to the pharmacist include the following among others:

M ft caps dtd no xxiv (Mix and make capsules. Dispense 24 such doses).
Ft supp No xii (Make 12 suppositories).
M ft ung (Mix and make an ointment).
Disp tabs No c (Dispense 100 tablets).

DIRECTIONS FOR PATIENT OR SIGNATURA—The prescriber indicates the directions for the patient's use of the medication in the portion of the prescription termed the *Signatura*. The word, usually abbreviated *Signa* or *Sig* means *mark thou*. The directions in the signa commonly are written using abbreviated forms of English or Latin terms or a combination of each. Examples include:

Tabs ii q4h (Take two tablets every 4 hours).
Caps i 4xd pc & hs (Take one capsule four times a day after meals and at bedtime).
Instill gtts ii od (Instill two drops into the right eye).

The directions are transcribed by the pharmacist onto the prescription label of the container of dispensed medication. A list of some prescription abbreviations is presented in Table 101-1.

It is advisable and required by law in most states for the pharmacist to reinforce the directions to the patient when dispensing the medication because the patient may be uncertain or confused as to the proper method of use. Some pharmacists and physicians provide their patients with written directions outlining the proper use of the medication prescribed. Frequently, these directions include the best time to take the medication, the importance of adhering to the prescribed dosage schedule, what to do if a dose is missed, the permitted use of the medication with respect to food, drink, and/or other medications the patient may be taking, as well as information about the drug itself. As a requirement of law, certain manufacturers have prepared patient package inserts (PPIs) for specific products for issuance to patients (Fig 101-2). These present to the patient information regarding the usefulness of the medication as well as its side effects and potential hazards. Other PPIs are available to pharmacists for use in their practices from professional and commercial sources. For example, The United States Pharmacopeial Convention provides patient education leaflets containing supplementary printed instructions on many drugs and drug categories to physicians, pharmacists, and other health professionals for distribution to patients (Fig 101-3). The information is also available on computer software, allowing leaflets to be printed in the pharmacy as needed and with a compatible computer and standard line printer. Similar computer software programs are available from various other sources, designed to generate personalized patient-counseling information for use by the pharmacist in patient education.[2] Numerous sources of information for consumers are now available via the Internet. Pharmacists can refer patients to these web sites but may want to caution patients that all of the information on these sites may not apply to their individual situation.

In addition to instructions to the patient, most prescribers desire and laws dictate that the name and strength of the prescribed drug be included on the label of the dispensed medication. Prescribers indicate this to the pharmacist by including the name and strength of the drug in the signa or by simply writing in the word *label* in the signa. Some prescription blanks have the word *label* printed for circling or checking by the prescribing physician (see Fig 101-1). The advantages to having the name and strength of the drug identified on the prescription label include the facilitation of communication among the patient and the pharmacist and the physician and the rapid identification of the medication in times of accidental or purposeful overdose. When a generic drug product is dispensed, it is customary to include the manufacture of the product on the label as well.

The date after which the medication will be subpotent (expiration date) may be placed on the label based on information included on the original manufacturer's package. This precaution is important for certain drugs that rapidly deteriorate and lose their potency. For example, many oral liquid formulations of antibiotics remain stable for only a period of 14 days under refrigeration, and one-half that time when nonrefrigerated after their preparation by the pharmacist. Certain ophthalmologic preparations and most parenteral dosage forms have relatively short shelf lives once removed from refrigeration and thus containers must include the expiration date.

Physicians generally do not specify that expiration dates be noted on the label because they recognize that the pharmacist provides this information when dispensing such preparations. Statements on auxiliary labels such as *do not use after __ days* or *discard after __ days* serve this purpose. Some state laws require that pharmacists place the expiration date on the label of all medications dispensed, even those with no special stability problems.

SPECIAL LABELING AND OTHER INSTRUCTIONS—The number of authorized refills should be indicated on each prescription by the prescriber. In the event that no refill information is provided, it is understood that no refills have been authorized; however, it is advised that the label state such to avoid confusion. Most prescription blanks include a section where this information may be indicated (see Fig 101-1). Most states limit refills on a prescription to one year after the prescription was written originally. When a prescriber indicates that a prescription can be refilled *prn* "as needed," the pharmacist should refill it only with a frequency consistent with the directions. No refills are permitted for *Schedule II* controlled substances.

HOSPITAL MEDICATION ORDERS

Medication orders for inpatients in hospitals and other institutions are written by the physician on forms called the *Physi-*

Table 101-1. Commonly Used Abbreviations in Prescriptions and Medication Orders

ABBREVIATION	MEANING	ABBREVIATION	MEANING
aa	of each	MS	morphine sulfate
abd	abdomen	MTX	methotrexate
ac	before meals	MVI	multivitamin
ad	To, up to	m	Mix
a.d.	Right ear	N&V	Nausea and vomiting
ad lib	At pleasure, freely	non rep/NR	Do not repeat
AM	morning	noct	At night
amp	Ampul of medication	NS	normal saline
aq	Water	NTG	nitroglycerin
a.s.	left ear	OA	osteoarthritis
ASA	aspirin	OCD	obsessive compulsive disorder
ATC	Around the clock	OJ	orange juice
au	each ear	O2	oxygen
BCP	birth control pill	ou	Each eye
bid	Twice a day	od	Right eye
BM	Bowel movement	os	Left eye
BP	Blood pressure	P	pulse
BPH	benign prostatic hypertrophy	pc	After eating
BS	Blood sugar	PEFR	peak expiratory flow rate
BSA	Body surface area	pm	evening
c	with	po	by mouth
Ca	calcium	postop	after surgery
CAD	coronary artery disease	pr	rectally
caps	Capsule	prn	when necessary
cc	cubic centimeter [milliliter]	pulv	A powder
CHF	congestive heart failure	PVCs	premature ventricular contractions
COPD	chronic obstructive pulmonary disease	PVD	peripheral vascular disease
CP	chest pain	q	every
CRNP	Certified Registered Nurse Practitioner	qd	every day
dil	dilute	qid	four times daily
dtd	Let such doses be given	qod	every other day
DC	discontinue medication	qs	as much as is sufficient
DDS	Doctor of Dental Surgery	qs ad	a sufficient quantity to (prepare)
DMD	Doctor of Medical Dentistry	qh	every hour
disp	dispense	RA	rheumatoid arthritis
div	divide	RN	Registered Nurse
DJD	degenerative joint disease	Rect	Use rectally
DM	diabetes mellitus	s	without
DO	Doctor of Osteopathy	ss	One-half
DW	distilled water	SC	subcutaneous injection
Dx	diagnosis	Sig	write on label
elix	elixir	SL	sublingual
EtOH	ethanol	SLE	systemic lupus erythematosus
Ft	Make, let it be made	SOB	shortness of breath
g or gm	gram	sol	Solution
GERD	gastroesophageal reflux disease	SQ or SubQ	subcutaneous injection
GI	Gastrointestinal	sq m, m^2	square meter
GU	Genitourinary	stat	immediately
gr	Grain	supp	Suppository
gtt	A drop	Susp	Suspension
HA	headache	Sx	symptom
HBP	High blood pressure	syr	Syrup
HCTZ	hydrochlorothiazide	T	temperature
HR	heart rate	tab	tablet
HRT	hormone replacement therapy	TB	tuberculosis
hs	at bedtime	TCN	tetracycline
HTN	Hypertension	TED	thromboembolic disease
inj	An injection	TIA	transient ischemic attack
IV	Intravenous injection	tid	three times a day
IM	Intramuscular injection	tiw	three times a week
ID	Intradermal injection	tbsp	tablespoon
IU	international units	TMP-SMX	trimethoprim-sulfamethoxazole
JRA	juvenile rheumatoid arthritis	tsp	teaspoon
KCL	potassium chloride	top	(Use) topically
kg	kilogram	Tx	treatment
L	liter	U	unit
mcg	microgram	UA	uric acid, urinalysis
MD	Doctor of Medicine	UC	ulcerative colitis
mEq	milliequivalent	ud	as directed
mg	milligram	ung	ointment
mg/kg	milligrams/kilogram	URI	upper respiratory infection
mg/m^2	milligrams/square meter	ut dict	as directed
mL	milliliter	UTI	urinary tract infection
mOsmol	milliosmole	WA	while awake
m or min	Minimum	wk	week
MOM	Milk of Magnesia		

Figure 101-2. Example of manufacturers' patient package inserts intended to enhance patient understanding of the medication prescribed.

cian's Order Sheet. The type of form used varies between institutions and even within the institution, depending on the unit rendering the care. Because these orders are written in a controlled environment, many of the requirements and restrictions placed on prescription orders for outpatients do not apply in the institutional setting. Institutional pharmacy practice is discussed in Chapter 127.

PROCESSING THE PRESCRIPTION ORDER

The manner in which a pharmacist processes a prescription order is important in fulfilling his/her professional responsibilities and can enhance his/her image with the physician and the patient. Proper procedures are given below for receiving, reading and checking, numbering and dating, labeling, preparing, packaging, rechecking, delivering and counseling, recording and filing, and pricing the prescriptions.

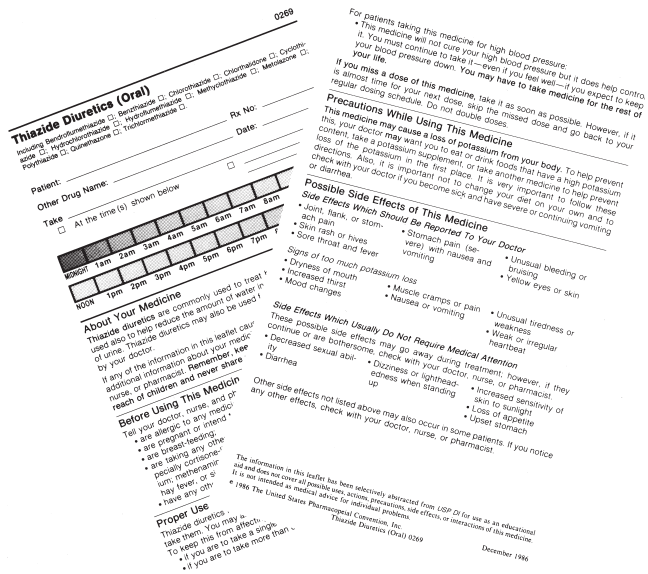

Figure 101-3. Examples of USP Patient Education Leaflets. The information also is available on computer disk for use in the pharmacy (courtesy, The USPC).

RECEIVING THE PRESCRIPTION—It is desirable that the patient present the prescription order directly to the pharmacist because this enhances the pharmacist–patient relationship and facilitates the gathering of essential disease and drug information from the patient. This is critical for the provision of quality pharmaceutical care. In situations in which this is not practical, the individual receiving the prescription should be trained to accept it in a professional manner and obtain the correct name, address, and other pertinent patient information. Patients having a prescription filled for the first time at a pharmacy may be asked to complete a brief health and medication history to establish a database in the pharmacy's computer for the patient. It is important to determine if the patient's medications are provided through insurance coverage and whether the patient wishes to wait, call back, or have the medication delivered. If the pharmacist is unable to receive the prescription order personally, he/she should be available to provide an estimate of the length of time required for filling the prescription and to price it if requested by the patient. Many pharmacists make it a practice to price prescriptions before dispensing, especially in the case of unusually expensive medication, to avoid subsequent questions concerning the charge.

READING AND CHECKING THE PRESCRIPTION—The prescription order first should be read completely and carefully. There should be no doubt as to the ingredients or quantities prescribed. From the pharmacy's prescription computer (or other record of the patient's medication history), the pharmacist should determine the compatibility of the newly prescribed medication with other drugs being taken by the patient and also consider if any drug–food or drug-disease interactions may exist. Most prescription computer software programs identify possible drug–drug interactions. However, these software programs do not always identify the potential significance of the drug–drug interaction. This is the point at which the pharmacist must use information specific to this patient to determine the significance of the interaction and to determine if the prescriber should be contacted. In addition, references may be used for this purpose, such as *USP Dispensing Information (USP DI)* or *Drug Interaction Facts*. Should the probability or likelihood of a drug interaction exist, the pharmacist should first consider alternative drug products that might be used and then consult with the prescriber to determine best therapeutic alternative for the patient and be prepared to make recommendations. The same would apply when a medication is prescribed for a patient who has a known drug allergy or sensitivity to the prescribed drug or to other drugs of the same chemical class. If something is illegible or if it appears that an error has been made, the pharmacist should consult another pharmacist or the prescriber. *A pharmacist should never guess at the meaning of an indistinct word or unrecognized abbreviation.* Unfamiliar or unclear abbreviations represent a source of error in interpreting and dispensing prescriptions.[3] No *official* or standard list of prescription abbreviations exists. Many of those in use are derived from the Latin and generally are recognized (see Table 101-1). However, many others may be simply shorthand creations of the individual prescriber.

Common prescriber abbreviations for drug names include *Pb* for phenobarbital, *HCTZ* for hydrochorothiazide, *MTX* for methotrexate, and *ASA* for aspirin. Diseases and conditions also are commonly abbreviated (eg, *CHF* for congestive heart failure, *BPH* for benign prostatic hypertrophy, *URI* for upper respiratory tract infection, *HBP* for high blood pressure). Other abbreviations, such as *ATC* for around-the-clock, *WA* for while awake, and *BM* for bowel movement, also are used in prescription writing.

The use of Latin words, phrases, and abbreviations in prescriptions is a carryover from the time that Latin was considered the international language of medicine. Latin was used extensively in writing prescription orders until the early part of

the 20th century. Although its use gradually has diminished, it is still used widely, in the form of abbreviations, in the subscription and signa portions of prescriptions.

Pharmacists are frequently confronted in their interpretation of the prescription order with the names of drugs that look alike or sound alike. These similar names are a potential source for errors. Knowledge of the patient's medical problems and diagnoses can often provide the pharmacist with insight into which of the look-alike or sound-alike drugs is intended for the patient. There have been numerous cases in which the brand name of a drug product has been changed after several months on the market subsequent to confusion with other marketed drugs with similar brand names. Examples of drugs with similar names are listed in Table 101-2.

The pharmacist must take great care and use his/her broad knowledge of drug products to prevent dispensing errors. A telephone call to the physician, made so as not to alarm the patient, serves to verify the meaning of a prescription that is unclear and at the same time bolster the professional reputation of the pharmacist as a careful practitioner and valuable member of the health team.

Omissions, such as the failure to specify the desired strength of a medication or its dosage form, must be corrected. In such a case, the pharmacist should never elect to dispense the usual dose or dosage form but instead should consult the prescriber. To detect such omissions and provide the physician with the necessary information, the pharmacist must be familiar with available strengths and dosage forms of prefabricated drug products. Knowledge of available dosage forms also enables the pharmacist to suggest a more appropriate or easy-to-use method of drug delivery for a particular patient.

The amount and frequency of a dose must be noted carefully and checked. In determining the safety of the dose of a medicinal agent, the age, weight, and condition of the patient (eg, liver function, kidney function), dosage form prescribed, possible influence of other concomitant drugs being taken, and the frequency of administration all must be considered. Several guides are available to the pharmacist in evaluating the safety of a prescribed dose. The *USP DI* provides usual doses and dosage ranges for many drugs in use. Manufacturers' catalogs, file cards, and package inserts provide dosage information on their products. References such as *Physicians' Desk Reference, AMA Drug Evaluations, American Hospital Formulary Service Drug Information, Drug Facts and Comparisons, Handbook of Clinical Drug Data, Pharmacist's Drug Handbook, and Pediatric Dosage Handbook* are useful general sources of such information. Some computer software programs now can check doses for pediatric patients when the child's weight is entered. In the case of a suspected error in dose, appropriate references should be checked prior to consulting the physician.

Measurement of liquid medication may lead to dosage variation caused by differences in the capacity of household spoons and interpretation of which measuring device to use by the patient. The problems associated with teaspoonful dosage have long been recognized. A standard teaspoon has been established by the American National Standards Institute as containing 4.93 ± 0.24 mL. For practical purposes, the standard teaspoonful is considered to be equivalent to 5 mL, although different household teaspoons vary widely in capacity. Thus, 1 fl oz (29.57 mL) of a medicated liquid is considered to provide approximately six standard teaspoonful doses.

Table 101-2. Examples of Look-Alike and/or Sound-Alike Drug Names

Adriamycin	Achromycin	Methotrexate	Metolazone
Albuterol	Atenolol	Myleran	Mylicon
Alupent	Atrovent	Nicardipine	Nifedipine
Amikin	Amicar	Orinase	Ornade
Apresoline	Priscoline	Pediapred	PediaProfen
Brevital	Bretylol	Penicillin	Penicillamine
Carafate	Cafergot	Percodan	Percocet
Cefoxitin	Cefotaxime	Phenobarbital	Pentobarbital
Chlorpromazine	Chlorpropamide	Physostigmine	Pyridostigmin
Clonidine	Klonopin	Pitressin	Pitocin
Cyclosporine	Cycloserine	Prazepam	Prazosin
Digitoxin	Digoxin	Prednisolone	Prednisone
Dilantin	Dilaudid	Prednisone	Primidone
Diphenhydramine	Diphenhydrinate	Prilosec	Prozac
Dopamine	Dobutamine	Quinamm	Quinidine
Doriden	Doxidan	Quinidine	Clonidine
Doxirubicin	Daunorubicin	Quinine	Quinidine
Dyazide	Diazoxide	Ramapril	Enalapril
Enalapril	Anafranil	Regroton	Hygroton
Enduronyl	Inderal	Ritodrine	Ranitidine
Esimil	Estinyl	Salsalate	Sucralfate
Florinal	Florinef	Sandimmune	Sandostatin
Florinal	Fioricet	Stelazine	Selegiline
Fluocinolone	Fluocinonide	Tegretol	Tegopen
Folic Acid	Folinic Acid	Tenex	Xanax
Glipizide	Glyburide	Timolol	Atenolol
Haldol	Halcion	Timolol	Tylenol
Hydralazine	Hydroxyzine	Tolazamide	Tolbutamide
Hydroxyzine	Hydroxyurea	Tylenol	Tylox
Imferon	Interferon	Vanceril	Vancenase
Inderal	Isordil	Vicodin	Hycodan
Indocin	Lincocin	Vinblastine	Vincristine
Isomil	Isordil	Vistaril	Restoril
Lanoxin	Xanax	Wellbutrin	Welicovorin
Lithobid	Lithotabs	Xanax	Zantac
Lorazepam	Alprazolam	Zarontin	Zaroxolyn
Mesantoin	Mestinon	Zofran	Zantac
Metaproterenol	Metoprolol	Zovirax	Zostrix
		Zyloprim	ZORprin

To avoid errors in liquid dosing, pharmacists often dispense calibrated measuring devices with liquid medication. Some of these devices are shown in Figures 101-4 and 101-5.

NUMBERING AND DATING—It is a legal requirement to number the prescription order and to place the same number on the label. This serves to identify the bottle or package and to connect it with the original order for reference or to renew the prescription. Consecutive numbers are assigned by prescription computers or manually by use of numbering machines.

Dating of the prescription on the date filled is also a legal requirement. This information is important in determining the appropriate refill frequency, patient compliance, and as an alternate means of locating the prescription order should the prescription number be lost by the patient. The prescription computer may be employed for these purposes.

LABELING—The prescription label may be typewritten or prepared by computer, using the information entered by the pharmacist or pharmacy assistant. Figure 101-6 demonstrates a computer-prepared prescription, including the label, patient-counseling information, and receipt. The type and quality of computer printer used by a pharmacy can have a major effect on the readability of a prescription label. Newer laser printers produce a label with a type font and boldness that is much easier for most patients to read.

A prescription should have an aesthetic and professional-appearing label. If the label and the container are not neat and professional in appearance, the patient may conclude that the prescription medication itself was also prepared in a careless manner. This may result in a loss of confidence in the pharmacist or pharmacy.

The name and address of the pharmacy are legally required to appear on the label; the telephone number is also commonly included. The prescription number, prescriber's name, patient's name, directions for use (in easy to understand language for the patient), and the date of dispensing also are legally required; and the name and strength of the medication are also frequently included.

Some state laws require that the name or initials of the pharmacist dispensing the medication appear on the label. Some pharmacists indicate the refill or renewal status of the prescription on the primary label or use an auxiliary label to indicate this information. Occasionally, the manufacturer's lot number for the medication dispensed is entered on the label to aid in rapid identification of medication that might be recalled.

Labeling requirements for controlled substances are presented in Chapter 111. Auxiliary labels are used to emphasize important aspects of the dispensed medication, including its proper use, handling, storage, refill status, and necessary warnings or precautions. A *shake-well* label is indicated for a prescription containing ingredients that may physically separate on standing (eg, suspensions, lotions, and emulsions). The use of labels such as *For the Ear, For the Eye*, and *External Use* is recommended because of the added safety these offer, even when the primary directions indicate their proper use. Other precautionary labels may be used to warn that the medication should not be swallowed, used internally or should be kept out of reach of children and others for whom it is not intended.

Figure 101-4. Examples of medicinal spoons of various capacities, calibrated medicine droppers, an oral medication tube, and a disposable medication cup.[4]

Figure 101-5. An oral liquid dispenser for the accurate delivery of small doses of liquid medication to infants (courtesy, Baxa).

Auxiliary labels are available in various colors to give them special prominence. They should be placed in a conspicuous spot on the prescription container. Examples of some auxiliary labels in English and Spanish are shown in Figure 101-7.

In certain circumstances it may be desirable for the pharmacist to supplement the instructions or directions of the prescriber. Some states have passed regulations that recognize that a need may exist for the pharmacist to add to the directions of the prescriber to either clarify or expand the prescriber's instructions. Such regulations indicate that when, in the judgment of the pharmacist, directions to the patient are necessary, either for clarification or for insurance of proper administration of the medication, the pharmacist may add such directions or cautionary messages to those indicated by the prescriber on the original prescription. For example, a pharmacist might advise that a medication be taken with a large volume of water or that certain foods or activities are to be avoided when taking the medication.

The federal government has required that patient product information be provided with the dispensing of certain drugs to ensure that the patient is apprised of proper use of the medication, its benefits and risks, and the signs of adverse reaction. Examples of these are shown in Figure 101-2. Other types of patient information sheets have been noted in this chapter and may be used by pharmacists in their practice. Virtual all prescription computer systems are programmed to provide supplemental instructions to patients (see Fig 101-6). These printed instructions may be used by the pharmacist to reinforce his or her personal efforts in patient counseling. Pharmacists may need to assist some patients interpret the information contained in these product information sheets. This is especially the case when dealing with poorly educated patients, patients who have impaired cognitive function, or when dispensing a drug product that has many potential indications.

PREPARING THE PRESCRIPTION—After reading and checking the prescription order, the pharmacist should decide on the exact procedure to be followed in dispensing or com-

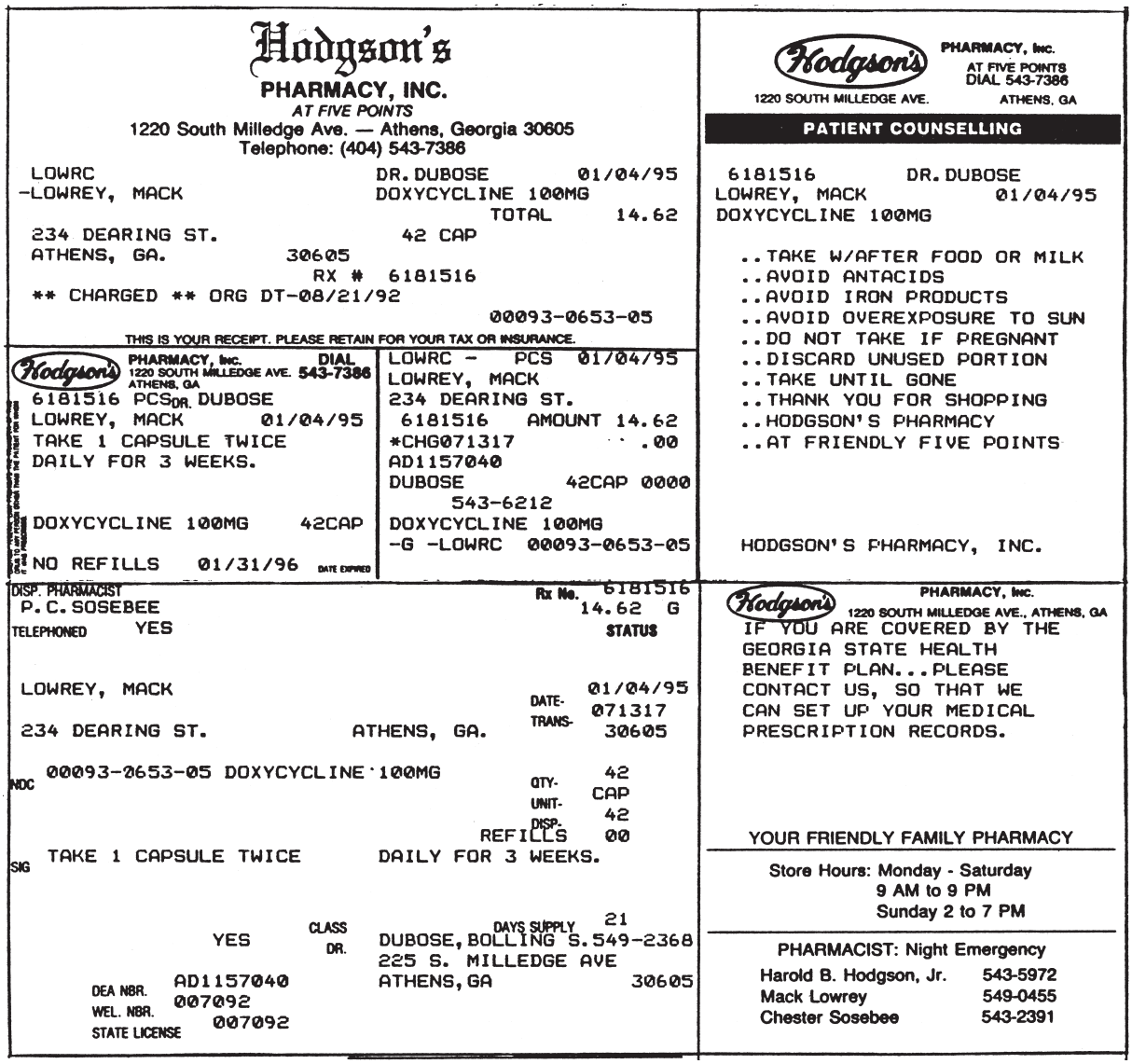

Figure 101-6. Example of a computer-prepared prescription record, label, patient receipt, and patient-counseling information.

pounding the ingredients. Most prescriptions call for dispensing medications already prefabricated into dosage forms by pharmaceutical manufacturers. Care must be exercised by the pharmacist in making certain that the product dispensed is of the prescribed dosage, form, strength, and number of dosage units. As noted above, when substitution is permitted, the pharmacist is responsible for the selection of the manufacturer's product to use in filling the prescription. He/she performs this responsibility on the basis of his knowledge of the quality, effectiveness, and cost to the patient of the selected product.

In preparing prescriptions with prefabricated products, the pharmacist should check the manufacturer's label, comparing it with the prescription order, before and after filling the order, to make certain of its correctness. Products that show signs of poor manufacture, which look deteriorated or are past the stated expiration date on the label should never be dispensed.

Solid, prefabricated dosage forms generally are counted in the pharmacy using a device such as that shown in Figure 101-8. Such a device facilitates the rapid and sanitary counting and transferring of medication from the stock packages to the prescription container. To prevent contamination of tablets and capsules, the counting tray should be wiped clean after each counting, as powder, especially from uncoated tablets, tends to remain on the tray. Many high volume pharmacies use automated counting machines (eg, Baker Cell, Drug-O-Matic, AutoScript III) that are activated by the computer when the prescription order is entered. In some practices, unit dose packages are dispensed as shown in Figure 101-9.

Although the number of prescriptions that now require compounding represents only a small percentage of the total, the pharmacist must acquire and maintain the knowledge and skills necessary to prepare them accurately. The extemporaneous compounding of prescriptions is an activity for which pharmacists are qualified uniquely by virtue of their education, training, and experience. *Pharmacy compounding* is defined as the preparation, mixing, assembling, packaging, or labeling of a drug or device as a result of a practitioner's prescription-drug order or initiative based on the prescriber–patient–pharmacist relationship in the course of professional practice.[5] In addition to the compounding of individual prescriptions when received, guidelines of the FDA permit the preparation of small quantities of compounded products in anticipation of prescriptions for individual patients based on regularly observed prescribing

Figure 101-7. Examples of pharmacy auxiliary labels in English and Spanish. Actual labels available in color (courtesy, PHARMEX).

patterns. However, unless licensed as a manufacturer, pharmacies may not engage in the large-scale preparation of drugs for other pharmacies or entities for resale.[6]

Extemporaneous compounding is essential in the course of professional practice to prepare drug formulations in dosage forms or strengths that are not otherwise commercially available. The process may include the use of readily available bulk pharmaceutical chemicals, or it may require the use and conversion of a commercially available dosage form into another form. For example, it is not uncommon to fortify or reduce the strength of an active ingredient in a dermatological preparation, to reformulate adult dosage forms, such as tablets or capsules, into an oral suspension for use by pediatric patients, or to prepare intravenous admixtures in the hospital, nursing home, or home-care setting.[7] In each instance of compounding, the pharmacist must apply his/her technical and scientific knowledge and use available informational sources to assure product efficacy and stability. Information about the preparation and stability of drugs into suspension formulations can often be obtained from pharmacists' colleagues at pediatric hospitals where the preparation of such formulations may be commonplace.

When a prescription requiring compounding is received, the pharmacist should take into consideration the chemical and physical compatibility of the ingredients, the proper order of mixing, the need for special adjuvants or techniques, and the mathematical calculations required.

Once deciding on the procedure, the pharmacist assembles the necessary materials in a single location on the prescription counter. As each ingredient is used, it is transferred to another

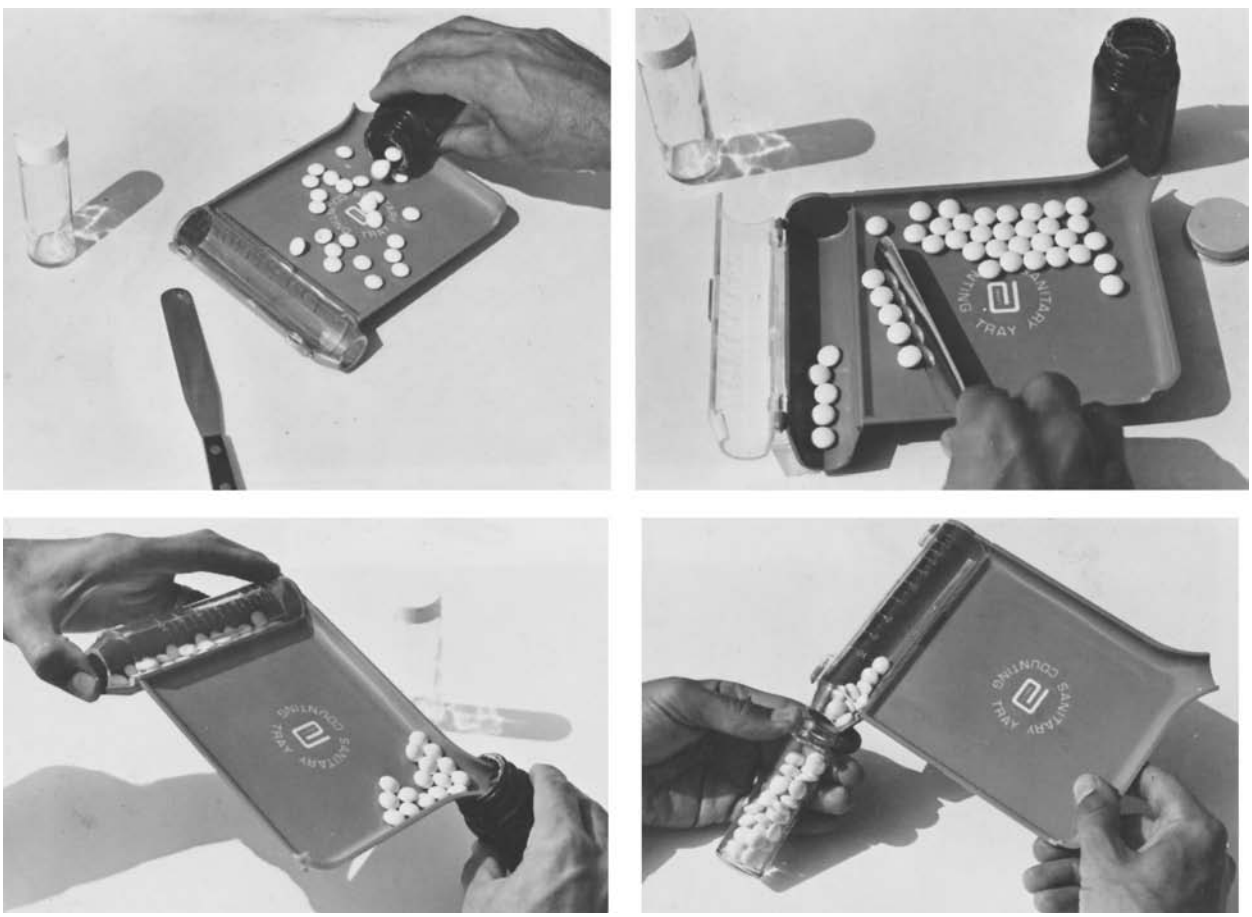

Figure 101-8. Steps in the hygienic counting of solid dosage units with the Abbott Sanitary Counting Tray: (1) placing units from the stock package onto the tray, (2) counting and transferring the units to the trough, (3) returning the excess units to the stock container, and (4) transferring the counted units into the prescription container.

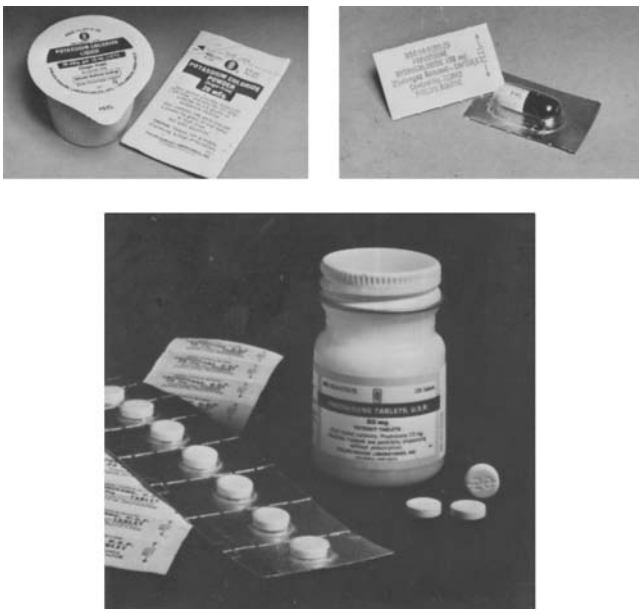

Figure 101-9. Examples of multiple-unit and single-unit packaging, including patient cup, unit dose of powder, blister packaging of single capsule, and strip packaging of tablets (courtesy, Roxane).

location away from the workstation. The use of this technique provides the pharmacist with a mechanical check on the introduction of each ingredient. If the pharmacist is interrupted during the process, there is then no doubt as to which ingredients already have been used. When the pharmacist has finished, all the ingredients are returned to their storage places. Through this process, the pharmacist has the opportunity to read the label of each ingredient three times: once, when the container is removed from the storage shelf, again when the contents are weighed and measured and, finally, when the container is returned to the shelf.

Any calculations or compounding information that would be useful in refilling the prescription at a later date should be noted either on the face or back of the prescription order and also in the computer system. Adjuvants used, order of mixing, amount of each ingredient, capsule size used, type and size of the container, name and product identification number of the manufacturer, auxiliary labels used, clarification of illegible words or numbers, price charged, and any special notations should be recorded. The failure to do this may result in differences in the appearance of the prescription when refilled and possibly create doubt and apprehension in the mind of the patient.

PACKAGING—When dispensing a prescription, pharmacists may select a container from among various shapes, sizes, mouth openings, colors, and composition. Selection is based primarily on the type and quantity of medication to be dispensed and the method of its use.

Among the types of containers generally used in the pharmacy are

Round vials: Used primarily for solid dosage forms as capsules and tablets

Prescription bottles: Used for dispensing liquids of low viscosity

Wide-mouth bottles: Used for bulk powders, large quantities of tablets or capsules, and viscous liquids that cannot be poured readily from the narrow-necked standard prescription bottles

Dropper bottles: Used for dispensing ophthalmic, nasal, otic (ear), or oral liquids to be administered by drop

Applicator bottles: Used for applying liquid medication to a wound or skin surface

Ointment jars and collapsible tubes: Used to dispense semisolid dosage forms, such as ointments and creams

Sifter-top containers: Used for topical powders to be applied by sprinkling

Hinged-lid or slide boxes: Used for dispensing suppositories and powders prepared in packets

Aerosol containers: Used for pharmaceutical aerosol products (These are pressurized systems dispensed by the pharmacist in the original container.)

Most of the prescription containers usually are available in colorless or amber-colored glass or plastic. Amber-colored containers are most widely used because these provide maximum protection of their contents against photochemical deterioration. Plastic amber containers are generally used except in situations where moisture sensitive drug products dictate the use of glass bottles of vials. The containers shown in Figure 101-10 are examples of such containers. The use of outer wrappings or cartons also may be used to protect light-sensitive pharmaceuticals. Pharmaceutical manufacturers select and use containers that do not affect the composition or stability of their products adversely. Similar types of containers should be used by the pharmacist in dispensing the medication to the patient. FDA regulations require pharmaceutical manufacturers to include in their prescription-product labeling the type of container to be used by the pharmacist when dispensing the prescription drug to preserve its *identity, strength, quality, and purity*. The regulation does not apply to products intended to be dispensed in the manufacturer's original container. Many manufacturers now package their products in quantities which correspond to 30 or 90 day supplies which allows the pharmacist to affix a label directly on the container thus streamlining the drug packaging and dispensing process.

The closure on a prescription container is as important as the container itself. By law, prescription containers must be moisture-proof and thus the ability of the closure to restrict entrance of moisture into the container is of prime importance. Moisture has a deteriorating effect on many dosage forms, especially capsules, tablets, and powders. For example, aspirin tablets are hydrolyzed in the presence of moisture and broken down into acetic acid and salicylic acid. Sublingual nitroglycerin tablets are always dispensed in their original glass bottles to minimize exposure to air and moisture. Many pharmacies use screw-cap glass or tight-fitting closures to reduce moisture penetration (Fig 101-11).

Plastic containers have widespread use in the pharmaceutical industry and in prescription practice. The advantages of plastic over glass containers include lightness of weight,

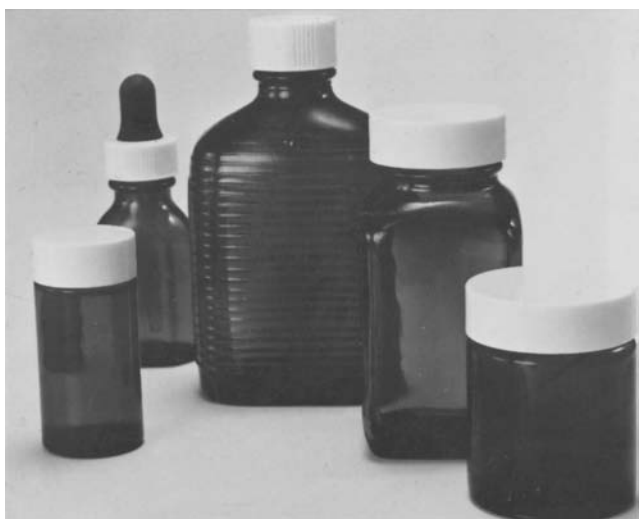

Figure 101-10. Examples of light-protective amber prescription containers for, from left to right: small numbers of solid dosage forms, such as tablets and capsules; liquid preparations administered by drops; liquid preparations; powders or large numbers of solid dosage forms; and semisolid preparations, such as ointments and creams (courtesy, Armstrong Cork).

Figure 101-11. Gross and cutaway views of moisture-tight prescription container (courtesy, Kerr Glass).

resistance to breakage on impact and greater versatility in container design. Flexible polyethylene is used widely in the packaging of squeeze bottles for medication to be administered as drops or as a spray. Nose drops, eye drops, and throat sprays, as well as oral medication to be administered in a dropwise manner, frequently are packaged and dispensed in these containers. Lotions, medicated shampoos, and creams also are packaged conveniently in flexible polyethylene containers. Pliable ointment tubes and flexible plastic containers for intravenous fluids also are used widely.

Rigid polystyrene vials are employed commonly by pharmacists to dispense capsules and tablets. This type of plastic also is used widely in ointment jars and box packages for suppositories. The modern compact-type container used for oral contraceptives, which contain sufficient tablets for a monthly cycle of administration and permit scheduled removal of one tablet at a time, is a prime example of the imaginative packaging possible with plastic. Examples of these containers are shown in Figure 101-12. These prepackaged containers, as obtained from the manufacturer, are labeled properly by the pharmacist and dispensed in the original container to the patient. Several manufacturers now market antibiotics and other medications used for a limited number of days packaged as individual dosage units on cards with the instructions for administration indicated next to each dose. This approach to drug packaging is designed to help assure compliance to the prescribed regimen.

Figure 101-12. Examples of plastic packaging used for oral contraceptive products. (From Ansel HC. *Introduction to Pharmaceutical Dosage Forms,* 4th ed. Philadelphia: Lea & Febiger, 1985.)

The increased responsibilities of pharmacists in drug distribution and inventory control in hospitals, nursing homes, and other patient-care facilities have had an effect on the development of the single-unit drug package, such as the strip package, the blister package, and the plastic disposable syringe. These single-unit packages are termed unit-dose packages at the time of administration to a specific patient. Examples are shown in Figure 101-9.

CHILD-RESISTANT CONTAINERS—The high number of accidental poisonings after ingestion of medication and other household chemicals by children led to the passage of the *Poison Prevention Packaging Act in 11010*. The initial regulation called for use of *childproof* closures for aspirin products and certain household chemical products shown to have significant potential for causing accidental poisoning in youngsters. As the technical capability in producing effective closures was developed, the regulations were extended to include the use of such safety closures in the packaging of both legend and OTC medications.

The Consumer Product Safety Commission has ruled that manufacturers must place prescription drugs in child-resistant packages if the original package is intended to go directly from the pharmacist to the patient. However, manufacturers need not place drugs in safety packaging if the drugs are intended to be repackaged by pharmacists.

All legend drugs intended for oral use must be dispensed by the pharmacist to the patient in containers having safety closures unless the prescribing physician or the patient specifically requests otherwise. A request for a non-child-resistant container may be applied to a single prescription or to all of a patient's dispensed medications. The pharmacist should clarify the patient's desires, obtain and file a signed waiver request, and maintain the information in the prescription computer for future reference.[9] There are some exceptions to the overall requirements, such as oral contraceptive packages because of their unique and useful design, and certain cardiac drugs (eg, nitroglycerin) because of the importance to the patient for direct and immediate access to the medication.

Exemptions also are permitted in the case of OTC medication for one-package size or specially marked packages to be available to consumers for whom safety closures might be unnecessary or too difficult to manipulate. These consumers include childless persons, arthritic patients, and the debilitated.

Further, drugs that are used or dispensed in inpatient institutions, such as hospitals, nursing homes, and extended-care facilities, need not be dispensed with safety closures unless they are intended for patients who are leaving the confines of the institution. Examples of child-resistant containers are shown in Figures 101-11 and 101-13.

RECHECKING—The importance of this step cannot be overemphasized. Every prescription should be rechecked and the ingredients and amounts used verified by the pharmacist. All details of the label should be rechecked against the prescription order to verify directions, patient's name, prescription number, date, and prescriber's name. Rechecking is especially important for those drug products available in multiple strengths.

DELIVERING AND PATIENT COUNSELING—The pharmacist personally should present the prescription medication to the patient (or family member, caregiver) unless it is to be delivered to the patient's home or workplace. Suggested questions to ask the patient when dispensing a new prescription include:

1. What did the doctor tell you the medication is for?
2. How did the doctor tell you to take the medication?
3. What did the doctor tell you to expect from the medication?

Appropriate responses to these questions by the patient gives the pharmacist assurance that the patient knows how to use the medication properly. When presenting the medication to the patient, the pharmacist should reinforce the information the patient already is aware of, call attention to any auxiliary

Figure 101-13. Example of child-resistant safety closure on a prescription container (courtesy, Owens-Brockway).

labeling instructions, and provide further information regarding the medication as may be desirable. When personal delivery of the prescription is not possible, the pharmacist should make certain that the appropriate instructions are provided to the patient and that the patient is encouraged to telephone the pharmacy should there be any questions. The pharmacist should take the initiative to telephone the patient when a product is dispensed with unusual or complicated dosing instructions and when specific precautions need to be reviewed.

There is an increased awareness that labeling instructions frequently are inadequate to ensure patient understanding of his/her medication and his/her adherence or compliance with recommended instructions. The responsibility that the patient receive specific instructions, precautions, and warnings for safe and effective use of prescribed drugs is the shared responsibility of the prescriber and the pharmacist. Reinforcement of the labeled instructions is through verbal communication among the prescriber, pharmacist, and patient, or as supplemental printed instructions, as noted previously (see Fig 101-3).

The *Omnibus Budget Reconciliation Act of 1990* (OBRA 90) amended the 1965 Medicaid law and, among other things, required the development of state drug-use review (DUR) programs and patient counseling activities by pharmacists. Although the law applies specifically to pharmaceutical care rendered to persons receiving Medicaid benefits, the individual states have developed and adopted similar pharmacy practice standards to apply uniformly to all patients.

The specific requirements of the Act are presented in Chapter 111; however, in brief, pharmacists must offer to discuss with each eligible patient—or caregiver of such individual—who presents a prescription, information on the drug, dosage form, route of administration, any special directions for use, common side effects or interactions and therapeutic contraindications that may apply, techniques for self-monitoring drug therapy, proper storage, prescription refill information, and action to be taken in the event of a missed dose. Written information may be used to supplement but not replace the oral counseling requirement.

Under the Act, the pharmacist also must make a reasonable effort to obtain, record, and maintain patient profiles of the patient's disease states, known allergies, and drug sensitivities; a comprehensive list of medications taken and medical devices used; pharmacists' comments relevant to the patient's drug therapy; and the name, address, telephone number, date of birth or age, and gender of the patient.

The state DUR programs must be prospective and retrospective to ensure that the medications are appropriate, medically necessary, unlikely to result in adverse medical results, and based on predetermined standards.

To assist the pharmacist in having up-to-date and pertinent information available for the counseling of his patients, several organized and conveniently arranged sources of dispensing information for patients are available. For example, *USP Dispensing Information, Vol I, Drug Information for the Health Care Professional*, and Vol II, *Advice for the Patient* (drug information in lay language), provide useful information on officially recognized medications for use by pharmacists in counseling their patients.

These references provide the pharmacist with resource information, including clinical indications and applications, ADRs, drug interactions, interference with diagnostic tests, known effects on the fetus and newborn, relevant biopharmaceutics and pharmacokinetics, excretion of the drug through breast milk, sugar and/or alcohol content of the medication, and other information deemed important.

RECORDING AND FILING—A record of the prescriptions dispensed is maintained in the pharmacy through the use of computer and hard copy prescription files. Newer centralized computer systems used by many chain drug stores allow pharmacists from anyplace in the system to access a patient's records and refill a prescription previously dispensed at another store.

Various prescription file types are available to maintain original prescription orders. Metal or cardboard units, which conveniently store approximately 1000 prescriptions are common. When these files are used, holes are punched in the prescription orders; the files are then slipped onto two metal rods firmly attached to the file and placed in a designated compartment in numerical order for safe storage and rapid retrieval.

Suitably partitioned drawers sometimes are used for filing. The partitions may be placed between every 100 or 1000 prescriptions, plainly marked with the numbers of the prescriptions filed in that section. This method permits the removal of a single prescription without preventing ready access to others, as normally occurs when metal rod files are used.

PRICING THE PRESCRIPTION—For a prescription practice to be successful, the pharmacist must be an effective manager of the financial aspects of his practice. To maintain the types of pharmaceutical services desired by his patients, the pharmacist must make a fair and equitable profit.

Each pharmacy should have a method for pricing prescriptions that is applied consistently by each pharmacist practicing in that pharmacy. The pricing method should be established to ensure the profitable operation of the prescription department. A uniform and consistently applied system is beneficial to the pharmacist and helps to avoid misunderstandings from patrons.

The charge applied to a prescription should cover the costs of the ingredients, including the container and label, the time of the involved pharmacist and auxiliary personnel, the cost of inventory maintenance and other operational costs of the department, as well as providing a reasonable margin of profit on investment.

Although many methods of pricing prescriptions have been used through the years, the most common are as follows:

1. *% Markup:*. Cost of ingredients + (cost of ingredients × % markup) = dispensing price
2. *% Markup + Minimum Fee:* Cost of ingredients + (cost of ingredients × % markup) + minimum fee (the minimum fee usually is established to recover the combined cost of the container, label, overhead, and professional services) = dispensing price
3. *Professional Fee:* Cost of ingredients + professional fee = dispensing price. The professional fee includes all the dispensing costs and professional remuneration. A true professional fee is in-

dependent of the cost of the ingredients and thus does not vary from one prescription to another. Some pharmacists use a variable or sliding professional-fee method, whereby the magnitude of the fee is varied somewhat on the cost of the ingredients.

In practice, the professional fee may vary widely between pharmacies, depending on the cost and types of pharmaceutical services rendered (eg, family record systems, delivery service, home health-care needs, cognitive services) and the professional desires of the pharmacist. Pharmacies using the professional fee commonly make adjustments for prescriptions requiring compounding to compensate for the extra time, materials, and equipment. Some pharmacies may charge their patients an annual fee for professional services. This fee then might entitle the patient to the following: routine professional service each time a prescription is filled, a yearly record of prescriptions, regular blood pressure checks, plus a yearly one-on-one consultation.

Governmental units, such as state human services agencies and most insurance companies and prescription card services, have adopted the professional-fee method for the reimbursement of pharmacists in filling prescriptions covered under their programs. Such third-party payers negotiate the professional fee to be used with pharmacists interested in participating in the programs. This practice has resulted in lower fees being paid to many pharmacists as large-volume pharmacies attempt to maintain profits by increasing prescription volume. Most of these programs have a *copayment* provision that requires the patient to pay a portion of the charge for each prescription he/she has filled. As the cost of prescription drugs has increased, most prescription drug plans have implemented a tiered *copayment* system where the percentage the patient must pay is reduced if generic drug or preferred formulary products are prescribed and dispensed.

PRESCRIPTION REFILLING—Instructions for refilling a prescription are provided by the prescriber, on the original prescription or by verbal communication. Although prescriptions for noncontrolled substances have no limitation according to federal law as to the number of refills permitted or the date of expiration, state laws may impose such limits. Many states limit refills to 1 year after the prescription was written. Refilling prescriptions for controlled substances is limited as described in Chapter 111.

Physicians and pharmacists should work together so that prescriptions are renewed only with the frequency consistent with directions for use, and the pharmacist should check with the prescriber after a reasonable time to assure himself/herself that his/her intent is being met. No prescription should be renewed indefinitely without the patient being reevaluated by the prescriber to assure that the medication as originally prescribed remains the medication of choice.

Renewals should be noted on the reverse side of the prescription order or in the prescription computer with the date, the quantity dispensed if different from the original, and the name or initials of the pharmacist dispensing the medication. If verbal authorization has been obtained from the prescriber, this should be recorded.

The maintenance of accurate records of renewals is important for following federal and state laws and for providing information on the patient's medication history.

COPIES AND TRANSFERS OF PRESCRIPTION ORDERS—Occasionally, these are requested by the patient or a pharmacist on behalf of the patient. In some instances, the intention is to provide information, and in other instances, the patient is desirous of having the copy refilled at another pharmacy. Patients who change residences either temporarily or permanently may request their prescriptions be transferred to another pharmacy. Chain pharmacies that have centralized computer systems can access a patient's prescription records from any of their pharmacies throughout the US and can easily transfer any remaining refills on the original prescription order.

Although the FDA maintains that a copy of a prescription order has no legal status and should not be honored, the agency has opened the door for honoring copies under certain circumstances. The FDA does not object to the exchange of prescription copies between pharmacies for the purpose of renewal, provided that certain safeguards are taken: (1) the original order is voided and marked to indicate that a copy has been issued, the individual to whom it has been issued, and the date of issuance; (2) the copy should be so marked and the location and number of original noted; (3) the copy shows the date of original dispensing, the date of the last renewal, and the number of renewals remaining.[8]

This procedure does not apply to *Schedule II* controlled drugs or if individual states prohibit such a procedure. In instances in which copies of prescriptions are provided by the pharmacist and in which the copy may not be refilled legally, the pharmacist supplying the copy should write *Copy—Not to be Dispensed* or a similar designation across the top. A copy should be made exactly like the original, including all pertinent information that a pharmacist might require in dispensing the medication as originally provided. The copy preferably should be written or typed on a preprinted form identifying the pharmacy.

The DEA amended the *Code of Federal Regulations* (CFR) in 1981 to permit the transfer of prescription orders between two pharmacies for controlled-substance prescriptions that may be renewed lawfully. The amendment allows for the transfer of an original prescription order for controlled substances listed in *Schedules III, IV*, or *V* between pharmacies on a one-time basis only.

To comply with these regulations, pharmacists first must ascertain if the transfer of a prescription order for renewal dispensing purposes is permissible under state or other applicable law. When a prescription order is transferred, it must be communicated directly between two licensed pharmacists, and the transferring pharmacist must record the following information:

Write *VOID* on the face of the invalidated prescription order.
On the back of the invalidated prescription order, the name, the address, and the DEA registration number of the pharmacy it was transferred to and the name of the pharmacist who received the information.
The date of transfer and the transferring pharmacist's name.

The pharmacist receiving the transferred prescription order must reduce to writing the following:

The word *transfer* on the face of the transferred prescription order.
All information required on a controlled-substance prescription order as it appears on the original prescription order.
The date of issuance of original prescription order.
The original number of renewals authorized on the original prescription order.
The date of the original prescription order.
The number of valid renewals remaining and the date of the last renewal.
The pharmacy's name, address, DEA registration number and the original prescription number for which the prescription order was transferred.
The name of the transferring pharmacist.

The DEA requires that the original and the transferred prescription orders must be maintained for 2 years from the date of the last renewal. Most states now allow the transfer of prescriptions via computers within their states, whereas some allow computer transfers from other states. Pharmacies electronically accessing the same prescription record must satisfy all information requirements of a manual mode for prescription transferral.

PATIENT COMPLIANCE WITH PRESCRIBED MEDICATION

When a prescriber writes a prescription, it is with the intent that the patient fills the prescription promptly and begins using the medication according to directions. Patient adher-

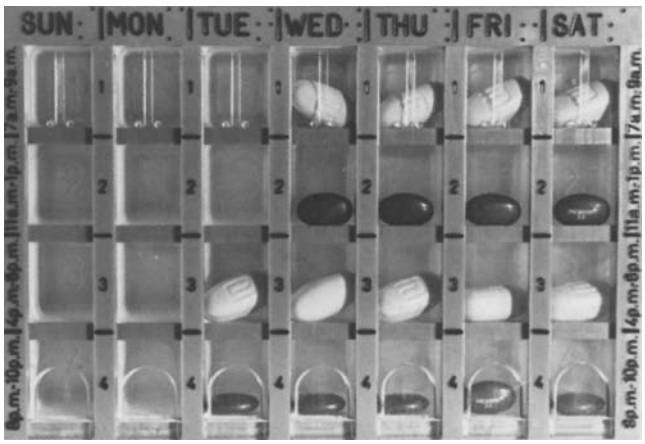

Figure 101-14. Example of the MEDISET medication container designed to assist patient compliance with prescribed medication schedule (courtesy, Drug Intelligence).

ence or compliance with the prescribed medication schedule has been a source of concern to the physician and the pharmacist.

Patients may unnecessarily delay the initiation of drug therapy or may wait to see if they *feel better* before having the prescription filled. Some patients discontinue their medication prematurely because they are feeling better and see no particular need to continue taking the medication. Other patients may take excessive doses of the medication believing that they will get better faster, whereas others take their medication at incorrect intervals or whenever they remember.

On refilling a prescription, a pharmacist generally can determine the compliance of the patient in taking his/her medication by comparing the dosage units dispensed *versus* the dosage units apparently taken over the treatment period. Pharmacists can often gain a great deal of useful information about compliance by simply having the patient describe how he/she takes the medication on a daily basis. Pharmacy computer systems are useful in determining patient compliance and can be used to generate refill reminder cards or telephone lists for courtesy calls to remind patients about the need to comply with their medication.

Specially designed medication containers are useful in assisting patients to adhere to their medication schedule. These containers have individual compartments for daily medication and generally hold a week's supply (Fig 101-14). Containers for oral contraceptive medication, previously discussed and shown in Figure 101-12, have proved effective in patient compliance during the monthly medication cycle. See also Chapter 98.

USE OF COMPUTER SYSTEMS TO PROCESS PRESCRIPTIONS

The use of computer systems in pharmacy practice is now standard because of the expanded informational needs of the pharmacist, the need for on-line prescription plan approval, the increased amount of paper work required in the practice, the need for efficiency, and the availability of computer technology and expanded databases to provide the necessary support. Most chain pharmacies are linked together by dedicated telephone lines or satellites, thus facilitating the sharing of information between pharmacies (Fig 101-15).

In general, computerized systems in pharmacy are used in three areas: prescription dispensing and associated record maintenance, clinical support and accounting, and business management. Most insurance and prescription plans now require on-line verification and authorization prior to the dispensing of any medication. Pharmacists can now use the Internet to obtain and download information about disease states and drug therapy for their patients.

Prescription Dispensing and Associated Record Maintenance

LABEL PREPARATION—Once basic prescription information is entered, the computer produces an error-free label or multiple labels if required.

PRESCRIPTION NUMBER ASSIGNMENT—Consecutive numbers are assigned to prescriptions by the computer, and the problem of lost and duplicate numbers virtually is eliminated.

RECEIPT PREPARATION—Prescription computers calculate the price of the prescription and store information. Thus, it is simple for the computer to prepare a receipt automatically for the patient that may include the amount paid for an individual prescription or for the total prescriptions filled over a given period. This information may be important to the patient for insurance or tax purposes.

PRESCRIPTION NOTATION—As a prescription order is processed, the pharmacist typically makes several notations, including the initials of the dispensing pharmacist, the drug cost and product dispensed, and special entries such as *dispensed only one-half at patient request*. This information may be retained by the computer and used in renewal processing.

RENEWAL PROCESSING—The computer-assisted renewal processing of prescriptions is almost automatic. If the computerized records indicate that the prescription renewal is allowable, the computer automatically prepares the new label and receipt, updates the renewal status of the prescription, recalculates the price on the basis of current cost information, and adds the entire transaction to the patient's medication profile. See also Chapter 117.

Clinical Support

PATIENT MEDICATION PROFILES—On command, the computer presents on its monitor the most recent medications that have been dispensed to the individual patient. This information is used by the pharmacist in ascertaining potential drug–drug interactions. Information pertaining to the patient's drug allergies and primary illnesses also permits the pharmacist to assess the drug therapy and dispense only rational and effective medications.

Figure 101-15. Pharmacist using a prescription computer system in his professional practice (courtesy, General Computer).

PATIENT EDUCATION INFORMATION—Computer-printed information is provided to the patient on the medication dispensed. The information generally includes the proper use and administration of the medication, precautions, possible side effects, a brief description of the purpose of the medication, and how to proceed if a dose is missed. Some computer programs also may generate a picture of the dosage form.

DRUG UTILIZATION MONITORING—By tracking the dispensing dates and quantities dispensed, a pharmacist can determine a patient's compliance in taking the prescribed medication properly.

Accounting and Business Management

BUSINESS RECORDKEEPING—The computer may be programmed to provide accounts receivable, payroll, general ledger, accounts payable, third-party claims processing and records, inventory control and ordering, sales analysis functions, and daily summary of business.

PRESCRIPTION ANALYSIS—The computer provides retrievable information on daily, monthly, or yearly prescription totals; new *versus* refilled prescriptions; medication costs per prescription filled; and profit per prescription filled.

DRUG-PRODUCT DEFECT AND ADVERSE-REACTION REPORTING PROGRAMS

Monitoring Drug-Product Quality

Monitoring drug-product quality is an important function of the practicing pharmacist. The medications dispensed on prescription and those sold OTC should meet high standards of manufacturing quality to assure safety and efficacy when used properly.

As contained in the *Code of Federal Regulations* (21 CFR 211), manufacturers of pharmaceutical products must comply with FDA standards for *Current Good Manufacturing Practice (CGMP) for Finished Pharmaceuticals* to ensure product quality. A section of these regulations includes provisions for the reporting and handling of drug-product complaints. A complaint or concern regarding product quality may arise from a patient or from a health professional and may be communicated directly to the manufacturer or brought to the attention of the FDA. In either case, the information is shared between the agency and the manufacturer, and each complaint is evaluated to determine whether corrective action is required. Complaints or concerns may relate to any factor of product quality or effectiveness, including dosage form integrity, stability, appearance, odor, taste, color, packaging, and labeling.

Pharmacists play an important role in the detection and reporting of product defects through participation in the FDA's *Medical Products Reporting Program* (MedWatch), a voluntary program for the reporting of concerns regarding the quality of distributed prescription and nonprescription drug products. Since the program's initiation in 1993, both the number of serious events reported has increased and the quality of adverse-event reporting to the FDA has improved, primarily owing to the efforts of pharmacists.[10] Information provided through this program becomes useful to the manufacturer and the FDA in maintaining quality standards.[11] Pharmacists may report drug-product quality concerns by telephone (1-800-FDA-1088), on the FDA's web site [www.fda.gov], or by mail using the MedWatch form provided for this purpose (Fig 101-16).

Specific information requested on the FDA MedWatch form includes product name, dosage form, strength, and size; National Drug Code Number, if available; lot number and expiration date; name and address of manufacturer, distributor, or labeler; name, address, and profession of person reporting the suspected product defect; a description of the problem noted or suspected and the date and the signature of the person filing the report. The option is given to the person filing the report to remain anonymous in the subsequent FDA communication to the affected manufacturer or distributor.

Monitoring Adverse Drug Reactions

The FDA has specific requirements for drug manufacturers of investigational and marketed pharmaceutical products to report adverse drug reactions (ADRs) or adverse drug experiences (ADEs).[12] Pharmacists have the opportunity to participate in reporting such incidents through practices in the institutional and community pharmacy settings. Observations of reactions to investigational drugs generally are observed in the clinical (usually institutional) setting during controlled clinical studies as investigational drugs are evaluated prior to FDA approval for marketing. Reactions to marketed drugs may be observed during any postmarketing clinical studies and through surveillance by health professionals during the course of their practice.

The postmarketing surveillance of pharmaceuticals for adverse reactions is essential in establishing a complete safety profile for marketed drugs. Once marketed, the number and diversity of patients receiving a new drug is far greater than during the controlled clinical trials. Thus, some ADRs and drug interactions that escape detection during the clinical trials are seen initially after the drug product is marketed. During the past decade, there are several examples of newly marketed drug products that subsequently have been removed from the market after postmarketing surveillance by the FDA and the manufacturer has detected the occurrence of rare but potentially lethal adverse reactions or drug interactions.

Pharmacists and other health-care providers who observe suspect reactions to drugs are encouraged to report these to the FDA. Serious reactions, observations of events not described in the package insert, and reactions to newly marketed products are of particular importance. The FDA provides the MedWatch form for filing a voluntary—or in the case of user facilities, distributors, or manufacturers, a mandatory—report. The form includes space for entering patient information; adverse reaction information, including a description of the reaction experience and relevant laboratory tests or data; suspect drug information, such as the drug name, manufacturer, lot number, daily dose, route of administration, dates of administration and duration of administration; concomitant drugs taken and record of administration; and name and contact information for the person or manufacturer filing the report. In some institutions in which clinical studies are conducted, computer programs are used to record, monitor, and report suspected ADEs.[13] ADR reports may result in changes in product labeling, warning letters to health-care professionals regarding safe conditions of use, requirements for further clinical or safety studies or, in some instances, withdrawal of the product from the market.[14]

LEGAL CONSIDERATIONS

All aspects of manufacture, distribution, and possession of drugs are controlled by both state and federal laws and regulations. State laws and regulations governing the practice of pharmacy generally are administered by state boards of pharmacy composed of varying numbers of pharmacy practitioners and in some instances by consumer representation. These boards generally regulate the licensing of pharmacy interns, pharmacists, and pharmacies, and enforce rules and regulations pertaining to the legal and ethical practice of pharmacy within the state. State regulations regarding drugs frequently include and extend the federal law. Federal laws are administered by various federal agencies and pertain primarily to products considered interstate commerce.

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ___ of ___.

Form Approved: OMB No. 0910-0291 Expires: 12/31/94
See OMB statement on reverse

FDA Use Only
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
___ lbs
or
___ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ___ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ___

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other

5. Expiration date (mo/day/yr)

6.
model # ___
catalog # ___
serial # ___
lot # ___
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ___ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name, address & phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 (6/93)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Figure 101-16. FDA MedWatch Reporting Form.

The laws governing the practice of pharmacy are presented in Chapter 111.

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CHAPTER 102

Providing a Framework for Ensuring Medication Use Safety

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Sharon Murphy Enright, MBA, RPh

The US health care system is paradoxical, offering at once the promise of death-defying state of the art care, and also the threat of injury, and even death, resulting from flawed and sometimes dysfunctional performance. In 1998, the Institute of Medicine sponsored National Roundtable on Health Care quality, published a report that called attention to an alarming problem[1]:

"Serious and widespread quality problems exist throughout American medicine. These problems . . . occur in small and large communities alike, in all parts of the country, and with approximately equal frequency in managed care and fee-for-service systems of care. Very large numbers of Americans are harmed as a result."

This realization was brought sharply to public and professional attention with the publication in November 1999, of *To Err is Human: Building a Safer Health System*, the first report of the Institute of Medicine (IOM) Committee on Quality. This benchmark report reframed medical error as a chronic threat to public health, and galvanized media attention to the issue. Some startling findings included[2]:

- 98,000 Americans die annually as a result of preventable medical errors.
- National costs (including lost income, lost household production, disability and health care costs) of preventable adverse events–medical errors resulting in injury–are estimated between $17 and $29 billion, of which health care cost represents over half.
- More Americans die of medication errors annually than from workplace injuries.
- Even medication errors that do not result in actual harm have a cost, calculated at as much as $2 billion annually.

Because these hospital-based studies do not even account for errors in other settings where they occur with at least equal frequency, the figures offer only a modest estimate of the real target of actual errors. *Err* recommended a comprehensive approach to improving patient safety, which would demand a broad-based response. There was no magic bullet, no single solution, no single recommendation as *the answer*. Preventing errors means designing the health care system to build in safety at all levels.

Eighteen months later, IOM followed with a second–even more comprehensive–report, *Crossing the Quality Chasm: A New Health System for the 21st Century,* that calls for nothing less than redesign of the US health care system.[3] *Chasm* paints a graphic and detailed picture of how and where the health care system fails to meet the needs and expectations of the patients it serves. The report addressed three problem categories introduced in *To Err is Human*: overuse, underuse, and misuse that contributed to problems with patient care. Misuse–failures to execute clinical care plans and procedures properly. Overuse–use of health care resources and procedures in the absence of evidence. Underuse–failure to employ health practices of proven benefit. Among the observations[3]:

- Health care today harms too frequently and routinely fails to deliver its potential benefits.
- Tens of thousands of Americans die each year from errors in their care, and hundreds of thousands suffer or barely escape from nonfatal injuries that a truly high quality care system would largely prevent.
- During the last decade, more than 70 publications in leading peer-reviewed clinical journals have documented serious quality shortcomings.
- Waste, medical error, lack of access to clinical information, unnecessary duplication of services, long waiting times and delays, and overuse of services where the harm outweighs the benefit, contribute to a system that, as a whole does not make the best use of its resources. The current system cannot do the job. Trying harder will not work. Changing systems of care will.

With a current annual investment of over $1 trillion in the health care sector expected to grow to $2 trillion or 16% of Gross Domestic Product by 2007, *Chasm* reports that a sizable commitment on the order of $1 billion over 3 to 5 years, will be required for the rapid and significant change that is needed.[4]

Err offered a similar conclusion relative to safety: flaws are unacceptable and common. The effective remedy is not to browbeat the health care workforce by asking them to try harder to give safe care, when in fact, the courage, hard work, and commitment of health care workers are the only real means to stem the tide of errors latent in the health care system.[5] Unfortunately, workers must rely on outmoded systems and poor workflow design that sets them up to fail, despite efforts to the contrary.

Growth in knowledge and technologies has never been so profound and prolific. However, research on the quality of care demonstrates that the health care system falls short in its ability to translate knowledge to practice and to apply new technologies safely and appropriately. One realizes that knowledge of best practice is not applied systematically or rapidly, in fact the diffusion of innovation of best practice is frustratingly slow. An average of 17 years is required for new evidence-based knowledge to be incorporated into common practice.[6] System redesign, more rigorous information technology to support clinical and administrative processes and improved knowledge management capabilities will be required.

The IOM committee sets forth six Aims for Improvement, establishing what should be attainable common goals: care should be safe, effective, timely, patient-centered, and efficient. Yet, *Chasm* reports that as it exists, the American health care system is incapable of providing the public with the quality it expects and deserves and offers few of these basic aims consis-

tently. Quality problems occur typically not because of failure of goodwill, knowledge, effort, or resources, but rather because of fundamental shortcomings in the way care is organized.[7] If, as *Err* suggests, exhortation, blaming, and trying harder cannot get the necessary job done, what system redesign considerations must be considered?

Chasm calls for change at four levels (Fig 102-1):

Experience of patients and communities. The focus for improvement must shift from the health care system itself to being patient-centric, tying quality issues more closely to patient's values and expectations, actual experiences, cost and social justice.

Microsystems of care. The small work units that actually give care to patients represent the microsystem level. This team of people, with their information system, client population of patients, and a defined set of work processes represents where *work* or *care* happens, where quality occurs or does not. Care at the microsystem level must be knowledge-based, patient-centered, and systems-minded. The quality of a microsystem is its sustained ability to provide ever-improving levels of care: safe, effective, patient-centered, timely, efficient, and equitable.

Health care organizations (or macrosystems). The quality of an organization lies in its ability to support microsystem's ability to sustain ever-improving care levels. Through their culture, policies, and the tools provided for work, health care organizations frame the capacity for microsystems to achieve care improvements. Organizations need to develop more robust and persistent systems for identifying, diffusing, and adopting best practice. Access to information and decision support systems must be available to create a supporting network of knowledge at the microsystem level. Because human assets are a fundamental differentiating factor, organizations need to invest in recognition and development in the persistent improvement of knowledge, skills, and competency within the workforce. Beyond individual knowledge, skills, and competency, effective and collaborative teams and teamwork will be essential to achieving improvement goals, as will coordination of care among services, departments and across the continuum of care, particularly with respect to patients with chronic illnesses. Finally, organizations need to commit philosophically and in practice to a data-driven measurement and assessment of performance and outcomes.

Health care environment. Sweeping and difficult changes will be necessary in the external environment, including capital and operating financing, regulation, accreditation, litigation and tort reform, professional education, and social policy. Needed change at microsystem and organizational levels reflect *toxicities* resulting from the external environment. Who would pay for telephone-based or e-mail care? What will be the source of capital for much needed information technologies? A safety culture functions on the basis of openness, transparency, and trust but without tort reform to ease pressures of litigation and in an environment of *blame and shame* can that be a reality? The quality of the health care environment may determine how well organizations and microsystems can achieve their quality goals.

Err and, to an even greater extent *Chasm*, reflect a solid base in systems thinking. Solidly tying experiences of patients to the fundamental definitions of quality, judgments of performance, delivery systems, organizations, and policies and procedures can only be made in the context of health status, satisfaction, and reduction of morbidity and mortality. Improving patient safety relies on an understanding of systems thinking, complex adaptive systems, and learning in complex systems.

While *Chasm,* has provided the framework for improvement, additional work by the IOM, through the *Quality Chasm Series* continues to build the body of evidence, understanding, and necessary action steps to keep patients safe. In January 2003, the IOM released the report entitled *Priority Areas for National Action Transforming Health Care Quality* that clearly identified 20 priority areas that collectively address preventive measures, care coordination, patient self-management, and health literacy issues that cross acute, chronic, and palliative care domains.[8] A subsequent report, *Fostering Rapid Advances in Health Care: Learning from System Demonstrations* identified the need for primary care redesign, improved information and technology infrastructures, insurance coverage changes, and malpractice reform strategies necessary to make care patient-centered and safety focused.[9]

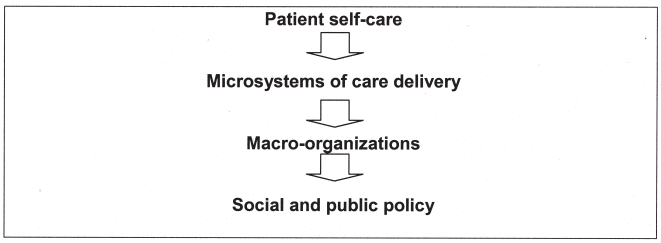

Figure 102-1. Levels of quality-focus in health care. Data from Berwick DM. A user's manual for the IOM's "quality chasm" report. *Health Aff (Millwood)* 2002; 21(3):80.

In *Leadership by Example: Coordinating Government Roles in Improving Health Care Quality,* the IOM goes further to recommend a multi-pronged approach to care improvement by suggesting the federal government take advantage of the influence it has to set the standards for national health care quality.[10] Specifically, the report indicates that clinical data reporting requirements, purchasing strategies, standardized performance measures, and quality reports should be developed to accelerate the development of knowledge and tools that have been demonstrated to improve quality. An additional report, *Patient Safety: Achieving a New Standard For Care* outlines the IOM recommendations for enhancing knowledge, developing tools, disseminating results in order to build the necessary health data interchange and work plan to develop data standards applicable to the collection, coding, and classification of patient safety information.[11]

The IOM also identified that to provide safe and effective care, health professional education requires a major overhaul to address changing health system expectations, evolving practice requirements, new information and technologies and staffing arrangements. The first report released by the IOM, *Health Professions Education: A Bridge to Quality* provides a mix of approaches necessary to improve training environments, research, public reporting and leadership.[12] The focus of this report identifies the need to integrate a core set of competencies—patient-centered care, interdisciplinary teams, evidence-based practice, quality improvement and informatics—into health professions education. A second report, addressed nursing workforce issues, *Keeping Patients Safe: Transforming the Work Environment of Nurses*, identifies necessary safeguards for safe and effective care.[13] While specifically focused on an evaluation of nursing practices, resources, and environment, the report highlights changes that could impact all care professionals and patient safety efforts: effective leadership, adequate staffing, organizational support for ongoing learning, interdisciplinary collaboration, appropriate work design, and organizational support through governance and culture that supports safety as a priority.

The IOM and other groups continue to build the body of evidence necessary to identify strategies for sustainable and effective care improvement. What has been identified to date? There are clear conditions and priorities for care improvement action that requires attention. A need exists for leadership to be passionate and engaged for safety improvement to occur. Comprehensive strategies must be implemented to develop the workforce to provide the sustainable, change needed to improve care delivery. The findings in the Quality Chasm Series to date highlight the breath and diversity of issues that must be addressed to improve local as well as natural health care quality.

DEFINING THE SCOPE OF THE SAFETY PROBLEM

Safety is an implied minimum standard in providing health care. Yet many Americans are harmed as a result of medical error. While the horrific cases such as Betsy Lehman, a health reporter for the Boston *Globe* who died as a result of a chemother-

apy overdose or Ben Kolb, an 8-year-old boy who died during *minor surgery* due to a medication mix up make headlines, these events provide only the tip of an iceberg describing concerns regarding the safety of medication use.[14]

Research in the area of medication safety and error prevention has identified some serious concerns for patients and care providers. As health care delivery systems become more complex, it is evident that the opportunities for error abounds. A national, concerted effort by health professionals, organizations, purchasers, and regulators will be required to deal with this complex issue.

Reports published indicate that errors involving medications are responsible for an immense burden of patient injury, suffering, and death. Those involved in caring for patients and those who receive care agree that the errors observed should not happen. Current research has identified some issues, previously only discussed behind closed doors, regarding the scope and seriousness of the problem of medication errors:

- The costs of medication-related morbidity and mortality are high.
- Many medication errors are preventable, and physicians, nurses, and pharmacists can play a vital role in diminishing medication errors.
- The medication use process is highly complex, problem-prone, and requires a systematic approach for improvement.

Reports indicate that adverse drug events (ADEs)–injuries caused by the use (or nonuse) of a medication–affects as many as 1.3 million hospitalized patients annually.[15]

Several large studies have identified that medication-related errors occur frequently in hospitals. In 1993, medication errors were estimated to account for 7,000 deaths annually in the US.[16] In a second study conducted in New York, adverse events due to medications accounted for 19.4% of all injuries.[17] A third study evaluated 39 prospective studies utilizing a data set obtained from the literature between 1966 and 1996. The overall incidence of serious adverse drug reactions in hospitalized patients was 6.7% and of fatal ADRs was 0.32%. In 1994, it was estimated 2,216,000 hospitalized patients experienced serious ADRs and 106,000 had fatal ADRs making these reactions the fourth and sixth leading causes of death in the US.[18] A final study that requires discussion is a matched case-control study of patients admitted to a tertiary care institution in Salt Lake City. Classen et al identified that adverse drug events represented 2.43 of 100 admissions to their facility. The occurrence of an adverse drug event was associated with an increased length of stay of 1.91 days and an increased cost of $2,262. The increased risk of death among patients experiencing and ADE was 1.88.[19]

Not all medication errors that occur result in actual harm to patients, but evidence suggests that those that do cause harm are also costly. One study conducted found that nearly 2% of admissions experienced a potentially preventable ADE resulting in an increased hospital cost of nearly $4,700 per admission.[20] When that cost is annualized for the 700-bed teaching facility, this results in an overall cost of $2.8 million. If the findings are placed in the context of national admission rates, ADEs in inpatients could result in costs of $2 billion for the nation as a whole.[20]

Hospitals only represent a fraction of the total population at risk for an adverse drug event. Injuries from medication use have been documented during the vulnerable peri-discharge period. An evaluation by Forster et al evaluated 400 consecutive patients discharged home from a general internal medical service.[21] The patient's post hospital course was determined by conducting a medical record review and a structured telephone interview approximately 3 weeks after the discharge. A total of 76 (19%) were found to have some type of adverse events after discharge. Of interest is that adverse drug events were the most common type of adverse event reported at a frequency of 66%.[21]

Additional studies frame the issue of medication-related errors in other settings by identifying errors in prescribing and dispensing of prescriptions in an outpatient environment. There is evidence that ADEs account for a sizable number of admissions to inpatient facilities; however, it is unknown how many of these ADEs are directly associated with error. One study found that between 3% and 11% of hospital admissions were attributable to ADEs.[22] ADEs are often identified as a reason to seek care at a physician office or emergency room. In a study evaluating 1,000 patients in a community, office-based medical practice, patients were observed for adverse drug events. It was determined that 42 patients presented with an ADE of which 23 were found to be potentially avoidable.[23] In another evaluation, 1.7% of 62,216 patients seen in an emergency department visits were identified as associated with medication noncompliance or inappropriate prescribing.[24]

Adverse drug events can also occur in nursing homes. A study by Bootman et al in 1997 demonstrated that for every dollar spent on medications in nursing facilitites, $1.33 is consumed in the treatment of medication-related morbidity and mortality.[25] Total costs for the nation were estimated to be $7.6 billion, with a significant portion of the costs, $3.6 billion estimated to be avoidable.

Patient nonadherence with medication regimens also appear to be a significant quality issue. However, the extent to which nonadherence contributes to error is not known. With a greater emphasis on community-based, long-term care, increased ambulatory surgery, shorter hospital stays and greater complexity in therapy, patients themselves play an increasingly more important role in the administration of medications. Greenberg et al identified that 4.3% of the elderly enrolled in Medicare social HMOs in 1988 required assistance in administering medications.[26] In a meta-analysis conducted by Sullivan et al in 1986, it was estimated that 5.5% of admissions can be attributed to medication therapy noncompliance, resulting in 1.94 million admissions and potentially $8.5 billion in hospital costs.[27]

It has been estimated that for every dollar spent on ambulatory medications, another dollar is spent to treat new health problems caused by the medication.[28] This has resulted in projections that the health care cost of treating medication-related morbidity and mortality in the ambulatory setting to be as high as $76.6 billion in 1994.[29] Not all of this medication-related morbidity and mortality has been identified as preventable. However, numerous evaluations in population-based studies of patients in the community, health plans, hospitals, and nursing homes suggest that prescribing, dispensing by pharmacists, and unintentional nonadherence on the part of patients contribute significantly to this problem.[30–33]

Appropriate medication use is a complex process involving multiple organizations and professions from various disciplines combined with a working knowledge of medications, access to accurate and complete patient information and integration of interrelated decisions over a period of time. The growing complexity of science and technology requires health care providers to know more, manage more, monitor more, and involve more care providers than every before. Current methods of organizing and delivering care are not able to meet the new expectations of patients and families because the knowledge, skills, care options, devices, and medications have advanced more rapidly than the health care system's ability to deliver them safety, effectively, and efficiently. The potential for errors of omission or commission to creep into the process is extraordinary. No one clinician can retain all the information necessary for overseeing sound, safe, best practice. This is especially true in the case of pharmaceutical delivery and development. The average number of new medications approved per year has doubled since the 1980s. Between 1990 and 1999, more than 300 new medications were approved by the United States Food and Drug Administration.[34] Costs of care as well as the complexity of managing the use of existing and new pharmaceuticals are only expected to intensify as a result.

One of the consequences of these advances in medicine and technology is that people are now living longer. Changing mor-

tality patterns, increasing numbers of individuals 65 years of age and older, and increases in incidence in prevalence of chronic conditions have important implications for the health care delivery system. Unlike the episodic care that occurs in acute care, effective care of the chronically ill requires a high degree of collaboration. Delivery of care must include joint development of care plans, goals, targets, implementation strategies, patient self-management training, sustained follow up and monitoring, and decision support systems. This collaboration requirement adds another layer of complexity to the delivery of care. The potential for the development of medication errors, adverse events, and mismanagement issues within and along the care system is enormous.

Access to treatments and use of best practice guidelines have lead to national quality improvement initiatives and priority action items to assure that change and improvements are made. As medical science and technology has advanced at a rapid pace, the system used to support and distribute care has not been able to keep up with the pace. Research indicates that the health care system currently falls short of being able to translate knowledge into practice. Variation of health system performance varies greatly. Many patients remain without health care insurance and have little to no access to basic health care services. For those without insurance, care is unobtainable except in emergency situations. A highly fragmented system lacks information capabilities, frequently provides duplication of services, long waiting times and delays.

Despite the vast range of available guidelines, best practices, standards, and evidence-based practice recommendations, a gap exists between the care people should receive and care they do receive. This is the case for acute, chronic, and preventive care and whether overuse, underuse, or misuse of resources are evaluated. Medication use examples can emphasize this point. Influenza vaccine is recommended as a preventive measure in adults over the age of 65, yet vaccination rates seldom occur over 60% of those at risk.[35] Antibiotic overuse continues to be a concern, which has lead to increase bacteriologic resistance. Antibiotics are not considered appropriate care for patients exhibiting symptoms of the common cold. Several studies in the 1990s identified that for 44–60% of patient visits diagnosed with a common cold were treated with antibiotics.[36] In other studies, such as those conducted by the Center for Medicare and Medicaid Services (CMS, formally known as the Health Care Financing Administration or HCFA), these identify that for patients suffering from myocardial infarction, use of aspirin, beta blockers, and other agents used to preserve or improve cardiovascular performance are not used as frequently as they should be and vary based on regional factors.[37]

National estimates indicate that as many as 70% of adverse drug events are due to errors and may be preventable.[38] Yet, since the reports of these findings it appears that little progress has actually been made. Clearly, a new approach is needed within health care organizations to improve the safety of medication use. Building the required safer medication system will mean redesigning processes of care to ensure patients are safe from accidental injury. A number of practices have been shown to reduce error in the medication process and are recommended to be in place in health care settings. Recommendations for building a safer medication use system include redesigning processes that govern medication use, involving all members of the medication use team and creating a new culture that identifies medication safety as a priority for the organization. Despite the availability of tested methods in health care and other industries, regulatory mandates, and published resources, gaps continue to exist between current recommendations and actual practice in organizations due to a variety of attitudinal, educational, and system barriers.

What issues are preventing organizations from improving the safety of medication use? Inconsistent reporting and fear of sanction for identifying errors can make it difficult to identify what is contributing to an adverse event. As a result, organizations are not able to track and trend information that could yield effective strategies for adverse event prevention within a care setting.

If errors occur, but are not reported, investigation and prevention strategies cannot be developed. Because some published studies indicate that as many as 95% of medication errors go unreported, this could be a significant issue for any organization.[39] Having a clear understanding of error, error theory, risks, and capabilities influencing safe and effective medication use is essential to impact and transform the current systems in place for providing care. Understanding human system interactions and elements that have been identified in other industries may hold the cues and clues needed for the system overhaul required by health care.

UNDERSTANDING ERROR

Health care systems have traditionally operated under the assumption that if care providers are well educated and follow well-developed policies, procedures, or guidelines, errors will not happen. That is in fact, not the case. Errors reoccur despite the best educational and planning efforts.

To understand what is or is not known about medication-related adverse events, common definitions must be established and understood. Organizations must come to a common understanding regarding medication errors, reporting requirements, and risks to capture and act upon error potential within their own medication use systems. While the literature has provided practitioners with a series of operational definitions, the following, developed by the Institute of Healthcare Improvement, reviews some commonly accepted definitions associated with medication use safety.[40]

Adverse Event: An injury caused by medical treatment, not necessarily due to an error.

Adverse Drug Event (ADE): An injury, large or small, caused by the use (including nonuse) of a drug. It can be as harmless as a rash or as serious as death from an overdose. There are two types of ADEs: (1) those caused by errors and (2) those that occur despite proper usage of a medication. If an ADE is caused by an error, it is by definition, preventable. Nonpreventable ADEs (injury, but no error) are called adverse drug reactions.

Preventable Adverse Drug Event: An injury due to an error in the use of a drug (including failure to use).

Potential Adverse Drug Event (PADE): A potential ADE is a serious medication error—one that has the potential to cause an ADE, but did not, either by luck (eg, the patient was not allergic to the drug despite a note in the record stating so) or because it was intercepted (eg, the nurse recognized an order for a medication to which the patient was allergic and called the physician to get it changed). Examining potential ADEs helps to identify both where the system is failing (the error) and where it is working (interception).

Adverse Drug Reaction (ADR): Further defined by the World Health Organization, to characterize injuries caused when drugs are used in the usual accepted fashion. By definition then an ADR does not result from an error. Unfortunately many have used this term as synonymous with ADE, which blurs an important distinction.

These definitions provide the following insights regarding adverse events and medication use:

- Medication errors are considered preventable while adverse drug reactions are generally are not.
- If an error occurs, but is intercepted by someone in the process, it might not result in an adverse event. These potential adverse events are often referred to as *near misses*.
- Capturing information regarding *near misses* could yield vital information regarding system performance.

IDENTIFYING RISK

Research indicates that perhaps one of the best ways to address the problem of adverse drug events and medication errors is to

recognize that inherent risk exists with use of medications in patient care. This view is based on two concepts:

- Medications are inherently toxic, and there is a risk to taking them and, perhaps, not taking them. Each time a practitioner prescribes a product, a treatment risk *versus* benefit must be assessed. If a patient takes prescribed medications in a different manner than prescribed or if over-the-counter products and alternative agents are added, there are additional risks. Side effects and tragic rare reactions are also difficult to anticipate.
- Health care professionals are human and can make mistakes. Yet, during training and practice, they are immersed in an environment where there is no room for error. Reporting an error is often viewed as professional failure or negligence and is followed by sanction or punishment of the individuals involved. A zero error standard is demanded in health care. However, it is sobering to consider that each time care is provided many potential serious adverse events are possible. Increased patient complexity and decreased numbers of health care staff contribute to potential error. This results in health care workers worrying constantly about the ever-present reality of error.

Because errors are thought to be preventable, examining what happened when an error occurs is the natural response, a means to develop future prevention strategies. Unfortunately, in many organizations, the response to error targets the people rather than the system involved in the production of an error.

What is an Acceptable Error Rate?

Finding an *acceptable* rate of error consumes many organizations. What is an acceptable rate of error might just be the wrong question entirely. Is any error really acceptable? Is there really a target? What individual would truly desire to be involved in any significant error?

Everyone seems to be looking (unsuccessfully) for benchmarks for error rates related to medication use. Unfortunately, there are none! The Center for Medicare and Medicaid Services suggested several years ago that a 2% error rate was an acceptable target for health care systems for which to strive.[41]

- Is a 2% error rate acceptable to care providers?
- How would patients feel about an error rate of 2%?
- Would health systems reward staff for seriously injuring only 30 people a year?

Perhaps the best answer to these questions comes from a Deming example of the impact of errors.[42] Deming suggests that if the following systems were 99.9% safe, the United States would encounter:

- 84 unsafe plane landings daily
- 16,000 lost pieces of mail per hour
- 32,000 bank check errors per day

Literature reports have attempted to apply this concept of 0.1% error as a 'safe enough' system. Leape et al suggest that even a health care error rate of 0.1%, a 99.9% safe system, is simply not good enough.[43] Leape's work describes how an error rate of 0.1% effects the medication use process. He has noted that at a minimum, 10 to 14 steps commonly exist between a physician prescribing a medication and a patient receiving a medication.[44] Assuming each person involved in every step of a 10-step medication use process was operating at a peak efficiency of 99.9%, 10% of patients receiving medications within that system would be involved in some type of medication-related error.

Clearly, trying to predict an *acceptable* rate of error is not a reasonable approach. Goals should center on elimination of all error: a focus of zero error is the target, even while recognizing the impossibility of that goal. This creates an interesting paradox for care providers. Health systems often act like ostriches with heads buried in the sand, denying the likelihood of error that exists in the increasingly complex health care delivery system, expecting zero defect performance and yet continue to allow members of health care teams (physicians, nurses, and pharmacists) to operate as *captains of their own professional ships* in the care delivery process. No one individual alone has the scope of control or information to absolutely prevent error, yet each individual acts as if they can, with a growing fear that in fact control of the next accident waiting to happen is an individual's responsibility. When an error does occur, organizations have a fairly typical response: shame and blame, retrain and/or reorganize, then return to business as usual.

For the sake of argument and improved patient care, it is important to maintain a zero error standard. The focus, however, must shift from blaming individuals to prevention of future errors by designing safety as a component of the system to accomplish this. If blame and sanction continues in health care, reporting will not occur. Inconsistent reporting makes identifying patterns of occurrence difficult or impossible. This eliminates hope for creating effective prevention strategies. This does not imply that individuals can be careless. If in fact, to err is human and caregivers are expected to be vigilant and responsible, creating systems that minimize risk and error are paramount for advancing an agenda of safety.

Organizational Vs. Individual Error

When reviewing error types and error theory in the literature, one finds descriptions of individual and organizational errors. Individual errors in health care are far more common. Organizational errors are rare, but can occur in complex technologies such as health care. Complete system failures, such infectious or hazard exposures that affect large populations of patients and health care workers may occur in health care systems. Most examples of organizational errors include accidents in the aviation industry, nuclear power plants, banks, stadiums, etc, where the result of a system failure impacts a significant portion of the population or community.

Part of the challenge with preventing or resolving error is having a true understanding the development of errors within the organizational construct, the logic or chain of events, and methods to evaluate beyond the surface detail to identify potential solutions or mitigation strategies.

In most industries, including health care, built in protections and defenses are put into place to assure that safe, effective care of people and assets occur. Reason has identified that there are a variety of defenses put into systems to provide the following functions[45]:

- Create understanding or awareness of hazards
- Give guidance on how to operate safely
- Provide alarms and warnings when risk or danger is evident
- Place barriers between hazards and individuals or other systems
- Restore system to a safe state when conditions are not normal
- Contain or eliminated hazards if the barrier is not adequate
- Establish methods of escape and rescue should hazard containment fail

As Reason defines these, there is some implied depth to the layers of protection so that it makes in nearly impossible for something to go awry. In the case of medication use, these points of defense are often in place, although the depth and scope of their implementation may vary. Medication information, policies and procedures, guidelines, and restrictions are often in place to assure that medication use hazards are evaluated or mitigated. Dosing adjustments, review of orders by multiple, skilled practitioners, use of dosing thresholds, alarms on medication administration devices all present opportunities to alert the need for change or modification of a medication use process. When those barriers fail, often antidotes or rescue protocols are available to contain potential adverse events. The rigor with which these principles are applied can mean the difference between a fatal error or successful treatment process.

In an ideal world, all the defensive layers would be intact and no penetration of a possible failure could occur. Unfortu-

nately, in the real world, each defense layer can have weaknesses and gaps. Holes in defenses can occur. To identify how these failures can occur, the concepts of latent conditions and active failures must be described. These models hold the key to understanding methods to redesign the medication use process to control, contain, or mitigate errors within health care.

Latent Conditions and Active Failures

Complex systems such as those involved in health care are inherently hazardous by their very nature. It is not unexpected that all complex systems may have minor faults. When failures do occur, they are often the result of multiple apparently innocuous faults (referred to in the literature as latent error) that occur simultaneously or in clusters. Yet, the concept of latent error is not routinely evaluated in health care. This is error that has been defined as beyond the individual. It implies faulty design, poor maintenance, or error in overall management. Interaction between this system-related problem and individual may not be discernable and effect not immediate.

The Swiss Cheese metaphor has been utilized by Reason and others to represent a dynamic, moving picture of defensive layers (Fig 102-2).[46]

These defenses within an organization or process often move around based on local conditions. Consider how routine defenses in the medication use process could be removed deliberately (violation of procedure) or inadvertently (error) during calibration, maintenance, or testing of a medication delivery device. Each of these *holes* could be coming and going, shifting, shrinking, and expanding in response to the environmental condition or operator activity. Consider an example of an intravenous infusion device not adequately calibrated, not maintained, or with no maintenance plan in place. Continued use of the inadequately calibrated equipment could be producing small, relatively indistinguishable readings that could lead to decisions for care that could be problematic. Some operators of the equipment may recognize the variation and modify the device to override a problem; others may be unaware that any problem exists. Reporting of the concern may not occur or go unnoticed if no underlying plan for maintenance evaluation is in place. Other examples of latent conditions in the health care system might include:

- Lack of adequate patient information (eg, no information about prior treatments or allergies)
- Lack of appropriate communication (eg, failure to fully communicate order changes and ambiguous or misleading medication orders)
- Lack of medication information (eg, no maximum dose warnings)
- Lack of adequate medication labeling (eg, a syringe with no description of route of administration, IM or IV)
- Lack of adequate training or resources on a topic area

How are these types of latent failures identified by members of the health care team? How would a pharmacist or other care provider know if these failures are possible? What has been designed as a system safety net to capture possible accidents before they happen? The design of many care systems for patient have *built-in* features that pose latent error potential:

- Interruptions
- Workload and/or poor delineation of responsibilities
- Work schedules that are inappropriate and stress-producing
- Lack of standards leading to workarounds
- Lack of information
- Lack of training leading to variation in work habits and abilities

Health care is a complex system involving the interaction of large numbers of highly trained personnel in many diverse, interrelated, and interdependent activities. Redefining and redesigning what each team member does is necessary to reduce or prevent errors from occurring.

It is important to note that these types of latent failures can be present at any level of the organization. Latent conditions are present in all systems. They are a part of organizational life. This is not to say that latent conditions are always a result of bad decisions. The original design and allocation of resources to support the medication use process may have been based on sound information. System inequities can be unforeseen and create quality, reliability problems at some point within the process. No one individual or leader can possibly foresee all the future ramifications of current system design. Latent conditions, by definition, are seeded within the infrastructure of the organization and are often related to production or service design, contracting, regulatory, or governmental mandates. They can remain dormant. Development of these failures and exposure of latent conditions only become visible when they are instigated by humans at the front line or sharp end of the process; when the decisions are tested and applied. The concept of latent error demonstrates a new way of thinking for health care systems. Rather than being derived from a single massive failure, single component or person, system failures truly do arise from an insidious accumulation of individual faults. A series of defenses can fail *together* even in an extraordinarily safe system.

Because people design, operate, maintain, and manage complex systems such as medication use, it is hardly surprising that often people are implicated first in errors. Humans contribute to the breakdown of systems. Making decisions, juggling time, and weighing the evidence are common and necessary day-to-day, minute-to-minute health care worker activities. Practitioners and others are provided resources, data, and tools to care for patients. They apply knowledge and make judgments about care activities. Health care providers operate at the sharp end of the care process—the hazardous end that interacts directly with the patient. Care providers must interact with equipment, environments, other people and change each day.

In reality, the limiting steps to moving to a redesigned health care system that would minimize latent failures has less to do with technology than with the human aspect. When things go wrong, the technology is "blamed", but the social, behavioral, psychological, and cultural factors associated with the technology are the more likely culprits. Both simple fixes and more complex technology innovations have unintended consequences. In short, it is not possible to introduce a new technology into a system without changing behavior and altering outcomes, often in unanticipated ways, intentionally or not.

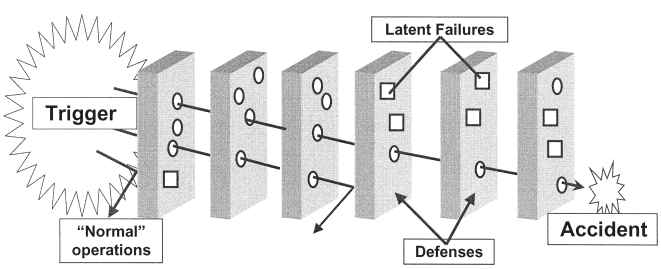

Figure 102-2. Latent failure: The Swiss Cheese diagram. Adapted from Reason J. *Human Error.* Cambridge, UK: Cambridge University Press, 1990:208.

Sharp End, Blunt End Interactions

Reason provides another model for consideration regarding the role of systems and supports for human interactions with those systems (Fig 102-3).[47]

Practitioners are directly influenced and affected by the *blunt end of the system*—the institutional structure, policy, other resources, regulations, and technology—but are truly working at the *sharp end* where care situations often vary. Work by Cook and Woods identifies that human functioning at

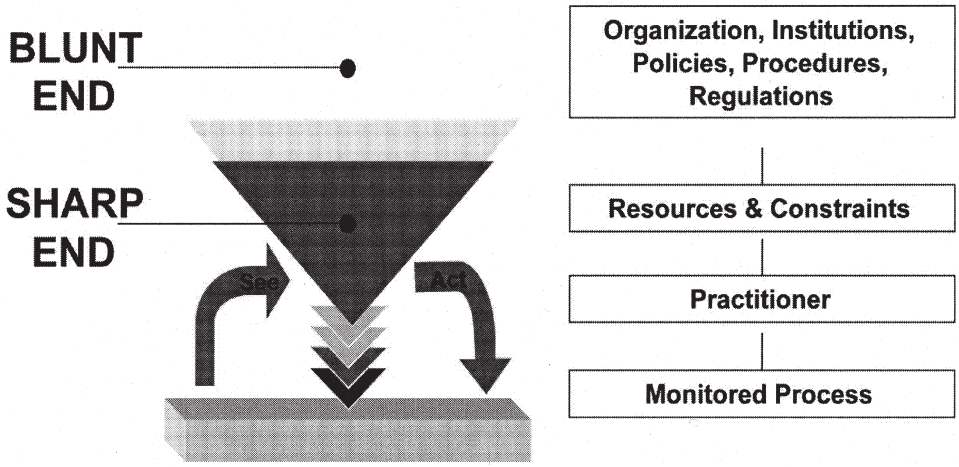

Figure 102-3. Sharp end / blunt end interaction. Adapted from Bogner MS, ed. *Human Error in Medicine.* Hillsdale, NJ: Lawrence Erlbaum Associates, 1994:295.

the sharp end in systems and health care in particular is extremely complex. Success or failure of a process, such as medication use, is dependent on:[48]

- The context in which the process occurs and how the practitioner is expected to perform in an environment that can vary
- The technology impact on the practitioner performance, because it has the potential to create new forms of error and failure
- Practitioner action usually involves a set of people affecting the medication use process
- Individuals who have shaped the *blunt end supports* for practitioners can create dilemmas or tradeoffs among goals that can compete at the sharp end of the process
- Attribution of the error at the sharp end is often a process of social judgment rather than a scientific conclusion

Consider what happens if blunt end components are absent or not well defined for medication use? A patient presents for treatment with co-morbidities that have the potential to affect medication use selection, dosing, and monitoring, but consequences and information are not clearly known by the care providers. What about a new scenario where policy has not yet been defined or distributed? A patient with a functional or cognitive impairment is potentially unable to self-administer his/her own medication with the administration equipment provided. What if the sharp end need does not match the blunt end support? The policy doesn't match the patient or the situation, as in the case of the prescribing of a medication for an unapproved use.

Practitioners of course must act and react at the sharp end. Resources and constraints at this sharp end can impact how the process actually plays out. As a result, resources are applied and outcomes occur based on what is available and what the sharp end user knows about.

When evaluating the medication use process or investigating an error, simply focusing on the sharp end interaction may lead to inappropriate and inaccurate conclusions. Investigations must consider how the blunt end of the process contributes to what was executed at the sharp end by the practitioner. Issues that contribute to errors and adverse events are often difficult to see because current tools use to evaluate health care systems are inadequate. Measurement and evaluation of all aspects of the medication use system does not routinely occur. Organizations may only collect and report selected information and reflect observations solely at the sharp end of the process. An understanding of optimal system performance and system vulnerabilities are part of the new-look understanding needed to identify safety hazards within the medication use process.

The Cycle of Error

A noted expert in the area of systems analysis, anesthesiology, and error theory, Dr. Richard Cook has visually described a cycle of error and what the investigation process looks like in a health care organization (Fig 102-4).[49]

Typically, reactions to a health care error involve associating a person with blame. It is easy to identify and blame a person present at the time the error occurred. In general, people involved in complex health care processes really do a great job managing at the point of their interaction with the process. Members of the health care team troubleshoot and react or modify when needed to reacting to changing patient conditions. In most cases, these skills of adaptation are rewarded and encouraged in health care.

Despite this balancing act by health care team members, actions after an adverse event usually focus on training or retraining those involved or accused. New rules, regulations or sanctions are implemented. Although these steps may result in heightened awareness of possible error prone processes, research suggests that these changes alone do not provide long lasting improvements.

Consider the following common response to an error associated with the overdose of chemotherapy. Typically, the action steps include:

- Development of new order forms
- Retraining of staff

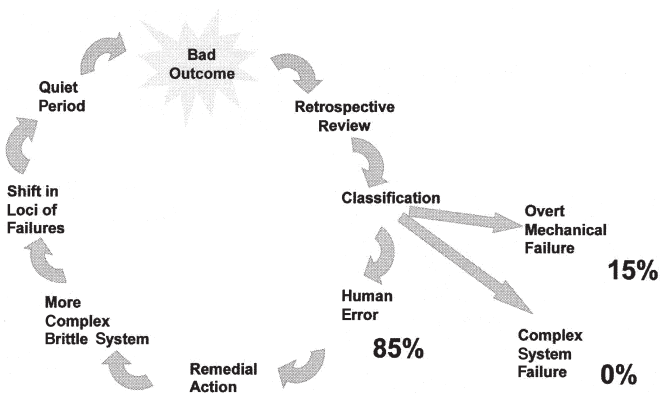

Figure 102-4. Error cycle. Bogner MS, ed. *Human Error in Medicine*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1994:29.

- Development of new policy, including restricting the use of the medications involved to specific physician groups
- Purchase or standardization of infusion devices and/or new calculation checking process is mandated

Oftentimes, these interventions alone may only increase complexity and introduce new opportunities for failure. As the previous diagram suggests, the error cycle tends to repeat itself when the usual quick fixes or incremental modifications are made in isolation within the system.

Cook suggests that in health care it is also highly unlikely that after an event occurs the correction of one set of specific flaws will be of value in preventing future errors. In fact, Cook describes that it is more likely that a combination of flaws actually contribute to the development of the problem within the system. If only one or two isolated steps are modified, the system may in fact become more vulnerable by shifting the locus of where the error may occur the next time.[49]

This new way of thinking about error analysis and system repair highlights the fact that the health care system is highly complex and interactive. This necessitates a true system view of the medication use process before rushing to an isolated solution or fix.

Factors that Contribute to Error in Health Care

Several specific factors have been identified that contribute to health care system error and provide some additional challenges for resolving the issues.[43] The culture of medical practice itself: complex, heroic, and focused on an expectation of perfection. Physicians and others fear implications of negligence and reporting may not occur as a result. In this environment, the physician is seen as the controller or gatekeeper of all aspects of care. Blaming activity is thus promoted when things don't go as planned.

Additionally, because of the complex nature of health care, adjustments and changes, of any type, often occur seemingly in a vacuum. Miscommunication or no communication can result.

When it comes to error investigation in health care, postaccident reviews often identify human error as the cause due to hindsight bias. This knowledge of the outcome makes the path to failure appear obvious to the investigator. It implies that individuals involved in the process could have foreseen what was about to happen even if they could not. In fact, the conclusion that practitioners should have known that the factors involved would inevitably lead to an accident actually poses some real obstacles to a thorough, unbiased investigation. Human performance analysis at this point may be far from fair or accurate as a result, yet this is the common method for accident investigation.

Error and Human Capacity

Human error can occur as a result of human capacity itself. Errors can be made by teams or by individuals. Some errors occur as a result of misinterpreting speech or written communication. The probability of an error increases with increased workloads and long or rotating shifts. Stress and fatigue also affect performance. Human capacity elements that affect decision-making and have error potential include memory, skill, rule, and knowledge.[50]

Human Error Types

Action errors attributed to an error of subconscious or automatic behavior are called "slips."[51] These have been referred to as errors that occur when individuals are in the automatic mode. "Slips" occur as a result of distraction. An example might be getting into a hospital service elevator and intending to go to the laboratory for medication blood level results, but walking off the elevator on the floor where the cafeteria is instead.

Errors associated with conscious thought are termed "mistakes."[51] These types of errors are often identified as individuals *not thinking straight*. Mistakes are rule-based and knowledge-based cognition errors. Essentially, a wrong rule is chosen and applied. This may reflect a lack of information, a misinterpretation of the situation, or an inability to apply information to a new scenario. As an example, consider how a health care provider addresses look-alike labels or sound-alike medication names. These examples are accidents waiting to happen.

Errors that people make are often traceable to extrinsic factors that affect capacity and set the individual up to fail, rather than intrinsic factors such as forgetting or inattention.

Preventing Error

Error prevention in health care has not focused on addressing these types of human factors. Instead it has relied almost exclusively on the training of personnel to perform perfectly. Conventional wisdom suggests that if something goes wrong, someone *goofed.* The presumption is that people are unreliable. As a result finding the culprit and assigning blame is the solution to combating future error.

The assumption has been that if clinicians are well educated and follow policies, procedures, or other guidelines, errors will not happen. It is believed that highly trained people will not make errors. In fact, this is not true. Highly trained people make mistakes. If the organization has the belief that people are intrinsically unreliable, it would follow that elimination of error could only be resolved by replacing humans with automation. Some organizations are moving in this direction; however, automation is not able to cope with infrequent situations and variable environments. Consideration of human factors and the humanness of care must still be evaluated and planned for even in highly automated environments.

Error Investigation in Other Industry

Other industries have identified these issues and have modified their approach to error analysis and prevention. Improving safety in these environments has been focused on understanding how the details of economic, organizational and technological factors create vulnerabilities and paths to failure. Because health care is also dynamic, improving safety may also require this new look perspective.

Safety can only be achieved by learning how system components interact. Organizations that have shown progress on safety have an understanding about how technical and organizational factors play out in real work and how people act and react in the face of these changes. Error theories in other industries focus on the following concepts:

- Errors are common
- Errors are a result of complex cognitive mechanisms
- Psychologists, human factors specialists, and engineers are critical to the investigation of error and development of error prevention strategies
- Man-machine interfaces need investigation for error potential
- Defining complex systems and their component interactions are crucial
- Work environment redesign, including ergonomic factors, must be included

Decision-making regarding medication use is complex and minor variations from patient case to case do not always allow for simple rules or routines to be followed. Safety engineers view workflow, interactions, distractions, coupling activities, handoffs, and timing as a part of an error generating system that must be evaluated and designed for safety. Members of other industries define systems clearly and focus on the whole rather on an isolated segment of the system.

Aviation Safety System Design

The aviation industry has made great advances in the area of error prevention and human factors research based on these key elements for change. The recognition of the role that human factors play in error development has produced a system that is focused on identification and prevention. The Federal Aviation Administration (FAA) and National Aeronautics and Space Administration (NASA) established the Aviation Safety and Reporting System (ASRS) in 1975. This program collects and responds to voluntary submitted aviation safety reports.[52] Data from these reports are used to:

- Alert authorities regarding deficiencies and discrepancies
- Support policy development and improvement planning
- Strengthen foundation of human factors safety research. This last component is probably the most important since it is generally realized that two-thirds of aviation accidents root causes are human performance error

Safety Advances in Anesthesia Practice

The medical specialty of anesthesia has embraced some of these ASRS techniques and incorporated a systems-approach regarding error analysis and prevention. As early as 1968, some fundamental changes in anesthesia practice were instituted to reduce the morbidity and mortality associated with anesthesia. A fundamental change was needed for this high-risk, problem-prone activity. Anesthesia supported investigation of workload, effects of stress and fatigue, incorporating a team approach, and a focus on error prevention.

The result of initiating change in these areas significantly reduced mortality. Groups such as the American Society for Anesthesia (ASA) have continued this effort by developing and establishing practice/treatment guidelines, as well as supporting continued research in the areas of workload analysis/fatigue. Additionally, ASA efforts focus on a team approach to care as well as providing for checks and balances in anesthesia activities. Advancement of credentialing activities/standards for the practice, development of position papers regarding safety, and educational programming are also provided by ASA.[53]

These ASA efforts have had a significant impact on mortality. Ten years ago, death rates associated with anesthesia were 1 in 10,000 to 20,000; now these rates have dropped to 1 in 200,000.[54–56] Anesthesia has led the medical profession in recognizing that system factors cause errors. Advances have been made because there has been a focus on designing fail-safe systems and in training to avoid errors.

This view also seems relevant to other health care environments. Consider a nursing unit at shift change or a pharmacy located in a high traffic area with multiple distraction points. There are many risks for misinterpretation or poor communication in this environment. Clearly, the nursing unit or a pharmacy in a bustling chain practice environment is a difficult place for high-level complex care to occur. Simply redesigning a component of the work (eg, a reporting form or format) will not be sufficient to address the complexity of the systems that influence how nurses conduct shift reports. Potential for error is great. With caseloads increasing and staffing shortages looming, the potential for error can escalate.

Factors Associated with Human Error Development

Three general factors have been identified that contribute to the development of human errors. Each item contributes to the development of human stress and fatigue. Organizations should incorporate strategies to address these factors to identify potential adverse drug event prevention strategies. These aspects are summarized in below[57]:

Psychological Precursors: These are associated with issues such as excessive care assignments, excessive work schedules, long shifts, inadequate physical working conditions, and strained work relationships. Development of physical stress and fatigue in these scenarios can lead to the individual being vulnerable to error.

Team Function: A lack of supportive leadership encouragement and group cohesion can lead to dysfunctional performance. Individuals will be unable to communicate effectively and function effectively. If power relationships exist, decision-making and communication may also be impaired. It is unlikely that suggestions for improvement will be made. Errors, if identified, may go unchecked or unreported in this environment.

Training: A lack of adequate training can predispose individuals to errors. Simply providing educational materials, however, is not enough. A method for assessing individual competency and capacity to apply new knowledge is also essential. Individuals must also be trained for teamwork and be willing to learn and teach each member on the team. If individuals do not understand their responsibility or have the necessary skills, errors are more likely to occur.

Organizational and Environmental Factors Contributing to Human Error

Additionally, many organizational and environmental factors contribute to the development of human error and must be identified and addressed within the organization. These factors include:

- Lack of a supportive environment
- A culture based on fear and retribution for mistakes
- Lack of teamwork
- Inadequate or limited training

To assess system performance, it is also necessary to understand the complex cognitive processes that health care providers use to perform their individual jobs. Plans for care are created and followed by individuals and as a team of care providers. Problem-solving activities can occur by individuals or as a team. Gaba provides a process model of anesthetist's real time decision-making and actions while providing care (Fig 102-5).[58]

Although focused on anesthesia care specifically, the model identifies critical action loop of care that can be applied to any health care provider activity[58]:

- Observation
- Decision
- Action
- Re-evaluation

In addition, this loop of activity must operate under several controls:

Resource allocation: including delegation of tasks and responsibilities during the procedure, monitoring and cross-checking activities, and attention to process.

Supervisory control: reviewing data, prioritizing activities, reacting to change/ interruptions and actions if necessary.

Sensory and motor control: routine observations, problem recognition, prediction of needs and outcomes, action planning regarding both abstract and procedural issues.

The anesthetist must have overall vigilance and sustained attention to detail. Ongoing observation and problem recognition is vital. Having a plan and a response for acute and unexpected situations is also necessary. Making sure that the plan is reviewed, data is evaluated and re-evaluated and that others are informed of the steps necessary for an optimal outcome are also essential components. All of these activities within the process model can be subject to human error and failures of the human capacity itself. The following items must be considered as medication use plans are developed:

- Infrequent or inadequate medication use data observation
- Responses to false medication use data
- Inadequate planning or forecasting responses to medication use problems
- Inadequate workload management for medication use process
- Inadequate crosschecking of activities
- Poor communication
- Poor leadership
- Increased fatigue and reduced vigilance

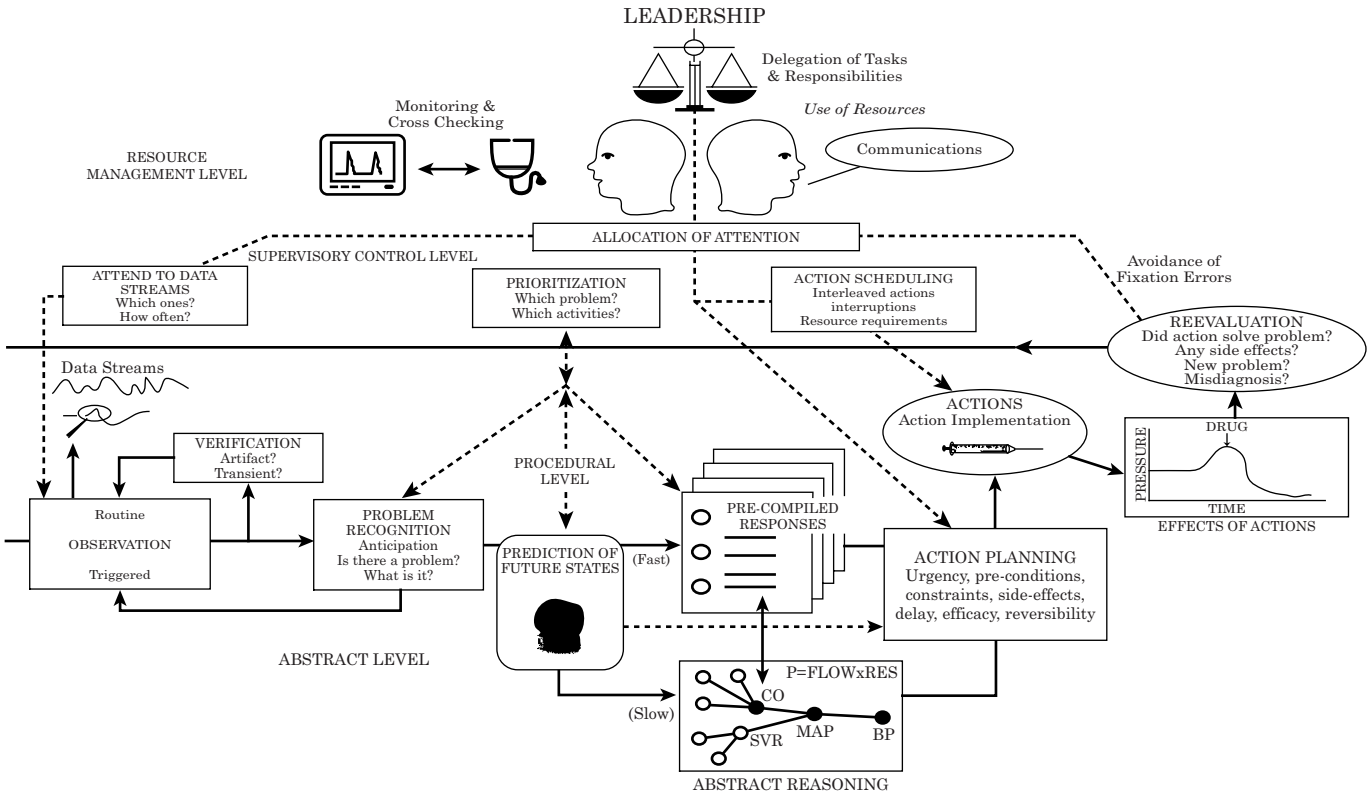

Figure 102-5. Anesthesia decision model. From Bogner MS, ed. *Human Error in Medicine.* Hillsdale, NJ: Lawrence Erlbaum Associates, 1994:209.

Certainly, lack of knowledge and skill can contribute to error in this environment, but suboptimal performance of these processes resides in how decisions and actions of humans are linked together in this complex care area. Many tradeoffs and decisions must be continuously balanced and refined. Although these activities might be slightly different for other areas of medicine, the concepts for improvement and attention for development of safer performance are similar:

- Training and competency assessment of practitioners is vital, but a new focus on problem-solving, supervisory control, and resource management is needed for assuring safety
- Ergonomics of the work environment must be evaluated to reduce the possibility of "slips"
- Communication and vigilance by the use of effective teamwork and crew coordination are essential for reducing risk
- Workload management, distribution of workload, and standards are necessary for safe performance
- Optimum planning of action and monitoring activities are needed

THE ROLE OF THE PATIENT IN MEDICATION USE

The Institute of Medicine identified 10 new rules to transition the general health care system to better meet patient care needs.[59] These rules and recommendations require partnerships between patients and care providers to improve health care processes, including medication use. These care rules have been adapted below to identify opportunities in medication improvement and include:

- Care based on continuing relationships that measure and monitor effects of medications
- Customization of medication treatments based on patient needs and values
- Patients as the source of control for medication use decisions
- Shared knowledge and free flow of information regarding risks and benefits of medication use
- Decision-making based on evidence of medication use findings
- Safety as a medication use system property
- Need for transparency so that all care providers and those involved in care have adequate and appropriate medication use information while respecting patient confidentiality
- Anticipation of medication use and monitoring needs associated with treatment and conditions
- Continuous decrease in waste of services, time, and expenses
- Cooperation among clinicians to focus toward a common goal for treatment based on patient's wishes

These rules are consistent with other quality initiatives and medication use improvement strategies that have as its focus providing safe, effective, timely, efficient, and equitable care that is designed and focused on meeting individual patient medication use needs.

The patient-clinician encounter is also a potential source for error, adverse events, or misaligned therapeutic goals. The unfamiliar environment of diagnosis, treatment, and information regarding use of medications is often intimidating and unsettling for patients. Pharmacies, hospitals, or outpatient examination rooms are often locations where pieces of health information and assessment are exchanged. Use or evaluation of prescription efficacy or toxicity may also occur over a telephone call. Information is not always conveyed by words alone during an exchange. Miscommunication, verbal and nonverbal, can occur in a conscious or unconscious fashion.

The two participants, the patient and the clinician, often have asymmetrical discussions. The provider often contributes to the discussion as an authority figure; the patient as a subordinate. Both participants often come from different socioeconomic backgrounds and educational experiences. Each participant may use different terms and vocabulary to describe symptoms, outcomes, and concerns. Additionally, cultural, ethnic, racial, gender, age, and religious differences contribute to differing sets of beliefs and values.

The environment along with social, educational, and personal factors can all contribute to miscommunication or misin-

terpretation of clinical findings and plans. While a common goal might be agreed upon, improving patient's quality of life through the use of medications, this goal could be perceived differently by each partner in the exchange and not fully realized by either party. Misunderstandings could lead to serious errors. Practitioners need to have an understanding of the patient's cognitive capability and competence, environmental and social situation as well as values and beliefs in order to effectively communicate and design safe and effective medication use plans. Patients should also be encouraged to be better health care consumers and become better informed. Patients should be encouraged to express their needs and concerns and receive as much information on medications and options as desired. Above all, there needs to be a dialog regarding their need for solutions to their perceived problems that respect their own wishes while respecting their independence whenever possible. For the practitioner, this means combining some common sense as well as innovative strategies to assess, adapt, and improve communication strategies for patients.

Patients, families, and health care providers often must make difficult and complex care decisions including those involving use or nonuse of medications. Unfortunately, despite regulations, guidelines, and research, many patients and families do not get the information they need to make informed decisions and practitioners often fear discussing risks with patients. Practitioners often have difficulty determining what risks to share and finding the words to convey the potential for risk with treatments. This communication can pose great challenges for physicians, nurses, or pharmacists involved in medication use. Some or all of the risks may not be known or understood. Perceptions of risk also vary. Is the risk of liver damage or headache from the use of a medication for diabetes more significant than the development of renal disease associated with diabetes disease progression?

Patients have a right to information regarding any proposed treatment as well as risks involved. This includes informing the patient regarding their condition, treatment plan, prognosis, complications, risks, benefits, alternative treatments, and other vital pieces of information regarding possible treatment in order to give consent to a specific care plan. Health systems and individual practitioners need to identify and implement a strategy for risk discussions with patients. Pichert and Hickson suggest the following framework for communications with patients[60]:

- Identify patient preferences for information (amount and format)
- Evaluate patient and family's desired decision-making role
- Provide assessment and response to patient ideas, concerns, and expectation
- Discuss clinical issue
- Review and define decision needed
- Identify all alternatives (include patient's ideas as well)
- Present and evaluate evidence available
- Discuss pros and cons (benefits and risks) and work with patient to explore impacts on values, life-style
- Ask patient to identify a preference
- Identify with patient any conflicts or concerns
- Determine methods to resolve conflicts and make or negotiate a final decision
- Agree on an action plan and a follow up plan
- Document the discussion and plan

In addition to discussing risks and benefits in advance, health care providers need to identify methods to disclose errors or adverse events to patients when they occur. Telling patients and families about unwanted outcomes and errors is not easy. Dealing with their response and reactions can be challenging as well. Accepting responsibility, investigating the event and possibly changing practice as a result of the investigation and findings requires a plan. When dealing with errors or adverse events, practitioners and health care organizations need to provide the necessary care, compassion and concern to create a climate that will help patients. Failing to communicate a concern or an adverse outcome can routinely lead to pursuit of legal counsel and malpractice litigation. Organizations must be willing to share and act upon findings of error investigations and make patients and families aware of actions that will be taken to mitigate or resolve the adverse outcome for their loved one. Patients are also often interested in knowing that strategies are put into place to assure that the same event will not recur for another patient. Health care organizations should have a plan to provide this information by taking the initiative in explaining adverse event. Recommendations for initiating these difficult conversations include[61]:

- If possible, seek counsel from the health care organization's risk manager
- Select a setting that will preserve dignity and confidentiality
- Deliver a clear message
- Discuss support options
- Wait silently for a reaction from patient and/or family
- Deal with the reaction
- Express empathy, but be careful that it is not interpreted as negligence
- Conclude interaction by reviewing discussion and asking if patient has understanding
- Document the discussion
- Consider a follow-up meeting
- Share findings with necessary organizational personnel

For each interaction or consultation with a patient receiving medications, there are some methods that practitioners can utilize to provide ongoing support of safe medication use by patients. Wiegman and Cohen suggest that patients must have the answers to the following 12 questions in order to ensure safe medication use[62]:

- What are the brand and generic names of the medication?
- What is the purpose of the medication?
- What is the strength and dosage?
- What are the possible side effects and what should be done if they occur?
- Are there medications that should be avoided while using this product?
- How long should this medication be used? What outcomes are expected?
- When is the best time to take this medication?
- How should this medication be stored?
- What should be done if a dose is missed?
- What foods should be avoided while taking this medication?
- Does this medication replace another medication currently prescribed?
- What written information is available to explain this medication?

Patients can and should play an important role in their medication therapy. Patients have a right to know about their medication therapies and practitioners have to assess that the information they are providing reflects not only the best scientific evidence available regarding risks and benefits but also considers alternatives, values, and concerns presented by patients. To assure that all options are discussed, practitioners should assure that medication information for patients are current and reflect clear goals and monitoring plans. Additionally, efforts should be undertaken to assure that communication is two-way and conducted so that messages sent are understood by all parties.

HEALTH CARE AS A SYSTEM

> "The problems we have created will not be solved by the level of thinking that created them." **Albert Einstein**

Improving patient care safety requires a systems view of the care delivery process, a unique perspective on reality that sharpens awareness of the system as a whole, including how its parts interrelate. Systems thinking teaches us that interactions between parts are often more important than actions of individual parts because interactions often produce valuable new and unpredictable capabilities that are beyond the capabilities of any single component.

One thinks and speaks of health care as a system. Yet, while the term *health care system* is in common use, there is no spe-

cific vocabulary that is commonly used to express the dynamic complexity of what the term means, either discretely in discussing an organizational entity (tightly or loosely coupled sites of care across the continuum) or globally to refer to the care delivery process available in America. In fact generically, *system* can typically have at least three meanings:

- *THE* system, the way things get done, how it works, the powers that be
- Groupings of elements for classification or analysis
- A functionally related group of interacting, interrelated, or interdependent elements forming a complex whole with a common aim

By definition, systems of things are complex. How the elements function together defines *systemness.* For purposes of this discussion, interdependence is a key feature. Deming defines a system as a group of interdependent people, items, processes, products, and services with a common aim.[63] Complex adaptive systems–slime mold, termite mounds, ant colonies, bee hives, flocks of birds, pods of whales, or health care organizations–must adjust to fluctuating environmental conditions to survive. Individual agents within the system are free to act in ways not always predictable and the actions of those agents change the context of the other agents in the system. No amount of data-driven forecasting, top-down strategic planning, management controls or policies and procedures can account for all the possible variables of fluctuation and change. As a result, complex adaptive systems must be continually emergent and self-organizing in response to the internal and external stimuli. Health care leaders have begun to recognize the wisdom of the basis of systems thinking: *The whole is greater than the sum of its parts.*

Complex adaptive systems have been described in a growing body of research, literature, and theory known as complexity science. Despite complexity, and apparent randomness, these intricate and leaderless operations and maneuvers–like flocks of geese flying south to the same destination at precisely the right time in response to changing conditions–don't descend into chaos and in fact demonstrate a stunning nimbleness, precision and efficacy.[64] As with ants in search of food for the nest, or birds migrating, humans have the capacity to self-organize to apply knowledge, experience, organizational support, and resources in delivering care.

Complex systems have *fuzzy* boundaries. Membership can change and agents can simultaneously be members of several systems, which can create unexpected actions. Internalized rules sets drive actions. Schooling fish, migrating birds, stampeding herds of animals need to follow only three instinctive rules: match your speed to your neighbor's, avoid collisions, and always move toward the center of the mass. Similar rules exist on a human level within health care, reflecting instincts, constructs, and mental models based on knowledge and experience. However, there is no need for them to be shared, explicit, or logical when viewed by another agent.[65] In everyday life, many complex behaviors emerge from relatively simple rules.[66] While no one directs our actions, one knows how to behave adaptively in commuting to work, to get where one wants to go.

Because the *rules* are not fixed, elements are changeable and may be simultaneously part of multiple systems, relationships are nonlinear, behavior is emergent and sensitive to small changes in conditions, complex systems are inherently unpredictable over time.[67] Paradox, tension, and anxiety are natural products of complex systems. Plsek identifies questions that aid in exploring the paradox[68]:

- How can we provide direction without issuing directives?
- How can we lead by serving?
- How can we maintain authority without control?
- How can we set direction when we don't know the future?
- How can we oppose change by accepting it? How can we accept change by opposing it?
- How can we be both a system and independent parts?

Systems naturally seem to resist imposed change, yet system behavior follows natural attractor patterns. Resistance is really poorly understood attractor patterns; dialog, listening, appreciative inquiry and a trust environment build understanding, shift attractor patterns, increasing the tension for change and the likelihood of success for complex change initiatives.

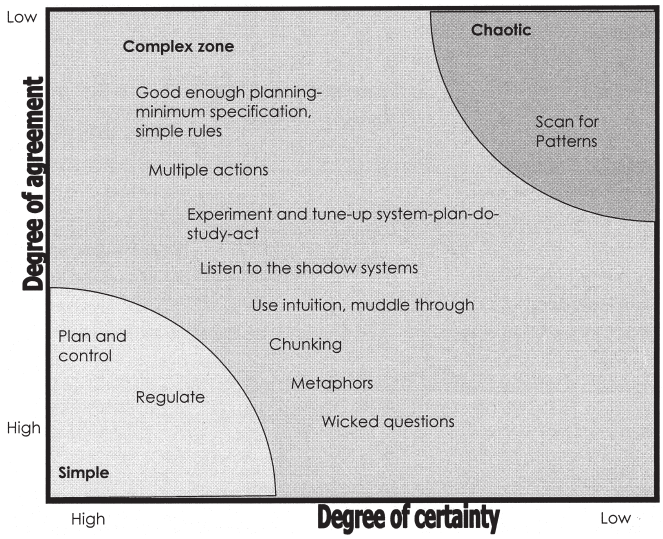

Figure 102-6. Certainty agreement. Adapted from Wilson T, Holt T. Complexity and clinical care. *BMJ* 2001; 323:687.

Too often in complex adaptive systems, individuals are expected to produce definitive answers to questions or issues in conditions of high uncertainty and low agreement. Figure 102-6 displays certainty-agreement diagram, reflecting the edge of chaos notion of complexity.

The middle zone reflects the lack of certainty and agreement so evident in clinical practice decision-making and in many of the decisions facing health care organizations, including patient safety improvement. View the system through a lens of complexity, learning flexibility, and adaptability as a leadership strategy. This zone of complexity is managed with a few simple rules, minimum specifications to provide direction and sense making opportunity, experimentation, including the Plan–Do–Study–Act (PDSA) cycle for testing improvement. In this zone, a *good enough* vision and the *next best step* in the right direction is more likely than perfection. In uncertainty, one balances data and intuition, safety and risk, control and acceptance of the unknowable. Techniques such as *chunking* (ie, creating categories of events to understand the underlying patterns of behavior) or analogy and metaphor are useful to understand behaviors. The result is the adaptive behavior of system elements reacting to the change around them.

One of the most compelling calls for the application of the principles of complexity science to health care appears in *Chasm*, which offers 10 simple rules for the 21st Century of Health Care (Table 102-1).

Systems thinking methods define a process for analysis, reflecting seven basic skills. Each skill plays a role in supporting one or more of the steps. The skills are not difficult, but are often counterintuitive to traditional thinking and organizational behavior. Figure 102-7 displays seven systems thinking skills and illustrates the process and the individual skills that must be mastered.

Systems thinking begins with the definition of a problem or issue of concern. Once that is defined, it is necessary to construct a model or hypothesis, which represents one's assumptions about how a particular part of the system works. The hypothesis is then tested by simulating the model. If the model can generate the problem, it is a valid hypothesis; if not, it needs to be modified and retested. Once a valid model exists, it can be communicated to others to begin the change process. It is important to realize that all models are always wrong to some degree, hence the value is not in how *right* the model is, but how

Table 102-1. Simple Rules for the 21st Century Health Care System

CURRENT APPROACH	NEW RULES
Care based primarily on visits	Care based on continuous healing relationships
Professional autonomy drives variability	Care customized according to patient needs and values
Professionals control care	Patient is the source of control
Information is a record	Knowledge is shared and information flows freely
Decisionmaking based on training and experience	Decisionmaking is evidence-based
"Do no harm" is an individual responsibility	Safety is a system property
Secrecy is necessary	Transparency is necessary
System reacts to needs	Needs are anticipated
Cost reduction is sought	Waste is continuously decreased
Preference is given to professional roles over the system	Cooperation among clinicians is a priority

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useful it is helping to clarify and understand the reality of the system. Every model is only as good as the thinking that goes into creating it and the seven basic thinking skills play significant roles in improving the quality of the thinking that leads to the hypothesis and model.

The seven skills are typically applied sequentially, to address three separate aspects of problem/issue identification and resolution[69]:

1. *Specifying the problem or issue and setting boundaries for the model*
   - Dynamic thinking
   - System as cause thinking
   - Forest thinking
2. *Constructing the model*
   - Operational thinking
   - Closed-loop thinking
   - Quantitative thinking
3. *Testing the mode.*
   - Scientific thinking

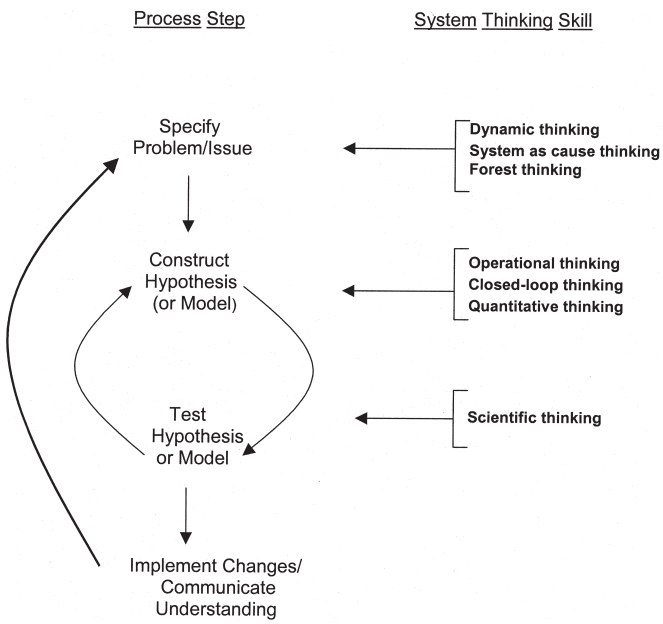

Figure 102-7. Seven system thinking skills. Adapted from Richmond B. *The "Thinking" in Systems Thinking*. Waltham, MA: Pegasus Communications, 2000.

Each skill brings a unique perspective to the analysis. Systems thinking and complexity theory reframe one's view of systems that are only partially understood by traditional methods.[70] These concepts allow for insights into organizational behavior and evolution, demonstrating sustainability, viability, health, and the capacity to innovate. They offer an alternative view and options for new approaches to complex issues like patient safety. Applying systems thinking and skills at the microsystems level offers the potential for new perspectives to target safety improvement where it matters most–at the point of care (Table 102-2).

TARGETING MEDICATION SAFETY AT THE MICROSYSTEM LEVEL

What to do about safety and performance is the key question for many professionals and health care organizations. How can individuals make a difference? What is the best first step? Will someone come up with a grand master plan that provides a roadmap? IOM's *Chasm* offers four recommendations for a tiered strategy[71]:

- Establish a national focus on patient safety by creating a center for patient safety within the Agency for Healthcare Research and Quality (AHRQ)
- Identify and learn from errors by establishing nationwide mandatory and voluntary reporting systems
- Raise standards and expectations for improvement in safety through the actions of oversight organizations, group purchasers, and professional groups
- Create safety systems inside health care organizations through the implementation of safe practices at the delivery level

For the most part, medical safety research, including research on medication safety, has focused on identification, quantification, and exploration of causal pathways of error, as well as well as the concept of safety culture and the structure that supports a safety culture. Organizations and individuals have been the focus of growing scrutiny, yet until recently, little attention has been addressed at the microsystem level of care delivery, where the vast majority of care is delivered to patients. In relative isolation, researchers have studied medical and surgical staff, interdisciplinary teams and specialty practice to discern what characteristics enhance safety. How structures and strategies of care delivery at the microsystem level affect performance and outcomes holds a promise for vast improvement opportunity. Additional research will be needed to develop and test better ways to prevent errors and improve safety at the microsystem level–the sharp end–of health care organizations.

The microsystems concept is based on systems theory and the work of Deming, Senge, Wheatley, and others who applied systems thinking to concepts of organizational development, improvement, and leadership discussed elsewhere in this chapter.[72–74]

The notion of a microsystem in health care springs from Quinn's theory of the smallest replicable unit, stemming from research of highly successful organizations that continually engineered the frontline interface relationship that connected the organization's core competency with customer need.[75]

Microsystems are defined as small, organized groups of providers and staff caring for defined populations of patients. Nelson et al define clinical microsystems in health care as[76]:

"A small group of people who work together on a regular basis to provide care to discrete subpopulations of patients. It has clinical and business aims, linked processes, and a shared information environment, and it produces performance outcomes. Microsystems evolve over time and are often embedded in larger organizations. They are complex adaptive systems, and as such they must do the primary work associated with core aims, meet the needs of internal staff and maintain themselves over time as clinical units."

Table 102-2. Traditional Thinking VS. System Thinking Skills

TRADITIONAL SKILLS	SYSTEMS THINKING SKILLS
Static thinking Focusing on particular events	**Dynamic Thinking** Framing a problem in terms of a pattern of behavior over time
System as effect thinking Viewing behavior generated by a system as driven by external forces	**System as cause thinking** Placing responsibility for behavior on internal actors who manage the policies and plumbing of the system
Tree by tree thinking Believing that really knowing something means focusing on the details	**Forest thinking** Believing that to know something, you must understand the context of relationships
Factors thinking Listing factors that influence or are correlated with some result	**Operational thinking** Concentrating on getting at causality and understanding how a behavior is actually generated
Straight line thinking Viewing causality as running one way, with each cause independent from all other causes	**Closed loop thinking** Viewing causality as an ongoing process, not a one time event, with the "effect" feeding back to influence the causes, and the causes affecting each other
Measurement thinking Searching for perfectly measured data	**Quantitative thinking** Accepting that you can always quantify, though you can't always measure
Proving truth thinking Seeking to prove models to be true by validating them with historical data	**Scientific thinking** Recognizing that all models are working hypotheses that always have limited applicability

Adapted from Richmond B. *The "Thinking" in Systems Thinking.* Waltham, MA: Pegasus Communications, 2000.

Focus on the microsystem offers the potential for greater standardization of common activities, while still offering needed customization of care for individual patients. An increased use and analysis of information and medical evidence to support daily work is a key component of improvement efforts at the microsystem level. Constant measurement and feedback of data to providers and patients offers the infrastructure and information flow that supports shared learning, understanding, and improvement of process, performance, and outcome. Open dialog, collaborative teamwork and multifunctional/multidisciplinary cooperation, respect, and caring are the hallmark of a highly reliable microsystem of care. Learning within and among microsystems offers an unsurpassed opportunity to identify and spread best practices. The results of interactions between patients, staff, and support processes produce results–clinical, economic, health status, and satisfaction outcomes—that combine to represent a relative value. There is also a gestalt, *what it feels like*, that includes relationships, culture, and climate. The structure, process, and patterns of behavior, sentiment, and results contribute to capability and reliability.

Weick and Sutcliffe have written extensively about highly reliable systems that function in highly complex environments, engage highly sensitive technologies, and have high demand for failure free results.[77] Air traffic control, nuclear reactor sites, and naval carrier commands are among the examples offered for organizations that operate with very low error rates and virtually no failures over many years. Among the behavioral characteristics noted in these highly functioning microsystems are awareness of the unit as a microsystem with its inherent responsibility of purpose and mindfulness of the need for reliability.

Mindfulness is demonstrated by a virtual preoccupation with failure and its consequences as a potential event. Operating in such an environment typically means that simple answers and solutions aren't readily accepted; the team takes deliberate steps to create a rich and detailed view of issues and problems, with full recognition of the complexity, unpredictability, and unknowability of the environment. Highly reliable microsystems fully understand and accept Reason's concept of *latent failures*, loopholes in the system's defenses, barriers, and safeguards and are attentive to these imperfections that can combine for calamitous results. These microsystems are resilient and have developed capacity to detect, contain, and bounce back from those inevitable errors. They are not error-free, but errors don't disable them. Through a combination of keeping errors small and improvising workarounds, they keep the system functioning. Finally, such systems defer to the expertise demanded by the situation and transfer leadership to the most appropriate team member for the situation. The more richly these practices are adopted and shared within the microsystem, the more mindful it becomes. The result is a radical *presentness*, a connection to the actual demands of the moment and current situation, coupled with a chronic unease that catastrophe might actually occur at any time.

Mohr and Donaldson studied clinical microsystems with the objective of identifying the characteristics that support these organizational units to achieve the success they do.[78] Their findings were reported in an IOM publication and outlined eight attributes associated with high quality, including:

- Constancy of purpose.
- Investment in improvement.
- Alignment of role and training for efficiency and staff satisfaction.
- Integration of information technology into workflow.
- Ongoing measurement of outcomes.
- Supportiveness of the larger organization.
- Connection to the community to enhance care delivery and extend influence.

Nelson et al studied 20 high performing clinical systems characterized by superior performance and initially identified nine, but updated their work to reflect 10 characteristics shared by the systems.[76,79] These characteristics interact and interrelate to support the delivery of outstanding performance, and no single feature can stand alone to produce high quality, high value results (Fig 102-8 and Table 102-3).

Leadership of the microsystem must maintain constancy of purpose, establish clear goals and expectations, foster positive culture, and advocate for the microsystem in the larger organization. Formal leaders, informal leaders, and on the spot leaders are all part of a shared web of leadership that is based on empowering individual autonomy and accountability. Leaders must balance selling and reaching collective goals

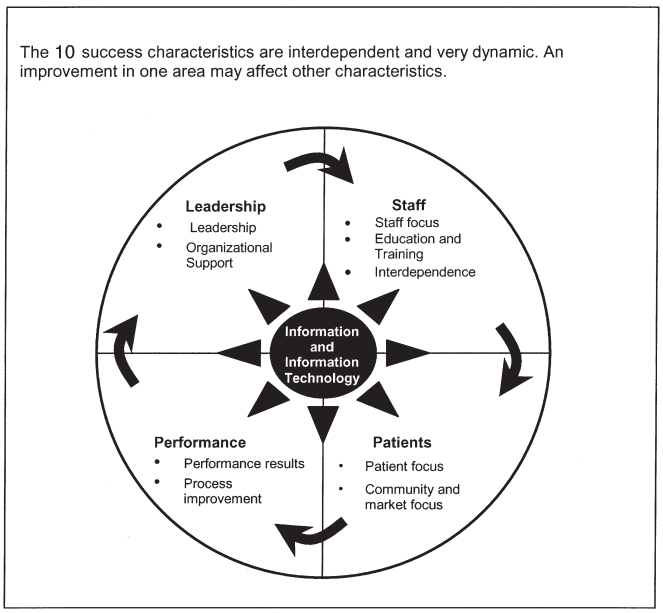

Figure 102-8. Clinical microsystems' 10 success characteristics. Adapted from Nelson EC, et al. Microsystems in health care: Learning from high-performing front line clinical units. *Joint Commission Journal on Quality and Safety* 2002; 28(9). Reprinted with permission.

with this autonomy through building knowledge, respectful action, thoughtful review, and reflection.

Organizational support is provided by the larger organization through recognition, information, and resources to legitimize the work of the microsystem. Coordination between microsystems is facilitated, and opportunities to connect and facilitate the work of the microsystem to the larger organization are fostered. Supports are in place to coordinate hand-offs between microsystems.

Staff focus includes attention to hiring the right people for the job, actively integrating new staff into work roles as well as the culture, and aligning competencies with the work. Expectations of staff are high: performance, continuing education, professional growth, and networking are part of the concept of human value chain, linking the microsystem's vision with people. Hiring, orienting, education and (re)training, incentives, and retention are priorities.

Education and training is the ongoing responsibility of the microsystem. There is a team-based approach to training and recognition that continuing education and development of competencies aligning with work roles is recognized as vital for success.

Interdependence is established and maintained through the development of trusting and collaborative relationships of staff based on willingness to help others on the team, understand and appreciate complementary roles and a belief that all contribute individually to a shared purpose. The team is multidisciplinary, and there is respect for each role on the team.

Patient focus is a primary concern, meeting all patient needs through caring, listening, educating, and in response to special requests. Patient focus is exhibited through innovation in response to patient need, provision of a smooth and timely service flow, and the ongoing nurturing of a relationship with the community and other health care resources. The patient is our reason for existence.

Community and market focus should be understood and served by microsystem. The relationship, how the microsystem serves the community, and how the community is a resource to the microsystem must actively connect patients to all available resources to meet their needs. A focus on excellence, partnerships, and innovative collaboration should be part of the individual microsystem and organizational outreach plan.

Performance results should focus on achieving high quality outcomes, reducing costs, streamlining care delivery processes, using feedback effectively, promoting positive competition, and establishing useful dialog about current practice performance and future goals for improvement.

Process improvement must be supported by resources. Within the microsystem and organization, an atmosphere for learning and redesign is supported by a plan for continuous system and practice monitoring, use of benchmarking, change assessment, and an empowered staff focusing on innovation and improvement.

Information and information technology IS THE CONNECTOR of staff to patients, staff to staff, needs with actions to meet needs. Technology can facilitate effective communication and both formal and informal channels must be used to keep everyone informed all the time to assure that learning and knowledge is linked to patient care. Communication, with reliance on technology and redundancy of communication channels keep everyone on the team informed, facilitate open dialog and keeps all team members in the loop on important topics and issues, with information access at the point of need.

Awareness of the need for change is a first step. Nelson et al have developed a short self-assessment instrument for use within clinical microsystems to evaluate development against the characteristics identified for microsystem success (See Appendix 1). Self-assessment should begin with introduction of the concept of clinical microsystems and completion of the evaluation by all staff members. Informational findings should be collated and distributed to the team. Then discussion of the results should occur using the findings as an opportunity to identify the strengths and development opportunities for the microsystem. Develop a plan for change based on the results. Focus on improving the level of microsystem performance: establish a few simple rules or minimal specifications, select a small number of measures, and provide regular, performance-focused data as feedback to gauge the level of performance. Develop a clear and compelling sense of organizational purpose. Find ways to recognize, promote, and reward performance, innovation, and improvement that supports the mission. Establish shared leadership, decentralized decision-making, and autonomy. Exercise *tight-loose-tight* controls; tight alignment of the mission, vision, and strategies, flexibility at the microsystem level to allow individuals and teams to achieve the mission as they see fit, tight control over accountability to deliver safety and performance results.[80,81]

Nelson and colleagues suggest that understanding and nurturing clinical microsystems may create an opportunity for leverage toward the goal of a safety and more effective health care system.[76] But, there is reason for caution. Galvin noted[82]:

> "New ideas in health care have a tendency to oversimplify and overpromise. Whether it be managed care, continuous quality improvement, or defined contribution, proponents seem to subscribe to the domino theory of health policy: if only this one idea could be applied appropriately, the great stack of complicated issues in health care would fall into place one by one."

The domino effect only works when all the dominoes are aligned. As described previously, attention to microsystem level activity and alignment has been a critical gap, but it is no silver bullet. Mastery at the clinical microsystem level can make a significant contribution to performance improvement for safety and outcomes, but it cannot effect the totality of change without equally effective attention at the self care (patient), relationship (patient-caregiver), macrosystem (organizational), and social (community and public policy) levels described in *Chasm*. There is no simple, quick fix to a complex, immense, and dysfunctional health care system dilemma like medication safety.

At the sharp end–microsystem level–one needs to understand the medication use process and the performance results it produces.

UNDERSTANDING THE MEDICATION USE PROCESS

While not all medication use systems are exactly the same, there are some constant and essential components of the medication use process that appear across the continuum of patient

Table 102-3. Scope of Ten Success Characteristics, Underlying Principles, and Safety Impact

SCOPE OF SUCCESS CHARACTERISTIC	UNDERLYING PRINCIPLE	SAFETY IMPACT
Leadership ▪ Maintain constancy of purpose ▪ Establish clear goals/expectations ▪ Foster positive culture ▪ Advocacy with in macro organization ▪ Formal, informal, on-the-spot	Leader balances setting and reaching collective goals with empowering individual autonomy and accountability	▪ Define safety vision ▪ Identify constraints for safety improvement ▪ Allocate resources for plan development, implementation, monitoring and evaluation ▪ Build input of microsystem to plan development ▪ Align quality and safety goals ▪ Provide update to Board of Trustees
Organizational support ▪ Recognition, resources, information ▪ Enhance and legitimize work of microsystem	Larger organization finds ways to connect and facilitate work of microsystem, including coordination and handoffs between Microsystems	▪ Work with clinical Microsystems to identify patient safety issues and make relevant local changes ▪ Put the necessary resources and tools into the hands of individuals without making it superficial
Staff focus ▪ Selective hiring ▪ Integration into culture and roles ▪ Aligning work with training competencies ▪ High expectations for performance, continuing education, professional growth, networking	Human resource value chain that links microsystem's vision with real people for hiring, orienting, continuously educating, retraining and providing incentives	▪ Assess current safety culture ▪ Identify gap between current culture and safety vision ▪ Plan cultural interventions ▪ Conduct periodic assessments of culture
Education and training ▪ Ongoing education ▪ Organizational learning ▪ Work roles and competencies aligned ▪ Best use of people and resources	Team approaches to training create learning that is collaborative and focused on quality, safety and integrated into work flow	▪ Develop patient safety curriculum ▪ Provide training and education of key clinical and management leadership ▪ Develop a core of people with patient safety skills who can work across microsystems as a resource
Interdependence of care team ▪ Trust ▪ Collaboration ▪ Willingness to help others ▪ Appreciation of complimentary roles ▪ Recognition of inputs to shared purpose	Multidisciplinary team provides care and every person is respected for individual vital role	▪ Build PDSA into debriefings ▪ Use daily huddles for AARs (after action reviews) and celebrate identifying errors
Patient focus ▪ Caring ▪ Listening ▪ Educating ▪ Response to special requests ▪ Innovating ▪ Providing smooth service flow ▪ Relationship with community resources	The patient is the common focal point, it's why we're all here	▪ Establish patient and family partnerships ▪ Support disclosure and truth about medical error
Community and market focus ▪ Partnership with community for resource exchange ▪ Outreach ▪ Innovation and excellence	Resource exchange and information sharing to assure that patient needs are met	▪ Analyze safety issues in community and partner with external groups to reduce risk to population
Performance patterns ▪ Patient outcomes ▪ Cost avoidance ▪ Streamlined delivery ▪ Data feedback ▪ Positive competition ▪ Open dialog about performance	Outcomes are routinely measured, with feedback to Microsystems leading to change based on data	▪ Develop key safety measures ▪ Create the "business case" for safety
Process improvement ▪ Learning and redesign focus ▪ Continuous care monitoring ▪ Benchmarking ▪ Tests of change ▪ Staff empowered to innovate	Studying, measuring and improving care are essential elements of daily work	▪ Identify patient safety priorities based on assessment of key safety measures ▪ Address the work that will be required at the microsystem level ▪ Establish patient safety "demonstration sites" ▪ Transfer the learning
Information and IT ▪ Information is key ▪ Technology links information and care ▪ Communication and channels	Information is a connector designed to support work of the unit for the right information at the right time	▪ Enhance error reporting system ▪ Build safety concepts into information flow (e.g. checklists, reminder systems, etc)

Adapted from Nelson EC, et al. Microsystems in health care: learning from high-performing front-line clinical units. *Joint Commission Journal on Quality and Safety 2002;* 28(9). Reprinted with permission.

care. These same steps occur in the inpatient, outpatient, acute care, long-term care, and home care settings. Medication use complication and errors can occur in all patient care settings; no patient care arena is immune.

Describing Medication Use

Medication use is a complex process involving, at times, multiple organizations and professionals from various disciplines. Risk factors can be identified along the medication use continuum. Knowledge of medications and timely access to accurate and complete information contribute to a series of interrelated decisions executed at various times throughout the patient care process. Error can creep in at any point. Safe medication use is dependent on a number of well-executed, sequential steps. Some errors are errors of commission (eg, administration of an improper medication); other errors are of omission (eg, failure to administer a medication that was prescribed). The diagram below depicts the steps involved in the medication use process. Consider how error may interfere with the appropriate and safe execution of the steps shown in Figure 102-9.

These steps involve participation of a variety of individuals and can range from expertly trained health professionals to the layperson in the ambulatory setting. At each step of the process, multiple factors can determine whether or not the step will be performed without error. An error-free final result depends upon error-free performance throughout the entire process. Thus, focusing on system change, rather than the individual practitioner, can yield more long-standing, predictable, and effective development of safety improvements.

Collaboration Across the Medication Use Process

Collaboration is essential to minimize patient risk in the medication use process. Health care providers within the organization need to understand and identify how these components function and who is involved in making these steps safe. Clear understanding of the critical safety issues at each one of these steps is of particular importance because the primary goal of adverse event identification is adverse event prevention. Each step can be considered a risk point and provides opportunities for internal checks and balances.

At each step in the medication use process, it is often assumed physicians, nurses, pharmacists, and other health care providers in the organization play a role in patient evaluation. This evaluation would include assessing patient characteristics, medication selection, concurrent medications, medication dosage selection, and medication administration methods appropriate for the condition to be treated. Additionally, it is also believed that by having this collaboration, each set of practitioner eyes can protect patients by catching a mistake made earlier in the process or by correcting for another individual's lack of understanding or poor judgment.

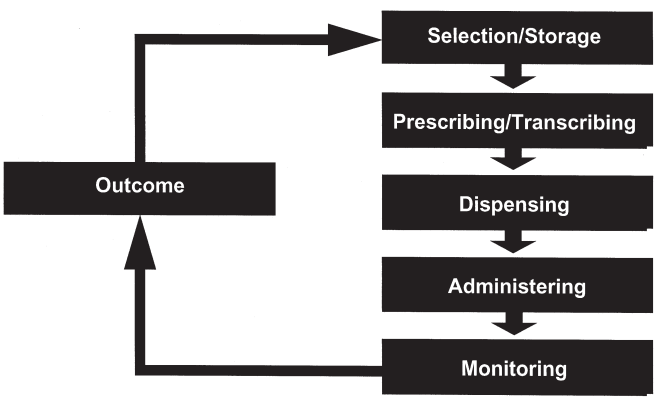

Figure 102-9. Medication use process. Adapted from JCAHO. JCAHO 2003 Hospital Accreditation Standards. Oakbrook, IL: Joint Commission Resources, 2004:175. Reprinted with permission.

Despite this practitioner-centered safety system, errors can—and do—occur.

This is not to suggest that the vital role of health care professionals should be ignored. Physicians, nurses, pharmacists, and others will continue to play an important role in ensuring the safe and appropriate use of medications. The current system of prescribing, dispensing, administering, and monitoring, however, often places the responsibility on the individual to avoid making the mistake. Because this expectation seems unreasonable, organizations should focus efforts to improve medication use safety by using a systems-based approach that identifies:

- Errors that occur most frequently
- Possible root causes of errors
- Error prevention strategies to make it harder for the same or similar errors to occur
- If the organization has a system that makes it harder to commit an error, it will be more difficult for mistakes to go on undetected and for harm to come to patients

System Failures Identified in the Medication Use Process

Varieties of systems failures have been identified in hospitals that have studied factors associated with adverse events.[83] These system failures are listed below:

- Deficiencies in medication knowledge, including prescribing of incorrect medications, doses, forms, frequency, or routes of administration
- Failure to verify the identity or dose of medication administered, often due to look-alike packaging or similarities between medication names
- Inaccessibility of patient information including laboratory test results, current medications, and information on the patient's current condition
- Incorrect transcription of orders, often due to illegibility of the physician's handwriting
- Failure to note known medication allergies
- Inefficient order tracking, making it difficult to determine when a medication has been given, missed/discontinued or changed
- Poor communication between services, including between nurses and pharmacists
- Improper use of administration devices
- Lack of standardized dosing schedules or disregard of existing standards
- Lack of standardized system for medication distribution
- Lack of standardized procedure across units
- Errors in preparation of intravenous medications (when performed in the patient care area)
- Poor information transfer when patients are moved from one patient care area to another
- Inadequate or nonexistent system for resolving conflicts related to medication orders
- Deficiencies in staffing or work assignments leading to excessive workloads, inconsistent availability of staff or inadequate management
- Lack of feedback and follow-up information on observed adverse drug events

As a result of this identification, a variety of improvement recommendations have been made for health care systems to consider as they identify methods to reduce adverse drug events.[84] Strategies include:

- Elimination of handwritten medical records and physician orders
- Institute fail-safe tracking of medications and laboratory tests to ensure that patients receive correct medications and tests on time

- Establish protocols and guidelines that outline standardized practices
- Provide all medications in unit dose packaging, ready for patient administration
- Standardize medication procedures such as protocols for the use of hazardous medications, medication terminology, and medication names
- Make it difficult for someone to do something wrong by error proofing
- Implement bar-coding
- Make relevant patient information available at the point of patient care
- Improve the patient's knowledge about treatment

Although, most of the suggestions provided could be implemented promptly and have been demonstrated to greatly reduce certain types of errors, these are not routinely incorporated into practice within organizations. Organizations must develop a systematic approach to evaluate their own medication use processes and establish a plan for improvement at each step: storage and selection, prescribing, dispensing, administering, and monitoring. Many recommendations have been provided in the literature for consideration to improve medication use safety.

Recommendations for Storage and Selection

Organizations of all types should develop a list of medications (a formulary) that is maintained and based on patient need and safety as well as economics. As this list is developed, proper storage and control of medications must be established. How medications are selected for routine use should consider parameters of need, given the type of diseases and conditions treated; effectiveness in terms of toxicities, pharmacokinetic properties; therapeutic or pharmaceutical equivalence; risk potential such as known incidence of adverse drug events or potential for error in the medication use process (prescribing, preparation, dispensing, and administering), and acquisition cost or patient cost impact.

Practitioners should also identify methods to reduce the chance of medication error causes by medications with similar names or similar packaging. It is not enough to *tell* practitioners to *be careful* as they select or store medications for use. Reading the label and product name selected out loud may help serve as a double check. For each product, repeating name of the medication, dose, and route may help identify if the wrong product is selected. Human nature leads practitioners to identify items by color, shape, font type on packaging, symbology as well as other visual characteristics. As practitioners select medications for use within their health care organization, an evaluation of reported safety alerts due to labeling and packaging should be considered. Known look-like or sound-alike products should be avoided. At a minimum, placing these look-alikes, sound-alikes in different locations and apart from each other in the storage area with additional labeling or signage warning of similarities may also assist in promoting correct product selection.

Manufacturers have also been called upon to improve the readability of medication labeling and packaging. Reducing label clutter on packaging, use of color coding along with distinctive background patterns or borders, providing two-sided labeling and assuring contrast of important medication name, dose and route information on packaging have all been suggested as methods to improve the medication labeling process.[85] Additional suggestions for standardizing display of medication concentration, strength, or terminology such as single dose and multi-dose packaging has also been advocated.[85] Often a display of additional advertising information and a display of company name and logo can interfere with product identification. Just as the medication ordering process can be improved by including standardizing terminology and warning information, use of standards could also improve safety. Some manufacturers have begun using distinctive typeface, serif or sans serif and upper- or lower-case letters to convey distinctive portions of look-alike or sound-alike names.

Recommendations for Prescribing Improvements

Many opportunities exist to improve the safety of the medication use process. The prescribing phase of the medication use process, however, encompasses the majority of medication errors that result in preventable ADEs. The knowledge that ADEs can be prevented compels organizations to identify the factors or system failures that contribute to the errors in the prescribing phase. Such factors identified in the prescribing phase include[86,87]:

- Availability of medication information at time of prescribing
- Access to patient information at time of prescribing
- Availability of dosing information at time of prescribing
- Availability of allergy information at time of prescribing
- Accuracy or completeness of order by prescriber
- Legibility of handwriting
- Use of abbreviations
- Use of decimals in expressions of weight and measure
- Use of varied units of measure
- Medication name look-alikes or sound-alikes

Error Potential in the Prescribing Phase

The three most common forms of prescribing errors include dosing errors, prescribing medications to which the patient had an allergic history, and errors involving the prescribing of inappropriate dosage forms.[87] In the examples listed, timely access and use of information is essential to avoid adverse drug events. Although not a panacea, use of a computerized medication order entry system can significantly contribute to the prevention of medication errors. The type of health care information that is best suited for computerization includes[88]:

- General information storage (eg, patient or medication information, retrieval)
- Repetitive functions (eg, dosage guidelines, medication names, allergy information)
- Complex processes that depend on reproducible results
- Items where legibility is essential
- Items that require timely attention
- Items where accuracy is vital

In the prescribing stage, lack of medication knowledge and lack of patient information account for the majority of errors. Many physicians find it a challenge to keep up with this data flood and often prescribe on the basis of incomplete or obsolete information, greatly increasing the risk of error. In addition, an enormous volume of new medical information is generated each year, including information on powerful medications available for acute and chronic disease. Dosing calculations are a well-recognized cause of medication errors. Performing routine, independent cross-checking of dosing calculations are useful when verifying dosages for pediatric, geriatric, oncology, transplant, or other populations with special medication requirements. For verifying dosages, use of both mg/kg and mg/m^2 (or other expressions as unit per weight or body surface area) in addition to actual dose calculated is recommended. Another potential safety improvement includes standardizing dosages whenever possible as well as the use of commercially available dosage forms. This will require prescriber approval and cooperation. However, avoiding complex calculations is one way to avoid calculation errors. If transcription of medication orders is part of the health care organization's practice to transfer prescribing information to a medication administration record, similar guidelines and standards for evaluating standards,

completeness, and accuracy should be put into place with a routine evaluation of practice compliance.

Other practices (eg, the use of verbal orders, electronic order transmission via facsimile machine, use of global prescription orders such as *resume all previous orders*) provide many opportunities for miscommunication. Whenever possible, verbal orders should be avoided. Only specific personnel (eg, physicians, pharmacists, nurses) should be allowed to dictate and receive verbal medication orders and only in approved circumstances. When used, verbal orders should be enunciated slowly and distinctly. Difficult medication names and instructions should be spelled out. Ambiguity should be clarified. The individual receiving the order should transcribe the order and then immediately read the information back to the prescriber. In the inpatient or long-term care setting, the prescriber should countersign and verify the verbal order as soon as possible.

Many health care organizations now use facsimile transmissions for prescription order transmission. Streaked, blackened, or faded areas and phone line *noise* appearing as random markings are often present on facsimile transmissions. Careful inspection of the copy is necessary to evaluate if extraneous markings interfere with the actual order. Transmission of prescription orders in this manner still can contain illegible, ambiguous, or improper abbreviations.

Failure to write a prescription order can also provide many opportunities for error. When medications are held or resumed or patient care is transferred to another location or provider, it is imperative that a complete review of medications is occurs. Simply stating *resume all, hold all,* or *continue all previous medications* is not acceptable practice. Reviewing all medications for appropriateness is good practice and also a systematic method to review the indication for use and monitoring plan in place for the patient.

Another technique used to assure safe and effective prescribing practice is the use of a medication formulary. While physicians often consider a medication formulary as simply a method to control expenditures, formularies can be used as instructional and quality tools to assure that only agents that are safe, effective, and necessary for use are provided for patients under care. An organized formulary process comprises of a systematic peer review of medications for use and monitoring within a health system. Medications are typically evaluated for safety, effectiveness, policy implication, and practice requirements. Use of a formulary can assure that information is provided in a timely fashion, because the product has been thoroughly evaluated for use.

Executing a safe and effective prescription order requires communication of complete information to all intended readers. A complete order should contain, at a minimum:

- Patient name
- Patient specific data
- Generic and brand name (ideally, both names should be provided; if only one name used, generic is preferred)
- Medication strength, in metric units by weight
- Dosage form
- Amount to be dispensed, in metric units (terms such as bottle, tube or ampule should be avoided)
- Complete directions for use including route of administration, duration, dosing frequency, medication purpose, and number of authorized refills

While abbreviations might appear to be a time saver, their use can lead to confusion, misinterpretation, and increase the potential for error. Misplaced or missing decimal points also pose concerns. Recommendations for improving orders requiring fractions or decimal indications include adding a zero before a decimal point and eliminating trailing decimal points and zeros. Various organizations, including the Institute for Safe Medication Practices, have published lists of abbreviations and decimal point miscommunications that have been associated with medication errors and should not be used.[89] To reduce error potential, preprinted order forms have been suggested to reduce error potential. It is important to note that if preprinted orders are not carefully developed, they may actually induce errors. As standard orders, algorithms or preprinted guidelines are developed, all disciplines involved in the ordering process, should be involved in the development, review, and approval of these documents.

Prescribing improvement efforts should include development of policies and procedures that support safe medication use and ordering. Practitioners should routinely be required to assess and document the need for and selecting the correct medication. Regimen selection should assure that specific, individual treatment goals are identified. Improvement efforts should also include attention to avoiding delay in treatment or in responding to a medication use concern, including inappropriate indication (or no clear treatment indication) and failure to provide preventive care or prophylactic treatment. Prescribing plans should include monitoring or follow up treatment.

Prescribing can be improved if prescribers have the necessary data to assure that decisions can be made (ie, indications for use, potential for interactions, risks and benefits, monitoring concerns). The process of medication prescribing via computer order entry would greatly affect the rate of errors associated with ADEs. A computerized medication ordering system could provide alerts regarding specific prescribing concerns in the medication ordering process (eg, identifying dose, allergy, drug-drug interactions). Having a routine approach to detect, intercept, and prevent these problems will reduce the potential for an adverse event to occur.

Clinical information systems can also assist in reducing adverse drug events and medication errors by:

- Increasing patient profile access and systematic screening of medication orders
- Alerting medical staff of abnormal doses, medication interactions, or allergies (based on patient profile)
- Generating 24-hour patient medication updates
- Recording medication administration

Computer support in the prescribing process is beneficial due to the fact that this process demands attention to detail related to the medication product, patient, and population characteristics, clinical information, and administrative issues.

It is important to remember that practitioners receiving the information within the organization are still required to use the appropriate skills to determine the relevance of this information for the patient. Simply automating the prescriptive process does not in and of itself make it safer.

Lessons have been learned in other domains regarding the impact and implications of technology.[90] If one thinks technology can solve security problems, then the person doesn't understand the problems and the technology. New technologies have enormous capacity, but what is seldom thought about is not how well it works, but how well it fails.

The most important element of any safety measure is people, not technology. The trick is to remember that technology can't save the day. The system has to be built around the people. Highly trained and motivated people bring to a task a quality not found in and technology: human judgment. Human beings do make mistakes of course, but they can recover from failure in ways that machines and software cannot. The well-trained mind is ductile. It can understand surprises and overcomes them. It fails well. *Key Learning*: Automating the process may, in fact, introduce new errors into the process. There is no substitute for human judgment within the medication use process.

Recommendations for Dispensing

In general, pharmacies and pharmacists are responsible for assuring that medications are dispensed correctly. Most dispensing errors involve providing an incorrect medication, dosage

strength, or dosage form to a patient.[91,92] Other common dispensing errors are dosing calculation errors or lack of interaction or contraindication with other prescribed medications. Typically, these errors are due to commission or omission and as a result of a "slip" or a "mistake" as identified by Reason.[51]

Error Potential in the Dispensing Phase

Dispensing is a complex process requiring a series of sequential tasks including preparation and processing of the prescription, locating and preparing the product, delivering the product to the end user and potentially providing counseling, screening and assessment activities at the time the medication is provided to the end user. The dispensing process has both mechanical and judgmental components. As a result, prevention of dispensing errors will require a comprehensive approach including evaluation of:

- Work environment: workload, distractions, physical location of service, hours of operation
- Inventory management: outdated or unused products, look-alikes, sound- alikes, clutter, labeling, purchasing of unit of use products
- Information resources: available references, updates, consultants, computer or decision support technology
- Performance evaluation: evaluation of staff competency and practice skill, knowledge and behaviors, cross-checking redundancies
- Patient involvement: patient education and review with *show and tell* techniques

This includes developing policies and procedures that support safe dispensing and distribution of medications. Methods to assure complete review and processing of the order should be defined. Other recommendations include controlling the distribution of medications through the use of a patient medication dose system. In cases where dosing can be standardized, every attempt should be made to provide the medication in the most ready to use format to decrease the potential for error. If necessary, specific guidelines for compounding or preparing medications should be clearly outlined and evaluated for compliance. Medications should be provided for patients in a timely manner while including safeguards such as the review of all prescription orders by a pharmacist. Products should be safely labeled, adhering to appropriate law and regulation as well and using a standardized method.

Several critical steps have been advocated for improving dispensing accuracy[93,94]:

- Secure or sequester high-risk medications
- Develop and implement standardized storage procedures
- Reduce distraction potential and improve workflow in dispensing environment
- Use reminders (labels, computer alerts) to prevent look-alike, sound-alike mix-ups
- Keep prescription order, label, medication and the medication container together throughout dispensing process
- Perform a final check on prescription content including verification with original prescription order and label
- Enter a manufacturer identification code into the computer profile and on prescription label
- Perform a final check on the prescription label, if possible, using automation such as bar-coding
- Provide patient counseling

Use of automation to improve the safety of dispensing in the inpatient and outpatient settings has been on the increase. In the 1980s, automated dispensing devices became available with hopes to reduce medication error rates, increase pharmacy and nursing department efficiency, improve availability of medication access on inpatient units, and enhance pharmacy inventory and billing capability. These systems are essentially medication storage devices that electronically control and dispense medications as well as track medication use. Many commercial systems are available. These devices require user identifiers, passwords, and track access by health care provider and use of medications by patient. Some systems include medication information support and integrate with internal and external systems such as medication profiling systems, clinical information databases, and the Internet.

The goal for utilizing such devices is to provide a *closed loop system*. It is a system that allows integration of prescribing information, medication information, real time clinical screening, intervention, and medication administration activities.

Recently, the Food and Drug Administration proposed rules that would require the use of bar codes on medication labels. This regulatory action would require manufacturers to provide linear bar code labels for prescription and over the counter products. While the rule will require approximately 3 years to be implemented after the final rules are published at the end of 2003, it is anticipated that this action will result in 413,000 fewer adverse events over 20 years as well as a significant reduction in costs associated with injury, litigation, and malpractice insurance.[95]

While automation has the potential for controlling, standardizing, and distributing medications in a timely and monitored fashion, human intervention can prevent systems from functioning as designed. Practitioners can override some patient safety features. When automated systems are replenished with stock or when returns are made, refilling mix-ups can occur. If verification of the prescription order, access to only the medication required or real time patient verification cannot be performed at the same time as medication dispensed (ie, not a closed loop system for medication use), error can still occur within the medication use process. While this type of automation has great potential for decreasing medication errors, it also has the potential to increase the opportunity for error if not applied or maintained appropriately. Certainly, judgment in the dispensing process cannot be adequately automated or replaced by use of such as device.

Recommendations for Administration

Responsibility for safe medication administration is often inappropriately placed on one individual, the person performing the actual administration activity. In fact, safe medication administration is a team effort, relying on all of the individuals involved in the medication use process to detect and evaluate clinical practice as the decision is made to provide a medication for a patient.

Error Potential in the Administration Phase

The administration phase, serves as a last final check on processing the entire medication order itself and includes:

- Evaluating the written order for appropriateness and completeness
- Assuring appropriate indication for use
- Evaluating and interpreting use of terminology and order method (abbreviation, units of measure, use of verbal orders)
- Dosing calculation or verification
- Identification of the patient
- Timing of treatment in context of other therapies
- Preparation and possibly dispensing of medication
- Proper use of medication devices
- Patient education
- Documentation of treatment

Efforts to improve medication administration safety should include addressing all these aspects of administration through appropriate policies and procedures. This would include methods to assure that the right medication is administered to the right patient at the right dose, right time, right route, and for an indicated reason. Informing the patient about the medication and whenever possible including the patient in the medication administration. Prescription orders should be verified and patients identified prior to administration. Processes to as-

sure that medications are retrieved from the patient supply when they are discontinued from the regimen or recalled by the manufacturer should also be in place. Staff must also be evaluated regarding their skills, knowledge, and behaviors expected for safe medication use. This includes their capabilities in the use of medication devices, ability to complete or verify dosage calculations and prepare medications. An assessment of documentation, communication, and clinical problem-solving capabilities as well as other medication use competencies are necessary to assure application of knowledge at this final point of care to assure safe medication use.

Recommendations for Monitoring and Outcomes

Ongoing measurement and monitoring of medication use is essential to assure safe and effective medication use. As part of any safety improvement initiative, this would include developing policies and procedures that support monitoring of medication effects. Use of guidelines and clinical pathways are common methods to assure a systematic approach to monitoring therapy. Documentation and exchange of these medication use outcomes findings should be shared with patients and other care providers as required. Systems should be in place to assure that patient responses are monitored and that both benefits of therapy and unexpected outcomes are documented. This necessitates identification and reporting of adverse drug events as well as methods of re-evaluating medication selection, regimen, frequency, and duration. Efforts to collaborate and communicate between care providers and for including patients in the process should be established to allow for complete review and management of patients medication regimens. Including patient perceptions along with information from the medical record and medication profile or list is essential. The primary concerns that exist with current monitoring systems include lack of:

- Guideline use
- Therapeutic monitoring plans
- Collaboration on common goal or of therapy
- Patient involvement

Gaps in the monitoring process, design, or follow-through have the potential to cause medication use errors.

CHANGING SYSTEMS WITHIN ORGANIZATIONS

Improving organizational and environmental factors in health care, as demonstrated in the aviation industry, enables system change to occur. If teams in an organization can work effectively, communication improves, resulting in the motivation to understand error. Unless an organization has a culture that supports understanding and reducing errors, system changes may only be minimally effective. Ideally, a strategy to improve error prevention should be coupled with organizational transformation and structured process changes. Optimizing a work environment for safety, increasing mechanisms for communication, having a leadership agenda, and commitment for medication safety improvement are essential components for an organization.

The Institute for Healthcare Improvement has identified that prevention must be the organizational focus and has provided strategies that should be included in the plan for medication use safety. The following items have routinely been identified as a top 10 list for improvement in the literature[96]:

- Improving knowledge about medications (availability, access and timeliness)
- Dose/identity tracking of medications (process understanding of distribution)
- Available patient information (availability, access, accuracy and timeliness)
- Order transcription (elimination of process)
- Allergy defense (hard stop capabilities, access to patient information)
- Medication order tracking (streamlining and effective communication of patient needs)
- Communication (patient information, system performance, medication use)
- Device use (standardization and competency regarding use)
- Standardization of medication dose
- Standardization of medication distribution

The challenge of a list like this is simple: it does not represent a one-time fix. Rather, it is a life-long agenda that requires ongoing and persistent attention. Reducing errors within an organization requires mindfulness (ie, diligence, attention to detail, and ongoing re-evaluation of this very dynamic medication use process).

However, strategies that have been put into place to reduce error potential have traditionally focused solely on the following items:

- Unit dose or unit of use medications
- Protocol and checklist development
- Computerization of patient information
- Standards including dosing times, specific medications for specific procedures or guidelines
- Training and education programs
- Decentralized or increased availability of pharmacists

These system redesign efforts have been recommended in the literature for years and appear insufficient to address the latent error potential within the health care system. Although this list identifies an array of systems improvements, an organization must understand that people make safety possible within the system. Organizations must routinely investigate and identify their own risk potentials. Having discussions regarding *near misses* may help identify where potential risks exist. Ongoing staff dialog, creating a sense of mindfulness, or even a preoccupation with safety is necessary to assure that organizational membership will take the lead in identifying next steps for improving medication use . . . and where the true risks lie.

The ongoing challenge for leadership is that there is a need for operational diligence. Identifying the careful balance between describing and supporting system change and integrating a human factors approach regarding how to implement and use these system improvements. In a sense, this is about understanding and designing a practitioner-medication use system interface at an organizational level and measuring and monitoring its performance.

How are adverse events identified and discussed within organizations? What prevents learning from occurring? How are prevention strategies developed? Literature suggests that members of a health care organization are more likely to discuss their errors when provided protection from disciplinary action. This is important in light of the fact that 95% of all medication errors go unreported because staff fears punishment.[97]

By establishing a method for all health care professionals to contribute information on medication use safety and errors in a nonthreatening fashion, an environment can be created to focus on improving patient care. If teams are allowed to work in an effective and efficient environment, communication can be improved and personnel can become motivated to understand the cause of errors along with methods to report and prevent them. Process redesign is essential, but unless the organization has a culture that supports understanding and reducing error, the effects of process change will be minimal. The team is the critical component for implementing a successful safety strategy. Leadership must focus on creating vision and collaboration that will allow the team to be successful.

Leadership for Safety

Medical and health care professions have experienced a sharp shift of attention in recent years, and patient safety is the new focus for what ails the system. Leadership is a critical and re-

curring theme for the improvement of patient and medication use safety. In *Chasm,* the IOM calls for strong and clear leadership for patient safety throughout the system. Baldridge award criteria charge an organization's senior leadership to set directions and create a patient focus, clearly visible values, and high expectations. Leaders seeking Baldridge recognition must ensure the creation of strategies, systems, and methods for achieving excellence in health care, stimulating innovation, and building knowledge and capabilities.[98]

Leadership is an attribute that allows some people to attract the loyalty and trust of followers by the simple fact of existing. Their resonant message, created infrastructure, amassed commitment, evidence, and rightness of vision captures follower's minds. While it is not the only, or even the most important factor, charismatic ability to communicate a heart-felt belief in a goal, the passion of commitment and the certainty of success serves to capture the hearts of followers. Capturing their souls with a belief system cements the bond of a shared goal and begins the distribution of leadership more widely.

Leadership is a term that has traditionally been used to identify formal leaders who are designated by position, and whose responsibilities include setting directional vision, mission, and achievement targets for the organization. They are also responsible for the setting and maintaining the culture, climate, and values that define how the organization behaves, grows, and interacts, internally and externally.

It is misleading to think that leadership is only provided by a few highly positioned people in the organization. This is particularly true for achievement of complex objectives like improving patient and medication use safety. Increasingly, the concept of leadership is becoming *democratized*, to recognize situational, informal, and *on-the-spot* leadership, and the growing notion that leadership must exist in everyone, to varying degrees, as health care organizations (*Read:* complex adaptive systems) learn to learn in a complex and evolving environment.

Leadership inspired by complexity theory acknowledges that change occurs naturally and continually within systems and that individuals engage in that change for a variety of reasons and to varying degrees. In the systems view, the leader's primary responsibility is to create systems that widely disseminate rich and credible information about better practices in ways that are meaningful to the various target audiences– those individuals who can influence performance and outcomes at the sharp end of the system, where care is delivered to the patient.

Fundamentally, health care organizations must, therefore, evolve to be learning organizations and to implement a strategy to eliminate *blaming* behavior, transitioning to the ubiquitous *safety culture.* Senge defines leadership as being about creating a domain in which human beings continually deepen their understanding of reality and become more capable of participating in unfolding the world.[99] Ultimately, leadership is about creating new realities.

There is no question that leadership for safety needs to start at the top. The real value is to commit to investment in the organization–from the board of trustees to the caregiver to the security guard (whether physical or information) to the support staff–and to build a belief that with a concerted and best effort on the part of every individual, that the organization can survive and triumph, and that patients will be the real winners in the process. To accomplish this, leaders need to allow them themselves to be vulnerable, to admit they don't possess all the answers, acknowledging that patient safety is a mutual and joint quest for innovation and solutions that reside in the collective minds of everyone (all the stakeholders.) This need starts with trustee leaders, who must ask:

- What initiatives are in place to assess quality?
- How is medication use safety addressed in the organization's mission statement?
- Is there an overall approach or plan for medication use safety?
- Does the plan include senior level leadership, provide defined objectives, commitment to the necessary personnel, and budget sufficient for goals?
- Is there a need for a chief medication use safety officer? Is the role focused on the importance of the medication use process? How closely is that role tied to the medication use process and delivery system?
- What commitments have been made to developing a safety of culture? What is the current state of the culture relative to safety?
- What measures are in place to ensure accurate, timely and relevant reporting for safety, with measures against progress?

This *starting at the top* will require change in attitudes and beliefs. Trust evolves from vulnerability (ie, the admission that no one has all the answers). Collaboration means letting go of insecure competition that assumes that one's gain is another's loss; being right destroys value. Communication must be ramped up and skills honed; this is the key to solving problems. Communication is also key to relationship building, which translates to understanding and openness; it is a lot harder to oppose what one understands. While there is some measure of risk associated with taking an untested course, there are no tested courses of action to improve safety, no guarantees. Leaders who will contribute to improvement and learning will be forced to take risks, to become the change they envision, reflecting a Gandhian philosophy. Finally, leaders need to personalize the need to change. If there are insurmountable problems, imposed external issues, the leader must assume the need to change the way the problem is framed, to change context, to assume that as some level, the organization, the leader, individuals are contributing to the problem or could behave differently to avoid it, minimize impact, or eliminate it.

Creating a learning organization requires a shared vision, inspiring individual workers–at every level, in every discipline–to embrace the effort and commit their best individual effort. This vision must be patient-focused, expectations set high but not impossible, sufficiently tangible, so that individual workers can identify with the vision and translate it to the context of their own day-to-day activities. Leaders, formal and dispersed, must take responsibility for fostering learning, through the use of champions, traditional education and training infrastructure and a culture-building that values, and rewards, innovative new applications of knowledge for performance and safety improvement. Learning opportunities should be designed to transcend passive assimilation of information, focusing on double-loop learning that is applied and reinforced by feedback of information that is close to the work and performance outcomes in both time and proximity.

It is a popular but confounding truism that every system is perfectly designed to get the results it gets. How then does one learn to redesign systems, to learn to change, to take action by deploying a plan to improve patient safety, particularly as it relates to medication use? To create change, leaders at every level of the organization will need to build knowledge, take action, and assess information to determine an enduring course of action.

Leaders–and every individual committed to improving the safety of the health care system–will need to commit to gaining new knowledge and skills that are not taught in the average health care–or pharmacy–curriculum. Needed knowledge and skills will include:

- Health care as a process, systems thinking, and a holistic view of managing and coordinating care
- Science of variation, measurement, assessment, data collection, analysis and reporting, including the concept of the balanced scorecard, statistical process control (eg, flow charting, graphing, pareto charts, run or control charts, RCA/FMEA, etc.)
- Customer and beneficiary knowledge and insight including what are the expectations and preferences of customers vs. what is possible given system constraints to influence the scope and boundaries of care decisions and to plan for the future
- Leading, following, and making changes, including change management, knowledge of assessment and influence of climate and culture, and the fine art of managing knowledge workers in an environment of scarce human resources
- Collaboration and reinforcement of individual capability for maximal impact, working effectively in teams to optimize the culture, climate and knowledge management of the organization, to create

the best work place environment, attract and retain the best employees and to become a world class example of quality and results
- Social context, reflecting community and organizational values, and fiscal and ethical accountability for responsible action
- Learning to develop new, useful knowledge based on empiric testing and application of evidence-based information for improvement
- Support and enhancement of individual professional discipline's subject matter with specific attention to evolving core competencies

Geller suggests that leaders need to focus transactionally on another, parallel agenda[100]:

- Focus on process
- Educate, train, and retrain
- Use conditional statements, not absolutes, and always leave the door open
- Listen, first, last, always
- Promote personal and individual ownership
- Create and encourage choice
- Set and enforce expectations
- Maintain a paradoxical balance between confidence and uncertainty
- Create more distinctions (not fewer) to generate a continuum of performance and value that will spread performance improvement opportunities and targets
- LOOK BEYOND THE NUMBERS; not everything can be measured

The IOM report, *Health Professions Education: A Bridge to Quality*, issued in 2003, recommended an overarching vision for the education and competency base needed for health professionals to be successful in a commitment to redesigning the health care system[12]:

"All health professionals should be educated to deliver patient-centered care as members of an interdisciplinary team, emphasizing evidence-based practice, quality improvement approaches and informatics."

Figure 102-10 depicts the overlap and relationship of these core competencies.

Leadership begins with vision, a full and in-depth understanding of the organization, its challenges in clinical quality and satisfaction, and the ability to create a culture that sustains quality and excellence in delivering health care to patients.

Culture begins with a commitment to lifelong learning, process redesign, and a belief that no one can ever know it all. In the safety culture, leaders support and sustain the belief that performance and outcomes must be continually measured and evaluated, that collaboration and teamwork must be the norm and are valued, and that organizational expectations demand care coordination and anticipated patient need to provide consistent and predictably high levels of care. Education must be transformed so that it is not solely focused on competence, but for capability (the ability to adapt to change, generate new knowledge, and continuously improving performance).[101] Successful, safe health systems will depend on organizations that focus on providing care that keeps up with the ever-changing context and landscape of health care delivery. Education for capability must focus on supporting learners who can identify and construct their own learning goals, receive feedback, reflect and move forward with new ideas to support best practices. Learning capability must be nurtured and supported. Reflective learners can transform as the environment around them changes; poor, ill equipped learners simply complain about the change, the demands and their involvement in the complexity of the care process.

Leaders, *even capital L* traditional ones, are not out there, alone. They rely on a powerful coalition of people who believe in the same vision, value, culture, and who share a time frame for achievement. This larger view of collective leadership in each individual delivers strength, rebound, and sustainability. Positional leaders need to act to:

- Remove obstacles
- Learn from mistakes
- Ask questions, listen and learn

Every system is perfectly designed to get the results it gets. Leaders must continually redesign the system for an emerging set of expectations, influenced substantially by existing culture and recognition of the value cultural change can bring.

Over the next 20 years, the health care system will have to treat proportionately more people, with more illnesses, using fewer dollars and health care workers. In the face of declining resources and growing demand, the health care system will have to be explicitly designed to implement new systems of care that are fundamentally sustainable. This reinvention will require a groundswell of leadership support to engage the consumer to maintain good health and actively manage illness, to employ technology where appropriate for improvement, and to assure systems that are intended to meet explicit needs, in contrast to the incremental and band-aid patched system in place today. Above all, as has occurred in other industries, these designed processes will need to be certifiably safe and efficient. By 2020, the current situation in which health care delivery actually contributes to morbidity and mortality through unavailable error, should be seen as a wretched historical anomaly.[102]

To redesign the system this dramatically, one will need to understand the behavior of complex systems and the science of system design, including informatics. Recognizing the complex interrelationships of technical and social systems, is the first step.[102] Whether enraptured by the promise of technology, or fear it, technology itself will not drive direction as much as the will and commitment of people. Cultural beliefs and values will shape the future of safety successes.

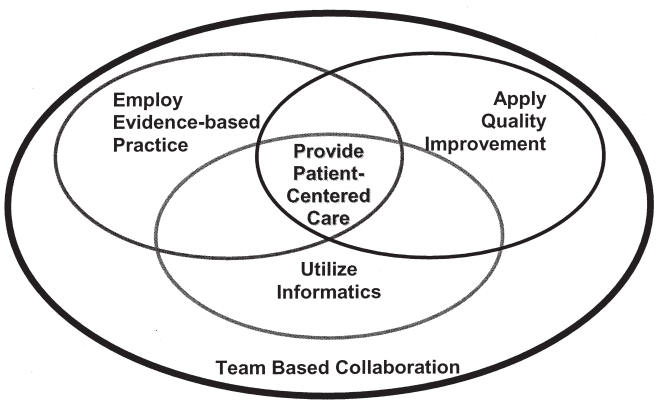

Figure 102-10. Overlap of core competencies for health professionals. Reprinted with permission from *Health Professions Education: A Bridge to Quality.* © 2003 by the National Academy of Sciences, courtesy of the National Academies Press, Washington, DC.

SAFETY CULTURE

"It must be considered that there is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle than to initiate a new order of things."—**Machiavelli**

Systemic change doesn't occur on command, nor is it a quick fix. It requires a long-term commitment. Typically, systemic change transitions require a period of 3 to 5 years, with the major factors of complexity, ambiguity, and the power of organizational culture contributing to the lengthening of the transition period. All too often the culture of an organization dictates success or failure of a change initiative.

Culture is a somewhat fuzzy concept. Schein defines it as the combined rituals, climate, values, and behaviors that shape what life is like within an organization. He further characterizes culture as define by six properties (1) shared basic assumptions, (2) that are invented, discovered, or developed by a group as it (3) learns to cope with its problem of external adaptation and internal integration in ways that (4) have work well enough to be considered valid, and therefore (5) can be taught to new group members as the (6) correct way to perceive, think, and feel

in relation to the problems.[103] Culture provides basic assumptions, shared values, and artifacts–visible markers and activities–that guide the way organizational members behave toward each other and approach their work. On one level, culture is a very simple concept, nothing elusive or magical: simply decide what the desired attitudes and behaviors are, identify the expectations and how people will be measured against norms. But as with many things in life, it really isn't that simple.

Culture is based on values. It reflects the vision and mission of the organization, as well as the goals that are set and the strategies that it employs to reach its goals. Leaders and top management must set the tone and expectation for the culture in the beliefs, values and actions that define expectations.

Communication from the top down must be credible, consistent, and relevant to be received and acted upon by workers, without any perception of hypocrisy. The perceived messages must resonate with workers, build in intensity toward a consensus and belief system. Reward systems must be aligned to support and reinforce the culture concept. Promotions, salary adjustment, approval, and reinforcement mechanisms should all flow in the direction of individuals acting on and supporting the culture, values, and beliefs, to avoid saying one thing, only to do another.

Individual roles and decision-making processes influence culture. Organizational systems–how training occurs, appraisal and reinforcement mechanisms, how goals are set–contribute to defining a culture. Job design, the complexity of technologies an organization adopts, and the interdependence of people in the culture play a significant role. Culture shapes what one expects from individual behaviors. Leadership, communication, and power distribution signal when and how cultures change.

Culture gives us a set of *felt* meanings in an orderly pattern, creating significance that provides individuals in the organization with a sense of belonging, order, and predictability. Culture is not what people do; it is what they feel. If people allow themselves to believe that culture is what people do, it becomes too easy to assume that parts, procedures, or goals can be changed without people being affected. Nothing could be further from the truth. Cultural symbols, rituals, and myths are not easily replaced.

Culture is a holistic concept. It is not one facet of work life, rather it is a complete set of feelings, affecting all individuals and groups, their attitudinal and structural behavior patterns. Cultures emerge to help cope with life's challenges and to teach the correct, accepted way to think, act, and behave in the larger organization. Every organization and group has a culture, no matter how dysfunctional it may be.

The prevailing culture in most health care organizations is an impediment to acknowledging error. Improving medication use safety will require cultural change.

Culture change is hard, slow, and subject to relapse. Schein suggests:

> Never start with the idea of changing culture. Start with the issue the organization faces in this case medication use safety; only when those business issues are clear should one ask the role of the culture in resolving the problem. . . .

If changes need to be made, try to build on cultural strengths rather than attempting to change those elements that may be weaknesses.[104] Creation or enhancement of a safety culture is dependent on deliberate manipulation of organizational characteristics believed to impact safety management.

Much attention has been devoted to the notion of a *safety culture*. A safety culture creates a perspective focused on minimizing exposure to danger or injury. Safety cultures are characterized by communications that are founded on mutual trust, shared perceptions of safety's importance and by confidence in efforts to ensure it is a high priority. The term *safety culture* first entered public awareness in the aftermath of the Chernobyl nuclear power disaster and quickly spread to the aviation and chemical processing industries. *Err*, which focused to closely on medication errors, reported[105]:

> Health care organizations must develop a culture of safety such that an organization's care processes and workforce are focused on improving the reliability and safety of care for patients.

Reason suggests that a safety culture is an informed culture, one where those who manage and operate the system have current knowledge about the human, technical, organizational, and environmental factors that determine the safety of the system as a whole.[106] Reason identified four subcultures that underpin a safety culture:

A *reporting culture* focuses on what gets reported when errors or near misses occur since safety cultures depend heavily on what can be learned from mistakes and near misses. Reporting cultures protect the safety and confidentiality of those who report, and they steadfastly trust the reports of those closest to the knowledge of the event. A safety culture must be informed and cannot exist with a flawed reporting relationship, where reports either do not exist or cannot be trusted.

How an organization apportions blame determines if it is a *just culture*, characterized a trusting environment that encourages, and even rewards, reporting of safety information. A just culture also has a clear line of demarcation between acceptable behavior that offers learning opportunity and does not deserve disciplinary action, and unacceptable behavior. In an environment where it is unclear what falls into the unacceptable range–about 10% of all events according to Reason–people are afraid and ashamed of error, only compounded in organizations that deal with errors inconsistently or routinely assigning blame. Trust is a pivotal factor in the just safety culture, with the solid knowledge that only clearly identified unsafe behavior is punished.

A *flexible culture* adapts to changing demands. In flexible cultures, information and decision-making tend to flow to technical expertise, hence they are less hierarchical. Mindfulness and its preoccupation with the potential for failure, creates an environment where any small symptom of concern is clue that safety may be at issue. When data are inconclusive, the default is to assume a safety risk, and to seek more data.

Knowledge changes culture, therefore, the concept of a *learning culture* is an important concept for safety. Learning cultures evolve when information is generated by knowledgeable people, and that information is widely shared. This access to information, coupled with a just and flexible environment, allows workers to become aware of best practices and to take action to adopt them. Dialog and open discussion about issues of controversy, where answers are not absolute and where variability is high, is characteristic of a learning culture. Learning can easily be stifled when management dismisses or *reasons away* issues that are raised, where promises are made and commitments are not kept or when individuals have a growing sense of the issues being far outside their control.

There is no absolute *cookbook* for building a safety culture. Several steps are important and support the development[107]:

Notice everything. Try to concentrate on mindful attention to patterns of the expected and unexpected events of routine operations. One might miss the unexpected unless you are looking for it.

Track down bad news. Try to understand the issues and causal factors, and just as importantly, notice what happens to bad news and the people who report it.

Clarify the onus of proof. Is the system assumed to be safe until disaster strikes? Or, dangerous until proven safe? Who decides? How many indicators would have to line up before there is a perceived problem?

Watch for unusual events and patterns. Encourage others to discuss and report unusual events. What are individuals not seeing? Try not to deny or rationalize the unusual event.

Define the near miss. Consider whether a near miss is a signal that safeguards are working, or that the system is vulnerable. Raise the comfort level to increase discussion of near miss events in the workplace.

Keep a holistic view and consolidate *explanations* for individual small deviations to avoid *de minimus* errors that cause us to explain away individual symptoms, and miss the diagnosis. Keep track of symptoms, diagnoses and alternative explanations.

Culture eats strategy for lunch. Don't overlook the power of social influence and the dominance of cultural systems, where strength is gained from mutual reinforcement.

Learning occurs and behavior changes when feedback is available, particularly when that feedback is proximate to the event. How does feedback occur? Is it passive or active? Is there an expectation that action will occur? Are feedback mechanisms and results a focus on ongoing attention and discussion?

Put individuals out there to actively stand for a safety culture. Public, irrevocable and actively chosen behavior with good purpose and aim, substantiated with values and reason, attract attention and often shape future behaviors.

Feelings are the engine of culture. Culture is about approval and disapproval, pride, despair, happiness, hypocrisy, shame and failure. It pumps intensity into what could be cool and impersonal ideas, and it makes one wince when something goes terribly wrong, fully knowing that it should not have occurred. Understand the feelings of your culture. Try to articulate what the culture means in terms of feelings and encourage others to express their perceptions. It will help to understand culture, to identify areas for improvement and to act to strengthen the influence culture has on behaviors and results.

Keep values simple. It may be as simple as do the right thing, do the right thing well, and continually improve. Keep it simple to ensure diligent attention, and to minimize confusion, dilution and a breakdown of consensus around the values.

Think safety first. Dwell on the mindfulness of failure, discover limits, uncover shortcomings and system flaws. Focus on the fear of failure, blaming behavior, the anxiety about errors that exists in the workplace. Provide supportive resources, training, positive role models, mentors, coaches, and a positive vision for what can be better in the future if some change occurs. Ask for and give help to move toward realization of the vision.

Realize that building a safety culture is an iterative process that will be reinforced as a result of ongoing continuous attention and activity focused on safety. Risk and hazards will not magically disappear one day when the goal is reached. This is a continual, endless quest toward a definitive victory that will require every part, every player's mindful attention, and the effective management of the team process.

TRAINING FOR TEAMWORK

Improving medication use safety will require substantial change in most health care organizations including change in culture, systems, and processes. Individuals and systems change because they learn. Adult learners choose to learn because they want to change, and in that learning process, they use existing competencies as a base for building new capabilities. Behavior change among adults derives from a complex mix of goal setting, deliberate action, feedback, and reinforcement, which is facilitated by appropriate education and training.[108] Culture changes over time, based on shared knowledge.

Learning, and therefore change, occur in a zone of complexity, where individuals engage items of knowledge in an unfamiliar and uncertain context and create a meaningful mental framework to make a transition from unfamiliar to familiar. This learning process is not passive, nor is it taught. Existing competencies are transformed and retuned for new circumstances within each individual.

As previously discussed, health care organizations are complex adaptive system. This perspective provides a point of reference to consider the learning process, where the behavior of individuals and the system itself evolves based on feedback regarding the actual and immediate impact of actions. Existing competencies become the base for transformational learning, and new capability evolves when new information is provided to learners about the impact of their own actions and those of others. The most successful educational processes offer feedback as it takes place. Not all learners transform feedback to capability at the same rate, in the same way. Reflective learners are open to this feedback and adapt their behaviors, transforming themselves and their impact as the world changes. Less adept learners are either not receptive to the feedback, or adapt inappropriately and complain.

In the past, knowledge was a scarce commodity, accessed by scholars and experts, held tightly in memory and brain capacity. Today everyone drowns in information. Knowing and acknowledging that one cannot commit all of the information to which one has access to memory–can't know it all–offers some relief from the burden of guilt that makes one feel that he/she should. Knowing what we don't know is an important step to understanding complex system events and finding a path to change. Beyond what we don't know, there is a frontier of unknowable and emerging information that represents uncertainty. This is information that is not yet integrated into a useful context to build knowledge and capability. In today's incessant flow of information, an expert's value lies in the ability to access *known* knowledge efficiently and with speed, to explore *new* knowledge to create new and relevant context, learning to create mental links between seemingly disparate ideas.

Because learning often occurs in the cracks between systems and system elements, understanding the interrelationships and connections between the elements can be more valuable than knowing the details of the individual parts. Yet health care organizations tend to *teach* in a more traditional, curricular, disciplinary, and fact-driven manner, the tendency is to provide factual content without context. It is no surprise that many learners don't understand the relevance, can't associate the new knowledge to other related information or their work, and as a result, fail to apply the learning to build competency and capacity for change.

Most education and training is planned to be formal and relies on narrowly defined learning objectives. Knowledge is presented as static, finite, and linear. The objective is to provide factual information that should be of interest to build knowledge, but traditional approaches seldom *connect the dots* to demonstrate how information can and should be applied, what the impact can be and how the information can create positive change for performance improvement. Alternatively, knowledge transfer can be dynamic, based on analysis, synthesis, and problem solving.

Learning tools–*cookbooks*, checklists, and reminder systems–are becoming more prevalent, and they are–no question–useful adjuncts, but they are only useful after learning has occurred, not as a substitute for it. In contrast to what is typically offered, what is needed in adult learning is context. Learning occurs when the information is immediately relevant and applicable and where social interaction is a component of the format and reinforces the learning. Rich use of examples, stories, and metaphors fire one's intuition and imagination to build relational connectivity between what is known and learning, fostering a sort of *sensemaking* that stimulates the mental leap to assimilate and apply new knowledge. Shared experience and dialog reinforce the applicability and capacity to use the new information. Small group problem-based learning involving a facilitator provides the opportunity for positive and negative feedback, allows ownership of the idea to evolve, and creates confidence and the motivation to act to use the new knowledge. Consider a range of methods including informal and unplanned learning, self-directed learning, and nonlinear approaches focused on process (Table 102-4).

Given the complexity of driving and restraining forces for medication use safety change, it is essential to consider and design related education and training with a system focus rather than targeting individual deficiencies or failures. The organization must honor learning above blame, and this must be clearly reflected in education and training. Interventions should reflect a range of methods to change behavior of physicians, nurses, pharmacists, and other health workers because multiple approaches are more likely to succeed than a single intervention or approach.[109]

Education and training are likely to be needed and are not interchangeable. Core knowledge of systems thinking, complexity concepts and principles of complex adaptive systems, aspects of teamwork, safety culture, conflict resolution, human factors must be provided. Training using experiential learning, practice with feedback, simulations, and reinforcement are just as necessary.

Table 102-4. Process-Oriented Learning Methods

Informal and Unplanned Learning
- ***Experiential learning***–Shadowing, apprenticeship, rotational attachments
- ***Networking opportunities***–Conferences and workshops, poster sessions, extended breaks
- ***Learning activities***–reflection exercises, suggestions for group discussions
- ***Buzz groups*** submerged in lectures–turn to neighbor dialog opportunities
- ***Facilitated email list servers*** for professional interest groups
- ***Teachback opportunities***–newly skilled workers training others in new techniques to share understanding
- ***Feedback***–response to provide the learner with information on the real or projected outcome of their actions

Self-directed Learning
- ***Mentoring***–named individuals provide support and guidance to self-directed learners
- ***Peer supported learning groups***–small group process used for mutual support and problem solving
- ***Personal learning log***–structured form for identifying and meeting new learning needs as they arise
- ***Appraisal***–regular, structured review of progress and goals
- ***Modular courses***–offer high degree of variety and choice

Non-linear Learning
- ***Case-based discussions***–grand rounds, clinical case presentations, significant event audit
- ***Simulations***–opportunities to practice unfamiliar tasks in unfamiliar contexts by modeling complex situations
- ***Role play***
- ***Small group problem-based learning***
- ***Team building exercises***

Adapted from Fraser SW, Greenhalgh T. Coping with complexity: educating for capability. *BMJ* 2001; 323: 802.

It is important to find opportunities for small wins and build on them. Use problems as treasured opportunities to test ideas for improvement, learn and share learning more widely. Small wins become long-term gains as they aggregate and rebound in the organization. Focus on the microsystem level of the organization with teams as the essential unit. Teams offer flexibility, redundancy and consistently outperform individuals, but they must function effectively to do so. Team training is an essential investment to establish an important building block for safety improvement.

Team cohesiveness, effective collaboration, and team processes are essential to having an effective, collaborative safety plan. The team must see itself as part of the bigger organization. They must be aware of the need for their independence as well as interdependence within the organization.

Team training must have an emphasis on safety. The focus of all team initiatives should be from the perspective of hazard avoidance. If well integrated into all aspects, the team can assist as the transformational leaders for an idea, relying on upstream supportive sponsorship for the vision and goals that drive the organizational initiative.

Creating team stability is also important, especially in those areas that are high-risk. Teams in emergency departments (eg, Code Blue situations, disaster response) allow for well-established relationships that produce smooth communication and decision-making in stressful circumstances.

Increasing Feedback

The team should be encouraged to monitor effectiveness of activities and report findings. Within the organization, the staff needs a mechanism to showcase their activities and actions for patient care safety improvement. The team should also be encouraged to identify problems and potential areas for improvement. These activities should be incorporated into standard communication systems (eg, common reporting processes, quality improvement, staff meetings, shift reports).

Improving Communication

Communication is the glue that holds the medication use process together. Therefore, organizations should focus on training all staff to avoid indirect communication involved in patient care activities. This can include activities to deal with difficult situations such as the emotions that occur during stressful, emergent events. Additionally, a focus on reduction of verbal orders or encouragement of *hear back* or *repeat back* processes with verbal orders to reduce the potential for error should be included in the communication training plan.

Development of Competencies Focused on Safety

Providing training opportunities for staff on safety is simply not enough. The IOM report, *Health Professions Education: A Bridge to Quality* clearly identified that clinical education practices have not kept pace or been responsive to the demands of shifting patient demographics and desires, changing health system expectations, evolving practice requirements, new staffing arrangements, new information, new technology, and the needed focus on quality improvement. In fact, the report identified the need to integrate a core set of competencies—ones shared across all professions—to provide the necessary leverage for safety and care improvement.[12] The committee proposed five core competencies that all clinicians should possess, regardless of discipline, to meet the needs of the 21st-century health system[12]:

- Provide patient-centered care—identify, respect, and care about patients' differences, values, and preferences are expressed needs.
- Work in interdisciplinary teams—cooperate collaborate, communicate, and integrate care in teams to assure that care is continuous and reliable
- Employ evidence-based practice—integrate best research with clinical expertise and patient values.
- Apply quality improvement—identify errors, risks, and hazards in care to continuously understand and measure the quality of care provided and use that information to understand and implement basic safety design principles.
- Utilize informatics—communicate, manage knowledge, mitigate error and support decision-making information technology.

Organizations must include methods for staff to demonstrate their knowledge and skills regarding safety, including these core competencies, as part of their routine competency evaluation. Additionally, staff should be able to demonstrate their ability to communicate, identify, and report adverse events. As part of the organization's routine staff competency evaluation process, organizations should identify method of evaluating the staff's ability to:

- Focus on risk reduction activities within the work environment
- Assess patient risk and selection for treatments
- Monitor effects of care
- Identify ADEs
- Respond to ADEs when identified

Collaboration for Change

Change efforts are often designed and implemented by individual departments, frequently with little or no integration with other departmental efforts. Change can be difficult for many reasons:

- The wide variety of styles, needs, and change preparedness within departments and individuals require collaboration on a regular basis
- Collaboration, communication, and working together as a team will help to achieve harmonious results with change efforts

Once an organization has accepted the idea that errors do happen, a focus on prevention, systems improvement and human factors is needed. But, what needs to happen within the organization?

For a new focus for change within health care to be sustainable, positive changes regarding safety improvement are necessary. These changes include:

- An ongoing focus and learning from safety and human factors research and its application to health care
- Specific leadership and organizational culture initiatives
- Ongoing scientific measurement of safety and safety practice conformance

ORGANIZATIONAL ISSUES

Health care professionals often wait for accidents to occur before taking appropriate preventive action. Too often, the focus is on the person involved in the error. Reactions include methods to hold the individual up as an example and to invoke discipline and educate others regarding what went wrong. Other high-risk industries (eg, aviation, nuclear energy) scrutinize their systems for error potential in an ongoing, proactive fashion while focusing on the relationship between man and system.

Experts indicate that errors are, in fact, rarely due to faulty people. Individuals rarely err on purpose. In fact, the systems in which people work have a marked effect on the incidence of human error.

A number of industries outside the health care system have developed and implemented strategies to prevent errors by correcting and avoiding system failures. The aviation industry, as an example, also strives for zero defects. To ensure safety, the airline industry has developed a wide array of systematic and organizational safeguards for safety improvement.

As a result of these strategies, the risk for passengers is greatly diminished. Health care, like aviation, involves a highly complex interaction of highly skilled personnel who provide diverse yet interrelated and interdependent functions.

Applications of aviation principles to health care practice may provide a fresh look at safety and vulnerabilities within the medication use process. In fact, many of the ideas embraced by pilots (eg, the use of checklists and standards) have been utilized within health care as a means to reduce variation and risk in the treatment of patients.

Health care organizations tend to make the same medication mistakes over and over because members tend to accuse individual employees rather than consider the real root cause of the error, a faulty system.

Implementing new strategies will require a profound change in the way health care does business. A new framework for guiding organizations will be needed to transition health systems to better meet patient needs. *Chasm*, highlights methods to guide these transitions and help organizations remain focused on the true agenda: safer care for patients.[110]

- Redesign care practices based on best practice
- Use information technologies to improve access to clinical information and support decision-making
- Develop effective teams
- Incorporate new knowledge and skills management
- Coordinate care across patient conditions, services and settings over time
- Incorporate performance and outcomes measures for improvement and accountability

Some distinct observations and conclusions have been made as a result of these adverse event studies:

- ADEs are common, more common than previously recognized
- ADEs resulting from error are preventable
- For each preventable error, three more near misses occur
- Ordering and administration of medications are most likely to be identified as error prone
- Costs of ADEs are significant and include injury, malpractice, additional care and work and overall damage to organization.
- Organizational redesign is needed
- There are costs for implementing safe systems; but the costs of inaction are much higher
- Error reduction strategies will require a systems oriented approach
- Many errors that are preventable are also often not reported; organizations must identify methods for health care providers to report and engage in prevention activities

A variety of factors can influence individual and team performance. Of growing concern are the effects of burnout, stress, and fatigue.

Burnout, Stress, and Fatigue

Providing health care is a highly complex and demanding process that is affected by a variety of psychological and workplace factors that can combine to create an environment conducive to errors.

Burnout–emotional exhaustion, depersonalization, and reduced personal capacity to accomplish–can be a contributing factor to medical errors. Research conducted to measure burnout and its effects, define the condition as[111]:

> "A state of emotional exhaustion in which service providers view recipients impersonally and their own performance disparagingly."

Workload demands, erosion in professional respect, limited resources, manpower shortages, heavier practice demands, industry consolidation, and many other stressors all contribute to the growing sense of frustration, discouragement, and disenchantment, and eventually to cynicism and despair. All of this contributes to a lack of effectiveness in the job, a declining focus, and gives rise to absenteeism, turnover, physical illness, and in some cases substance abuse. There is also significant deterioration in relationships with coworkers and patients, both of which further contribute to the conduciveness to error and sometimes, disastrous results for patients. Some more subtle stress factors must also be considered.

Health care is uncertain by its very nature, characterized by ambiguous data, an incomplete understanding of some biologic functions, variability in response to treatment, and the frequent need to act on incomplete information. And, the stakes are high. Clinical uncertainty can have a long-term negative effect on clinical caregivers and their performance.[112]

In today's health care environment, virtually all providers feel a sense of diminished control as a result of consolidation and reorganization, changing incentives, managed care and growing insurance restrictions. In conditions of perceived lack of control, individuals are more subject to the pressures of stress and distraction.

Research also demonstrates that crowding and the social density of the environment affects performance. Workers in a crowded space are less tolerant of frustration and less able to perform routine tasks reliably.[113]

Most organizations are facing the reality of doing more with less–people, budget dollars, and time–and this growing task load also has a negative effect on performance.

Stress impacts job performance and social interactions, and predisposes health professionals to medical errors. The cause of this is unclear, but three theories offer insight. The cognitive fatigue hypothesis suggests that prolonged stress reduces attention capacity because disproportionate resources are devoted to the stressor, reducing the capacity left for performance. Alternatively, learned helplessness teaches the individual over time that a response does not influence the stressor, and over time motivation to perform is eroded. Finally, the frustration mood theory suggests that building frustration resulting from stress establishes irritation and anger that diminishes ability to perform and effects interpersonal relationships.[114] Regardless of the theory, the resulting impact is that highly trained, well-meaning, dedicated health professionals can have performance impacted to the extent of being involved with a medical error. Perhaps most disturbing is the effect of stress and burnout on

social interaction and communication within the team or work group given the importance of the effectiveness of the team at the microsystem level.

Fatigue and sleep deprivation has been a long-standing concern in health care. The provision of health care has a 24/7 demand with round the clock staffing for continuous care, which naturally necessitates standard shift work as well as *ad hoc* nonroutine scheduling in response to demand.

Significant research efforts have demonstrated beyond a doubt that fatigue impairs performance.[115,116] An Office of Technology Assessment report documents that nonstandard work schedules and night shift work disrupt circadian rhythms and that frequently extended hours beyond a normal 8-hour shift has a negative impact on the worker's health, safety, and performance.[117] Night shifts lead to loss of sleep, difficulty performing specific tasks in the middle of the night, disrupted social and family life, and loss of concentration.

Beyond the difficulties associated with night shift work, a number of other factors contribute to fatigue. Whether due to manpower shortages, scheduling convenience preferences or the goal of amassing overtime benefits, long shifts, back-to-back and successive shifts, and extra shifts/moonlighting are common practice for health care workers. Inadequate rest, sleep loss, displaced or disrupted feelings of tiredness and continuous mental of physical activity all contribute to feelings of fatigue. But there are predictable consequences associated with fatigue, including slowed reaction time, lapses of attention to critical detail, compromised problem solving skills, decreased motivation, and overall lower level of vigor for completing important tasks. Overall, there is a diminished ability to do work and a subjective sense of tiredness.

Everyone is familiar with physical fatigue that produces a temporary loss of power to respond to demands. Often a result of continued physical stimulation over an extended work period, physical fatigue is characterized by muscle tiredness, diminished physical performance, back discomfort, and cognitive impairment. But there is also general or mental fatigue that produces subjective feelings of weariness after hours of repeated performance of nonphysical tasks. This type of fatigue triggers a decrease in afferent nerve impulses or decreased feedback from the cortex to the reticular activating system, which results in a lack of novel stimuli producing monotony or boredom. Combined with sleep deprivation, drowsiness contributes to the overall sense of fatigue. Reaction time and performance decline, mood and motivation drop precipitously, as do initiative and enthusiasm.

Fatigue can also be classified as acute or chronic. Fatigue from intense and excessive cognitive work is short-lived and can be reversed with sleep and rest. Chronic mental fatigue is the result of excessive cognitive work over weeks or months, coupled with cumulative stress, and is not relieved by rest. Time away from the work is needed, either in the form of a vacation or change of job responsibilities. This type of chronic sleep debt builds gradually and may be imperceptible. However, the individual is seldom maximally alert. While physical activity is not impaired to a great extent, mental acuity and performance degrade quickly. Initially speed of performance and response slows perceptibly. Continue sleep loss leads to the occurrence of brief mental lapses–or microsleeps of 1-10 second duration that contribute substantially to slowed response and errors of omission.[118] Mood, motivation, morale, and initiative erode dramatically. In combination, less work gets done, and attention to detail is lacking, potentially leading to mistakes, accidents, and errors.

Sleep loss has immediate negative effects. Loss of one night's sleep, followed by 18 hours of work can result in a 25% decrease in cognitive ability. At 24 hours, it can drop to 70% of baseline, remain stable for 18 hours, then fall dramatically to again about 40% of baseline.[119] The real problem is that the individual is seldom aware of the diminished capacity. Because both sustained workloads (8–12 hours or longer on the job) and shift work changes lead to loss of sleep and disrupted circadian rhythms, this is prevalent problem in society, and in particular among health care workers, who may be chronically sleep deprived.

With increasing sleep loss, there is growing difficulty actively monitoring static or slowly changing stimuli (eg, vital signs displays), as our ability to be vigilant decreases. Typically, decreases in reaction time and lower likelihood of identifying visual or auditory alarms occur as quickly as 20 to 30 minutes into the task. Sustained vigilance and mindfulness can fall victim to microsleeps, described earlier, resulting in slower response time, errors of omission and very long reaction times. As time on task increases, lapses increase in frequency and duration, and performance between lapses erodes as well. Vigilance decrements prompt job designers to build rest pauses, breaks, and rotational job assignment into such work as naval carrier command, air traffic control, and nuclear control centers. For health care workers, a failure of vigilance can lead to slowed recognition of changes in patient status, missing important signs and information or failure to deliver a treatment sequence in a timely fashion. While the effects of shift duration and recommended limits have not been clearly established, consideration must be given to the potential impact of back-to-back shifts, routine staffing with 7 days on 7 days off with 12-hour shifts, and other *creative* solutions to manpower issues within health care professions.

Clearly, the human side of performance and performance capacity must be evaluated in addition to system and process capability. Safe medication use requires a delicate balance of factors to achieve best care. How do organizations construct the framework to evaluate how man, machine and system interact? Planning, executing, evaluating, and assuring safe medication use requires a systematic approach. Incorporating medication use improvement activities into the health care organization's performance improvement and strategic planning process is one way to assure ongoing attention to this critical health care issue.

LINKING SAFETY AND PERFORMANCE IMPROVEMENT

Medical error prevention approaches have focused primarily on protocol development, training of care providers, and punishment when things go wrong. Although these approaches have an effect, they are not *the answer.* These efforts alone cannot be relied upon to create perfect performance in health care.

Clearly, implementation of these strategies alone are not greatly reducing error rates. Simply creating plans and policies has not proven to completely resolve the problem. A fine balance of integrating a wide range of strategies, identifying how staff implement and use these strategies and measuring their effects are necessary.

The quality of health care in the United States falls short of what it could be. Literature documents some serious quality problems. There is a gap, for some a *chasm,* between services that should be provided based on current professional knowledge, technology, and services that patients actually receive. This wake-up call for health care has inspired many organizations to rededicate their focus on identifying, measuring, and implementing performance improvement strategies to strive for better care services.

THE PERFORMANCE IMPROVEMENT PROCESS

All safety improvement efforts require making a change. Not all changes, however, result in an improvement. Therefore, it is essential that health systems identify the changes most likely to result in a sustainable improvement. One particular model for improvement, the Plan-Do-Study-Act learning cycle, has been advocated for use by health care systems to improve processes affecting patient care. The model was initially developed

by Thomas Nolan and his colleagues at Associates in Process Improvement.[120] This model has a demonstrated framework for a variety of system contexts including health care and can be used alone or in conjunction with other change models that are utilized within a health care system to accelerate improvement efforts. The Plan-Do-Study-Act (PDSA) process is dependent upon the work of a team that has an interest in evaluating a change and has knowledge of what the current process is and is capable of being (Fig 102-11).

The model has two parts. First a series of three questions must be answered.

1. What is the aim of the change initiative? A system cannot be improved without a clear and firm intention. The health system should clearly identify, in numerical or specific terms, what is to be accomplished by the change effort. Agreement on this aim by the organization or health system is crucial. The answer to this question can help determine the people, time, money, and other resources necessary to accomplish the desired goal. An example might be a goal of reducing adverse drug events that lead to injury by 50% on a hospital nursing unit.
2. How will the health system know if the change has resulted in the desired improvement? Knowing and articulating the current process serves as the foundation for the measurement process. Identifying clear, objective measurements are crucial to the improvement process. Health systems should identify quantitative measures to determine if the change resulted in an actual improvement. Another example might be to measure how many incomplete prescription orders were received in the pharmacy after an initiative to preprint routine prescription orders in an outpatient chemotherapy clinic.
3. What changes should be made to result in the improvement? Ideas for changing the medication use process can come from a variety of sources: results of root cause analysis or failure mode and effects investigations, scientific literature, a hunch, among others. The goal is to identify a change or series of changes to be tested in a real world setting to find out if the change improves care as the aim has described.

Second, use of a learning cycle, referred to as the PDSA cycle is used to test and implement the identified change. This cycle is really based on a systematic, trial and learning approach. The PDSA is a shorthand way of describing how a change is tried, observed, and then evaluated for future modification. The completion of a PDSA cycle leads directly to a next cycle. The team learns from the test, identifies what works or doesn't, and then determines what should be kept, changed, or abandoned for improvement. The challenges of each step of the PDSA process are as highlighted below:

Step 1 PLAN: The team should state the objective of the PDSA cycle. How will the change be tested? Who will be involved? What will be measured? Where will these observations be made? What data will be collected? How will training occur? This is the greatest challenge of the change initiative and the most time consuming, but it clearly sets the context and framework for the team to evaluate the change.

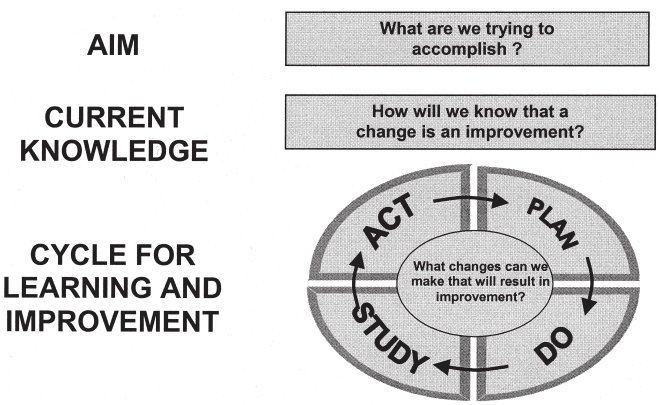

Figure 102-11. The Plan-Do-Study-Act learning cycle. Adapted from Nelson EC, Batalden PB, Mohr J, Plume SK, et al. *Joint Commission Journal on Quality and Safety.* 1996;22(4):243. Reprinted with permission.

Step 2 DO: This is the phase where the test or change is actually carried out. Documentation of the observations and findings begin at this stage. Data collection is occurring

Step 3 STUDY: At this point, evaluation of the data occurs. The team needs to compare the findings of the change initiative to the predictions made. A summary of learnings and findings must be provided.

Step 4 ACT: At this point, analysis of findings is complete and the team needs to determine what modifications are necessary, what gains should be held and what new knowledge has been identified. The team then must plan for the next change cycle. The team continues to link PDSA cycles to continue refinement of the change until it is ready for broader implementation. Linking small cycles of change and improvement can help overcome the natural resistance to change often felt by health systems. People are far more willing to test change if they know that modifications will be made as needed based on findings.

From the perspective of safe medication use, the improvement process must include a strategy to prevent ADEs at every step in the medication use process and methods to identify the prevalence of system failures versus individual negligence within the organization.

Several recommendations have been identified to minimize the risks in the medication use process. Reviewing recommendations in and of themselves are not the answer. If an organization is investing time, energy, and resources into implementing change, the expectation is to observe the result of measurable improvements. Organizations expecting to reach their objectives must implement performance improvement strategies.

Improving patient safety is a complex undertaking. Organizing a team of individuals with diverse skills, characteristics, and knowledge is an essential first step. Deciding who should be on the team begins with a focus on the strategic initiative.

The overall plan for the organizational safety initiative includes three steps that allow the organization to determine the aim or goal of whatever it is trying to accomplish. These steps include:

- Developing a strategy
- Analyzing organizational capabilities
- Developing an action plan

The first step in developing a strategy means asking the questions that uncover where the organization is currently when it comes to medication errors. Each organization must:

- State the aim of the project targeting medication use improvement
- Identify measures that will identify safety improvement
- Describe current practice, compare to the desired state or condition and predict changes likely to occur (gap analysis)
- Plan for the implementation of the improvement strategy
- Pilot the desired changes
- Check and restudy the results
- Act to improve
- Reflect on learning

This model is consistent with the Joint Commission as well as other national mandates on continuous improvement regarding medication use:[121]

- A system of continuous medication monitoring
- Medication use documentation system
- Plan for data aggregation and analysis
- Focus on high volume, problem prone medication use
- Assessment of all significant ADEs

TOOLS TO IDENTIFY, CONTROL, CONTAIN OR MITIGATE RISK

Failure detection, reduction, and prevention strategies are receiving new attention as the health care industry moves to respond to the challenges established in the IOM reports and in the literature. Since instances of medical errors have been reported with increasing regularity in the media, the public trust of health care systems appears to be eroding. Often health systems skip vital problem solving steps and *jump to*

solutions when a critical incident or error occurs. When adverse events occur, health systems must identify the causes of the event, the interrelationship of these causes, and implement improvement or redesign efforts to eliminate causes of error. Since errors are thought to be preventable, organizations must also identify methods to design or redesign systems *proactively*. These proactive efforts are aimed to prevent, or at least minimize, the likelihood that failures occur and also protect patients from the effects of failures when they do occur.

Regulatory and accreditation agencies have galvanized around the issue of responding to events and providing strategies to implement prevention initiatives. Two strategies, root cause analysis and failure mode and effects analysis have been identified as systematic methods for error investigation, reduction and prevention.

Identifying Errors and Cause

Variation in performance can produce unexpected and adverse outcomes. Sentinel events, as defined by the Joint Commission on Accreditation of Health Care Organizations (JCAHO), are unexpected occurrences involving death or serious physical or psychological injury or the risk thereof.[122] Error investigation requires a rigorous, systematic approach to evaluate basic or causal factors for variation in system performance. Root cause analysis, a technique utilized to identify the fundamental reason for system failure, focuses on systems and processes rather than on individuals involved in the system.

Root cause analysis (RCA) is not a single tool or strategy, but an investigative approach that utilizes many tools in combination to solve a problem.[123] The use of RCA helps identify clear factors or causes that result in, at best, performance variation, and at worst, adverse events or errors within a system. A root cause, by definition, is a single element that is directly attributed to starting a cause and effect chain that creates the problem observed. A root cause is the most fundamental reason a failure or situation where performance does not meet expectations, has occurred. The word *cause* does not imply or assign blame as part of the definition. Instead, *cause* refers to a relationship or potential relationship between factors that enable a failure or error to occur.

Now while it is possible that one single cause exists, it is often found that there are many causes of variation when failures occur and no one root cause can be identified as solely responsible for an error or bad outcome. Several causes might be identified. It is important that identification of all possible causes occur so that effective strategies to reduce these variations and their impact can be considered.

When an error occurs, health systems are charged with identifying:

- Why the event occurred
- How to prevent the event from occurring in the future

To do this, identification of proximate causes (obvious or immediate cause) and underlying causes (cause that lead to proximate cause) and their relationships *must be identified.* Root cause analysis helps to identify the apparent proximate causes to get at that root cause of interest.

Conducting a root cause analysis requires a team effort. Assembling a multidisciplinary team that understands the process under investigation is essential. The team assigned to conducting a root cause analysis works to understand the process(es) under investigation, the causes or potential causes of variation, and the process changes that would make variation less likely to occur. As part of the investigation, a root cause analysis examines common causes and special causes within clinical and organizational processes to identify potential system improvements.

Common cause variation is inherent within a system and a consequence of process design.[124] This type of variation is systemic and endogenous within the system. As an example, a health system might be investigating the length of time required to dispense a prescription to an outpatient in an ambulatory clinic. The time required might vary depending on how busy the pharmacy is, whether the prescription is a refill or new order, if the patient is new to the clinic, if the product requires compounding, or even the time of day the prescription is presented to the pharmacy staff. Variation in the process of providing a prescription is inherent, resulting from common causes such as staffing levels, availability of patient information, or access to medication supply. A process that varies only because of common causes is said to be stable. The level of performance of a stable process, or the range of the common cause variation, can only be changed by redesigning the process. If an organization desires to improve prescription wait time, what is expectation for improvement? If data collected suggests that wait times can be as short as 5 minutes or as long as 50 minutes, is that acceptable? Would further investigation of the 50-minute wait time yield valuable insight for process change? To reduce any variation, it is necessary to determine cause. If the variation is unexpected or unacceptable, redesign of the system may be necessary.

A special cause is variation which occurs from unusual circumstances or events that are difficult to predict.[124] Special cause is not inherent as part of the system; it is usually as a result of external influence and not part of the system as designed. The results of special cause variation often leads to process instability which is best described as intermittent and unpredictable. Examples of special cause variation in the medication use process might include manufacturer recalls, compounding equipment or automation failure, widespread professional staff sick calls, environmental/natural disaster or other *acts of God* that lead to failure. These special causes should be identified and eliminated. However, this will only affect the abnormal performance in that process. It cannot prevent the special cause from recurring.

Health care, however, is part of a larger system. In health care, special cause variation in performance may be a signal that common cause variation is occurring within the larger system context. In the example of manufacturer recall of a medication, is there a failure in the system that provides communication, support, or alternatives when a recall occurs? When automation fails, could that signal an outmoded or nonfunctional equipment maintenance program? In the case of a tornado, does the response plan provide adequate pharmaceutical care support for victims? By conducting a thorough root cause analysis and identifying common and special cause variation within the process, an opportunity exists to reduce special cause variation in one process by redesigning the larger system of which it is a part.

Root cause analysis is used reactively—to investigate the reason for a bad or unexpected outcome. That means that a failure has already occurred. Root cause analysis techniques, however, can also be used to probe near miss events or as a part of other performance improvement initiatives that focus on system redesign. A near miss is defined as an event that *almost occurred.* An example might be an overdose of a medication that was dispensed by a pharmacy. The patient did not receive the medication because a nurse or family member identified the dosing error and did not receive the product. Adverse consequences to the patient were avoided. A root cause analysis in this case could yield useful information about process failure. The best root cause analyses look at entire processes and support systems involved in an event to minimize risk as well as the potential for recurrence of the failure being investigated. All root cause analysis efforts should produce clear action plans for implementation to reduce the risk of similar events occurring in the future.

Steps for Conducting a Root Cause Analysis

There are several key features for health care organizations to consider as the conduct a root cause analysis[125]:

- Identify a multidisciplinary team to assess the error, failure, or adverse event of interest
- Establish a way to communicate findings and data elements required to conduct the analysis
- Create a plan with target dates, responsibilities, and measurement/data collection strategies required for the investigation
- Define all elements of the process and issues clearly
- Brainstorm all possible causes or potential causes
- Identify interrelationships of causes or potential causes
- Sort, analyze and prioritize cause list
- Determine which processes and systems are part of the investigation
- Determine special and common causes
- Begin the design and implementation of the change while engaging in the root cause analysis
- Repeat each of the steps listed previously as appropriate
- Focus on being thorough (Ask *why*) and credible (Be consistent, dig deep, and leave no stone unturned!)
- Target system improvement . . . particularly the larger systems
- Redesign to eliminate root cause(s)
- Measure and assess new design

Benefits of Conducting a Root Cause Analysis

Root cause analysis can help organizations identify risk or weak points in processes, underlying or systemic causes, and corrective actions. Information from root causes can be shared with practitioners to help prevent future failures. This knowledge can be shared in within health care systems to contribute to proactive improvement activities. The systematic approach outlined by root cause analysis techniques allows organizations to[126]:

- Focus on systems and processes, not individuals
- Use multidisciplinary participation to include views and values of process participants, customers and leaders
- Make links between special and common cause variation findings
- Allow root cause team to dig deep by asking *why* repeatedly
- Evaluate chain of causation, identifying both proximate and direct cause
- Determine risk points and their contribution to failure
- Identify change potential to reduce risk
- Create an action plan with assignments, timelines, and responsibilities
- Implement action or redesign consistent with other performance improvement efforts to test impact of change effort

Although a useful and essential tool to assist health care providers, root cause analysis is only part of the problem solving process. Analyzing processes only after bad outcomes occur must be joined with a prospective look at what could go wrong before failures occur. The use of failure mode and effects analysis (FMEA) is a proactive, prospective technique used to prevent process, system or product problems before they occur. This activity can provide a safety next to identify problems that could occur, provide prediction of failure severity and the health care system's ability to detect potential failures before they occur. Clearly the goal of utilizing FMEA in combination with RCA is to assure that harm to patients could be avoided, managed, or eliminated.

Preventing Errors and Cause

The concept of failure mode and effects analysis comes from the engineering industry. The technique has been around for over 40 years.[127] Industries such as aerospace, nuclear power, electronics, and food processing have utilized FMEA strategies to reduce or eliminate after-the-event correction strategies when failures occur.

FMEA is also a team based and systematic approach like RCA, but instead of used to investigate an error after it occurs, it is a proactive approach used to identify why a process or design can fail, why it might fail and how it can be made safer. If a particular failure is identified by a FMEA cannot be prevented, the technique then focuses on protections that can be put into place to prevent the failure from reaching the patient or mitigating the effects of the failure if it reaches the patient. FMEA requires a clear understanding of its component word parts.[128]

Failure: When a system, process or service performs in a way that is not intended or desirable. The failure could be evident as a lack of success, nonperformance, nonoccurrence, or complete breakdown or cessation of function.

Mode: The manner or method in which something, like a failure can occur. The term *failure mode*, is then the manner in which something can fail. A single failure may have many failure modes.

Effects: The results or consequences of a failure mode.

Analysis: An examination of the elements or structure of a process or service.

Conducting a failure mode and effects analysis also requires a team effort. Assembling a multidisciplinary team that understands the process undergoing redesign or newly implemented is essential. The team assigned to conducting a failure mode and effects analysis must work to understand the process(es) under analysis, the causes or potential causes of failures, and the necessary steps to assure that failures are less likely to occur. As part of analysis the team will identify many potentials for failure. Some may be very real others only hypothetical. The team will need to determine what failures to address and assign priority to these action steps. This activity, or prioritization, requires what is called a criticality analysis.

A criticality analysis is a method used to identify relative measures of importance for a failure mode.[129] For each failure mode identified, a rank is determined for its importance based on a combined evaluation of three factors:

- Severity: this rating estimates how serious the effect would be if in fact the failure occurred
- Probability of occurrence: this rating estimates the likelihood that the failure would happen
- Detectability: this rating estimates the degree to which the failure could be detected.

The team needs to agree on a scoring method to assist with this process. A numerical scale, such as 1 to 10 or qualitative scale, such as high, medium, or low, could also be utilized. In any case, the team must agree on definitions of the scales and how the scoring will occur. As part of this scoring discussion, it is a good idea to identify how disagreement on scoring or rating will be handled and how this will be resolved and consensus reached.

Because teams must focus their energies on addressing failures most likely to cause harm, the ranking process allows for evaluation of these three factors simultaneously. If a qualitative scale is used to determine priority, the group must agree which ratings or combination of ratings will require attention. If a numerical scale is used, a risk priority number (RPN) can be calculated. In some texts, an RPN is also referred to as a criticality index (CI).[129] An RPN is calculated as follows:

$$RPN = severity \times occurrence \times detectability$$

Failure modes with high RPNs require immediate attention. It might be helpful for organizations to identify a score that serves as a cutoff point for action.

This concept of FMEA is a relatively new one for health care organizations, but is growing in acceptance. In 1994, the Institute for Safe Medication Practices (ISMP) began recommending use of FMEA medication use process improvement and redesign.[130] As an example, the Department of Veteran's Affairs National Center for Patient Safety (NCPS) has introduced a prospective analysis model called Health care Failure Modes and Effects Analysis (HFMEA) which combines FMEA characteristics with the Hazard Analysis and Critical Control Point (HACCP) model developed to ensure food safety.[131] All VA facilities received training and moved forward with utilization of this tool in 2001. These efforts are contributing to a shift toward

a new way of thinking, describing, and evaluating errors within health care systems.

The term *error* is being utilized less because of the implication of human involvement and perception of blame or fault. Failure has been the preferred term because it can be utilized to describe latent or hazardous conditions that could result in harm to an individual without assigning blame. FMEA is a technique that assumes that no matter how knowledgeable or careful people are, failures will occur in some situations. The focus is on *WHAT* could allow the failure to occur, not *WHO*.

Conducting a Failure Mode and Effects Analysis

There are several key features for health care organizations to consider as the conduct a failure mode and effects analysis[132]:

- Select a high-risk process to evaluate and assemble a team. Consider a process that is likely to impact the safety of patients within the health care organization.
- Diagram the new or existing process of interest. Include the all the steps and identify the actual v expected performance.
- Brainstorm all potential failure modes within the process and determine their effects.
- Prioritize the list of failure modes identified. The basis for identifying priority actions should be based on the severity, occurrence, and detectability capability within the health care organization.
- Identify the root causes of failure modes.
- Redesign the current or create the new process.
- Analyze or test the changes or new process identified.
- Implement and monitor the redesigned or new process.

Benefits of Conducting a Failure Mode and Effects Analysis

The primary benefit of conducting an FMEA is that this technique has been used successfully to reduce the risk of errors and failures and increase the successful performance of a process. For medication use, this means a decrease in the likelihood of untoward or sentinel medication events. A true advantage is that this process can also provide protection for patients and evaluate systems for potential risk reduction strategies. FMEA can serve as an effective quality improvement tool in any health care organization with out the use of complicated tools or statistical analysis. Data can be evaluated for real or perceived failure potential and identify clear opportunities for improvement through a group process. FMEA explores how processes, design, or service can be improved or redesigned to reduce the likelihood of failure.

Data Collection and Reporting

Reporting and data capturing processes must be well defined and understood within the organization. Having a systems approach to reporting is another necessary component for improving safety. Consider the following tips for improving the reporting process:

- Define medication errors within the organization
- Provide automatic report distribution to key leadership within the organization
- Make reporting voluntary to encourage near miss reporting
- Consider use of an outside group to review reports and identify trends and trouble-spots
- Create a paperless system for ease of reporting
- Allow free-form reporting to capture all information
- Ensure that system for reporting is nonpunitive
- Involve the patient
- Evaluate ways to improve informed consent process and disclosing risks to patients
- Use benchmarking data
- Provide timely feedback regarding information collected from reports
- Identify actionable strategies for follow-up . . . and then *FOLLOW-UP*

Methods must be in place to measure, monitor, evaluate, and improve performance even in the face of an adverse event. Further, organizations should not wait until a problem arises in the organization to respond to this safety agenda. Organizations need to identify safety activities that are proactive and ensure that information regarding patient and staff incidents, measurement and monitoring activities, and communication plans are in place. The following items should be identified in a safety plan for medication use improvement:

- Incorporate measurement into performance improvement activities
- Trend data and create a dashboard of indicators of interest
- Focus on safety as a priority in job descriptions and performance appraisals
- Incorporate team safety training into orientation programs and ongoing competency assessments
- Create a plan to communicate information learned from reporting an error throughout the entire organization

IMPLEMENTING ACTION STEPS FOR CHANGE

Creating steps for successful implementation of medication safety improvements could be the most important part of an effective safety initiative. First and foremost, it is important for an organization to define the aim of a safety initiative. It is critical that all team members understand and can explain what the aim is of the improvement, and also the reason for implementing the change. Organizations must identify and involve key players who will assist in the implementation of the change. Teamwork and collaboration are essential at all organizational levels.

Define and Provide Resources

Organizations must find and allocate the resources that will be needed. Think of time as a resource, including time for team members to participate on the team, completing team assignments and communicating with other team members and target audiences. Identifying and securing resources for safety initiatives must be a part of the leadership and organization's priority.

Define the Change Needed

The desired changes for safety improvement should be well outlined in clear, measurable terms. Organizations must determine initial measures that will help assess if the change is an improvement. The team should identify how data will be collected, analyzed, displayed, and reported. Organizations should also identify resources to assist in the process. Many national support groups and resources exist. The Institute for Safe Medication Practices (ISMP-www.ismp.org), American Society of Health-System Pharmacists (ASHP-www.ashp.org), Institute for Healthcare Improvement (IHI-www.ihi.org), Joint Commission on Accreditation of Healthcare Organizations (JCAHO-www.jcaho.org) and others offer opportunities for dialog and exchange and have tools, tips, and networks to share the success strategies as well as examples of common problems encountered with medication use.

Communicate Findings

Utilize existing systems to communicate the change as well as reporting the results of safety performance improvement initiatives. Organizations must dedicate resources to create the message that will be delivered when introducing and imple-

menting the change, including who will deliver the message, the content, timing, and the audience that will be targeted. All too often, data points, such as error rates, percentages or other factoids are shared, but little context provided. As a result, people who receive this information and are charged to act upon the data, are often unable to *connect the dots* and identify how to use the data for improvement to achieve sustainable performance results. If the organization fails to utilize the data collected in a way to demonstrate a commitment to medication use, individuals may lose their enthusiasm for reporting important findings and progress toward improving medication safety within the organization impaired or impossible.

As part of this communication planning process, it is important to identify barriers and potential solutions. These issues must be discussed openly and honestly. Every opportunity *must be used* to encourage reporting, promote safety, and reward prevention strategies. Additionally, identify opportunities to review improvement activities, results, and key learnings in leadership meetings, staff meetings etc.

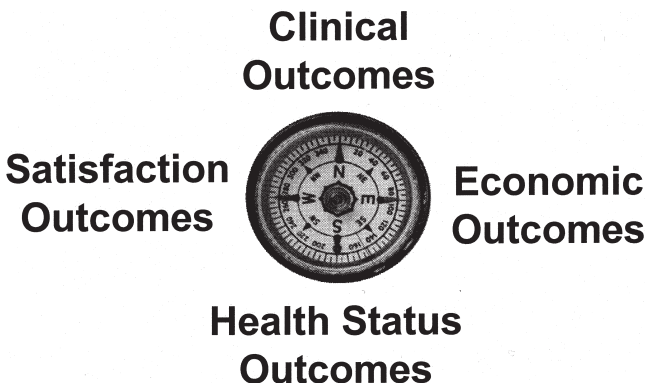

Figure 102-12. Outcomes Compass. Adapted from Nelson EC, Batalden PB, Mohr J, Plume SK, et al. *Joint Commission Journal on Quality Improvement* 1996; 22(4):243. Reprinted with permission.

Adopting Change

Assess mechanisms available to educate target audiences and to promote adoption of the change. It is important to remember that diffusion, dissemination, and adoption of any new innovation or change is dependent on each individual's capability and ability to make change happen—implementation of change occurs at different rates in different people. Everett Rogers described this phenomenon of how people accept adopt and influence change in his text *Diffusion of Innovations* in 1962.[133] His research sought to identify how and why innovations in agriculture, family planning, public health, and nutrition became adopted in developing countries of Latin America, Africa, and Asia. The goal was to identify how to speed up rates of infusion of new ideas since it was found that it often years passed before progress had been made. What Rogers found was that efforts for change should be directed toward those people who are most likely to accept new ideas and trial innovations. Efforts and energy should not be wasted on individuals who resist or fight against change. Within health care systems, it is important to identify who needs to be part of the safety improvement effort. Identifying those who are willing to lead the safety charge, be a willing team participant, and help with creative design are likely to help fuel process improvement success. It is important not to waste time on those who will never be convinced of the need for the change.

Determine what exists and what else may need to be developed. This plan should include all care providers including medical staff. In order to adopt change, find opportunities for medical staff to be involved in the peer review of adverse events, the credentialing process as well as involvement in safety initiatives. Methods to assess competency of staff providing care should also be included. Identify methods to integrate safety skill and action assessment into day-to-day activities of staff. This may include creating mentors in the area of best practices that support safe medication use.

Achieving Optimal Outcomes

Change may not always be desirable. To manage the health care environment to provide for optimal outcomes (ie, clinical, economic, health status, patient satisfaction) the organization must maintain an action plan that supports a continuous, prospective or concurrent, data-driven and measurable improvement process.[134] Organizations must understand that error can and will occur. The environment that the medication use process operates in is influenced and modified continually by external and internal forces. These forces must be evaluated and managed. Asking the question, "How will we know if we have implemented a medication use safety strategy that has resulted in an improvement?" is a critical one. It is important to note that this is an iterative process . . . and that additional questioning to determine if the change is STILL an improvement over time, is necessary (Fig 102-12).

This outcomes compass depicts the breadth of outcomes associated with medication use. Adverse events can also be described as negative impacts in any of these outcome areas:

- Clinical: an undesired physical response, drop in blood pressure, altered lab test
- Health status: patient unable to return to previous or improved level of functioning
- Economic: delayed discharge, use of other agents to resolve symptoms
- Satisfaction: lack of meeting patient or other medication use process customer expectations

The impact of medication safety initiatives should include evaluations of these global aspects as part of your design.

BARRIERS ASSOCIATED WITH SAFETY IMPROVEMENT

There are many reasons why organizations struggle with improving safety within their organization. Often, traditional methods such as medication error or adverse drug event reporting are cumbersome. Organizations have not adequately defined the process, the scope of collection, and members of the health care team do not understand why there is a need to collect and discuss the data. Many involved in the reporting end of the process never hear about the information gleaned from the analysis.

Additionally, data collection and discussion about medication errors or adverse events are often fragmented. Pharmacy might collect and discuss some of the data, while nursing may be responsible for other parts and risk management or QA may get involved for other issues. As a result, frustration occurs due to a lack of communication, integration, and input. Documentation systems are also cumbersome and often do not fit in well with other day-to-day care responsibilities. What happens with all these events reported? Fear that individuals will be blamed for the error and that punitive action will be taken also limits individual participation in the process.

Having a plan and an organizational understanding of the aim regarding safety improvement is essential. Many parts of the health care team contribute to the use of medications within the organization. All members within the organization must be aware of the importance of medication use safety, mindful of the potential for error and their role in averting it and what the organization has in place to assure that safety is a priority.

Integration of all data and associated knowledge regarding medication use is needed. The integration of existing data, including ADR, medication error, pharmacy/nursing interventions, and medication interaction data, into one organization-wide database is the key to an effective ADE quality management program.

The overall impact of the database could be measured by examining the impact that the reduced incidence of ADEs has on health outcomes: clinical, economic, patient satisfaction, and health status outcomes. Specific goals for adverse event improvement activities generally include:

- Increase documentation
- Aggregate data effectively
- Organizational education and training regarding prevention and detection
- Use data to improve the medication use system
- Minimize patient risk
- Maximize health outcomes
- Create an open and honest environment where there is a focus on system improvement and reporting
- Remove focus on individual and punitive process
- Meet regulatory standards

Many groups have identified methods to improve the safety of the medication use process. National and local groups have strategies to share and stories to tell. It is important to learn and replicate best practice and build on the success of others.

SOURCES OF LEARNING ABOUT PATIENT SAFETY

The following descriptions of organizations and initiatives for patient safety improvement are provided as background for this critical and dynamic field of endeavor. Many of these organizations are headed or staffed by physicians and other health care professionals, giving them a unique prospective on ways to improve on patient safety. All are accompanied by the website address for that organization's home page. This is not intended to be an exhaustive list, there are many pharmacy, nursing and other discipline-focused initiatives contributing to national safety improvement initiatives, but this provides a sample of what is available.

The Agency for Healthcare Research and Quality (AHRQ)

The AHRQ, a division of the Department of Health and Human Services, is the lead federal agency on quality of care research. Its mission is to support, conduct, and disseminate research that improves access to care and the outcomes, quality, cost, and utilization of health care services. The AHRQ has been fulfilling this mission since 1998 through its leadership role in the Federal Quality Interagency Coordination Task Force (http://www.quic.gov). This task force is spearheading the initiation of a number of federally funded research projects on patient safety. The AHRQ spends approximately 80% of its budget ($270 million in FY2001) funding research grants. It allocated $50 million for patient safety research grants in FY2001. Web site: http://www.ahcpr.gov/qual/errorsix.htm

The American Hospital Association (AHA)

The AHA makes available a wide variety of tools and resources to assist in improving care (http://www.aha.org/PatientSafety/Safe_home.asp). One tool, *Strategies for Leadership: Hospital Executives and Their Role in Patient Safety*, was developed by James B. Conway, chief operations officer at Dana-Farber Caner Institute in Boston, specifically for executives' personal use and reflection on their efforts to develop a culture of safety. Web site: http://www.aha.org/PatientSafety/CultureSafety.asp

Anesthesia Patient Safety Foundation (APSF)

The APSF was established in 1984 "to assure that no patient shall be harmed by the effects of anesthesia," as set forth in its mission statement. The APSF is noteworthy because it has been instrumental in the dramatic improvements in anesthesia safety. As such, it represents a good source of insight and precedence for activities-such as clinical investigations and communications programs-that can be undertaken to improve patient safety. Web site: http://www.gasnet.org/societies/apsf/index.html

Annenberg Patient Safety Conferences

The *Examining Error in Health Care Conferences* were held in October 1996, November 1998, and May 2001. The meetings were sponsored by a myriad of organizations, including the American Association for the Advancement of Science, American Society of Health-System Pharmacists, American Medical Association, and Annenberg Health Sciences Center at Rancho Mirage, CA. Ongoing, annual conferences provide updates and rigorous reviews of the collaborative system improvements necessary to improve health care safety. The Web site contains listings and descriptions of the disparate organizations involved in this interdisciplinary topic, names and titles of presentations, and order forms for proceedings and audiotapes of the sessions: http://www.mederrors.org

Institute for Healthcare Improvement (IHI)

The IHI is a Boston-based, independent, nonprofit organization founded in 1991 to foster systematic improvements in health care in the United States, Canada, and Europe. The IHI is a leading force in promoting and facilitating teamwork and collaborative care in a variety of health care reform initiatives. Its mantra is that people and organizations who share a common goal (eg, patient safety improvement) can achieve more by working together than by working separately. The activities of the IHI embody a systems thinking approach toward the goal of creating health care systems that are accessible, safe, easy to use, and satisfying for patients and communities. Web site: http://www.ihi.org/

Institute for Safe Medication Practices (ISMP)

The ISMP is a nonprofit organization that works with the major stakeholders in health care to provide information education about adverse drug events and their prevention. The ISMP works closely with the U.S. Pharmacopoeia (USP) to analyze data gathered through the Medication Error Reduction Program (MERP), which was launched by the USP in 1991. (The USP shares MERP data with the U.S. Food and Drug Administration, which operates its own adverse drug event reporting system, called MedWatch.) Web site: http://www.ismp.org/

Joint Commission on Accreditation of Healthcare Organizations (Joint Commission, JCAHO)

The patient safety standards that the Joint Commission has put into place address a number of significant patient safety issues including the implementation of patient safety programs, the responsibility of organization leadership to create a culture of

safety, the prevention of medical errors through the prospective analysis and redesign of vulnerable patient systems (eg, the ordering, preparation, and dispensing of medications), and the hospital's responsibility to tell a patient if he or she has been harmed by the care provided. The Joint Commission is in the process of standardizing and implementing similar patient safety standards throughout its accreditation programs across the care continuum. In addition to standards changes highlighting safety improvement, the JCAHO has established a list National Patient Safety Goals (NPSGs) for organizations to implement to assure that best practices are implemented to drive safety improvement. The JCAHO is also collaborating with the National Quality Forum (NQF) and others to establish national best practices and expectations. It is anticipated that one of the best practices, the use of barcoding for medication administration, will be required for all hospitals by 2007 as part of an NPSG. Web site: http://www.jcaho.org

Leapfrog Group

Established in 1990, the Leapfrog Group is a coalition of large, self-insured employers seeking to leverage their purchasing power to drive improvements in health care quality. Their strategy is to monitor the quality of health care services in communities in which their employees work and live, focusing initially on hospitals, and channel their employees to those facilities that achieve those objective measures of high-quality care. The group currently is focusing on three initiatives for quality improvement in hospital-based care: (1) evidence-based hospital referral, (2) use of intensivists, and (3) computerized physician order entry (CPOE). The CPOE initiative is of particular interest of this curriculum because research to date indicates that general use of CPOE can significantly reduce medical errors and their attendant costs. Web site: http://www.leapfroggroup.org

Malcolm Baldrige National Quality Program

The MBNQ Program has developed a questionnaire to assess how an organization is performing and learn what can be improved. The questionnaire is based on the Baldrige Criteria for Performance Excellence and is available at their Web site: http://www.quality.nist.gov/Progress.htm

Massachusetts Coalition for the Prevention of Medical Errors

The coalition participants include senior leadership and expert staff from organizations with a longstanding commitment to quality and public accountability. This includes professional associations representing hospitals, physicians, nurses, nurse executives, and long-term care institutions; state and federal agencies with responsibility for licensure and oversight; accrediting bodies; and clinical researchers. The coalition's goals are to identify and implement best practices to reduce medical errors in Massachusetts and to facilitate professional and public education regarding patient safety. Web site: http://www.macoalition,org/

Minnesota Hospital and Healthcare Partnership (MHHP)

The MHHP leads a coalition on patient safety within Minnesota's health care community to improve and enhance patient safety in all aspects of care delivery and strengthen public trust. The Patient Safety Committee address public policy, leadership, and best practices to position MHHP and its member facilities ad demonstrated leaders in patient safety. Web site: http://www.mhhp.com/psafety/leaderkit.htm

National Academy for State Health Policy (NASHP)

NASHP is at the forefront of examining how states monitor and respond to quality and patient safety issues. Areas of focus have included the state government's role in patient safety, actions the states have taken to improve patient safety, and other steps states are taking to improve quality of care. Web site: http://www.nashp.org

National Coalition on Health Care (NCHC)

The NCHC is the nation's largest and most broadly representative alliance working to improve health care in America. The coalition-which is nonprofit and nonpartisan-was founded in 1990 and comprises more than 90 groups employing or representing approximately 100 million Americans. Members are united in the belief that we need and can achieve better more affordable health care for all Americans. Web site: http://www.americanshealth.org/

National Committee for Quality Assurance (NCQA)

The NCQA is a private, nonprofit organization dedicated to improvement of health care quality, with its primary focus being on managed care organizations. Activities performed by the NCQA include oversight of health care quality, conducting quality improvement initiatives, and recognition of providers that demonstrate excellence in health care. The most widely known program run by the NCQA is its Health Plan Employer and Data Information Set (HEDIS), a body of standardized performance measures designed to insure that purchasers and consumers have the information they need to reliantly compare the performance of managed care plans. HEDIS report cards are now made available online at MedScape and CBS Health Watch. In addition to HEDIS, the NCQA administers a physician organization certification program, launched in 1997; to help managed care organizations and purchasers assess physician organizations. Web site: http://www.ncqa.org/

National Patient Safety Foundation (NPSF)

The NPSF was established in 1997 by the American Medical Association with the mission to help health care systems achieve measurable improvements in patient safety. It seeks to identify, create, and facilitate the application of a core body of knowledge about patient safety; to foster a culture of receptivity to patient safety initiatives; and to raise public awareness about patient safety. Among the activities sponsored by the NPSF are the national and regional educational conferences and dissemination of publications. Their online bibliography (http://www.npsf.org/clearinghouse2001.htm) contains a wealth of citations in the patient safety literature dating back to 1939, from peer-reviewed publications and authoritative textbooks. Web site: http://www.npsf.org

National Quality Forum (NQF)

The National Quality Forum is a private, not-for-profit membership organization created to develop and implement a national strategy for healthcare quality measurement and reporting. The mission of the NQF is to improve American healthcare through endorsement of consensus-based national standards for measurement and public reporting of healthcare performance

data that provide meaningful information about whether care is safe, timely, beneficial, patient-centered, equitable and efficient. The NQF, in collaboration with several other organizations and stakeholders, has identified 30 healthcare safe practices that should be universally utilized in applicable clinical care settings to reduce the risk of harm to patients. This list is provided in Appendix 2, with the full report available at the NQF website. Web site: http://www.qualityforum.org.

United States Pharmacopeial Convention (USP)

The United States Pharmacopeial Convention (USP) was established to promote public health and benefit practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other healthcare technologies, and related practices used to maintain and improve health and promote optimal healthcare delivery. The USP establishes enforceable standards and provides recommended guideline on the production, purity, content and quality of medications, diagnotic agents and nutritionals. While many of the individual standards established by the USP affect safety and quality of medications, the USP has three major areas that contribute to the general body of safety evidence for medication use:

Safe Medication Use Expert Committee: The USP Safe Medication Use Expert Committee (SMU EC) was established as a member of the Council of Experts at USP's meeting in April 2000, and is thus, a formal constituent of the standards-setting process. This Expert Committee represents medicine, nursing, and pharmacy and includes representation from academia, research, government, and consumer interest. The SMU EC functions to promulgate patient safety and safe medication use by proposing standards for incorporation in the United States Pharmacopeia-National Formulary (USP-NF), identifying "better practices", reviewing the MEDMARX^{SM} Annual Reports and analyzing medication error data to determine priority areas such as CPOE, imprint and bar-codes, errors in non-hospital settings, good products and labeling practices, consumer and clinical education, best practices, recommendations for pediatric medications, neuromuscular blocking agents and others, and high alert drugs such as insulin and potassium chloride concentrate. As an example of their ongoing work to improve medication safety, standards for safe pharmaceutical compounding for sterile preparations (USP NF 797) were established for implementation in 2004.

The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP): This is an independent body comprised of 25 national and international organizations. In 1995, USP spearheaded the formation of the National Coordinating Council for Medication Error Reporting and Prevention. This nationwide program allows for health professionals who encounter actual or potential medication errors to report confidentially and anonymously, if preferred, to USP. USP reviews each report for health hazards and forwards all information to the Food and Drug Administration and the product manufacturer. The MER Program is presented in cooperation with the Institute for Safe Medication Practices

MEDMARX Program^{SM}: A national database, MEDMARX allows subscribing facilities to access and share information. This landmark program has nearly 500,000 medication error records submitted by more than 700 participants. The MEDMARX^{SM} program is a comprehensive, Internet-accessible, anonymous medication error reporting program and quality improvement tool. The program facilitates efficient documentation, tracking, and trending of data to identify medication error prevention strategies. Web site: http://www.usp.org.

SUMMARY AND CONCLUSIONS

The IOM reports–*To Err is Human* and *Crossing the Quality Chasm* paint a vivid landscape of the crisis in the American health care system and offer recommendations to point to a path for change. Mindful that the Chinese word for crisis contains two elements, danger and opportunity, we are reminded that that the edge of chaos is where change occurs, where systems unfreeze and reform with renewed capacity to respond to environmental forces, and to adapt.

The path to safer medication use and improvements in patient safety is not about a destination. This is a journey that must involve iterative learning. There are no absolute solutions, no mystical pronouncements that will tell the profession of pharmacy what to do to fix the system. The problems it faces will not be solved by the level of thinking that created them. The profession is forced to consider new approaches, new knowledge and to consider ways of thinking, acting and being that are outside our traditional approaches.

Some hard lessons learned from other transformational change initiatives, health care, and other industries provide insight and wisdom for the journey:

- Gather and use evidence to define the path and to persuade others to follow it.
- Realize that if you build it, they may not come. People always do want what makes sense to them in their own context, in their own time. The context cannot be overlooked because it is believed that content is impressive and persuasive. Allow some time for sense-making and learning to occur, but remember to front-end-load the learning with vision, direction and feedback.
- Wanting to do the right thing is not the problem. The aggregated consequences of how things are done creates the outcomes, morbidity, mortality, and cost experienced. Redesign will be essential. Make it easy to do the right thing, not harder. Simplification is a key.
- Engage the culture. Do not wait for it to change. Miracles happen when knowledge and context are shared through feedback. Build on best knowledge to engage the culture, with the realization that culture changes when knowledge shifts occur.
- Knowledge is sticky. Without a systematic process, enablers, and system supports, it doesn't move easily. Posters, senior leader's speeches, newsletters, and slogans typically do not cause knowledge *to blow*. Use data, make personal connections, use champions to move knowledge to influence culture to create change.
- Think about absorptive capacity. What issues might compete or conflict with the priority of the safety issue. Consider timing, how full individual plates are and craft a compelling message to engage people in the process.
- Consider ways to increase the dialog about safety. Communities of practice and successful microsystems are powerful tribes. When they work, knowledge flows and best practices can be replicated. Dialog is the key to effective information flow and to uncovering tacit knowledge that holds keys to success strategies.

Ultimately, the judge of the quality of work, the services delivered and the outcomes of care is an increasingly well-informed patient, as well as their payors and regulators from the public and private sectors. Focus on patient needs and wants, less on how we do it around here.

Enjoy the journey.

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Appendix 102-1. Clinical Microsystem Assessment Tool

Instructions: Each of the following characteristics (eg, leadership) is followed by a series of descriptors. For each characteristic, please check the description that best describes your current microsystem and delivery of care OR a microsystem YOU are most familiar with.

	Characteristic	Descriptions			
Leadership	***Leadership:*** The role of leaders is to balance selling and reaching collective goals, and to empower individual autonomy and accountability, through building knowledge, respectful action, reviewing and reflecting.	☐ Leaders often tell me how to do my job and leave little room for innovation and autonomy. Overall, they don't foster a positive culture.	☐ Leaders struggle to find the right balance between reaching performance goals and empowering the staff.	☐ Leaders maintain constancy of purpose, establish clear goals and expectations, and foster a respectful positive culture. Leaders take time to build knowledge, review and reflect, and take action about Microsystems and the larger organization	☐ Can't Rate
	Organizational Support: The larger organization looks for ways to support the work of the microsystem and coordinate the hand-offs between microsystems.	☐ The larger organization isn't supportive in a way that provides recognition, information and resources to enhance my work.	☐ The larger organization is inconsistent and unpredictable in providing the recognition, information and resources needed to enhance my work.	☐ The larger organization provides recognition, information, and resources that enhance my work and makes it easier for me to meet the needs of patients.	☐ Can't Rate
Staff	***Staff Focus:*** There is selective hiring of the right kind of people. The orientation process is designed to fully integrate new staff into culture and work roles. Expectations of staff are high regarding performance, continuing education, professional growth, and networking.	☐ I am not made to feel like a valued member of the microsystem. My orientation was incomplete. My continuing education and professional growth needs are not being met.	☐ I feel like I am a valued member of the microsystem, but I don't think the microsystem is doing all that it could to support education and training of staff, workload and professional growth.	☐ I am a valued member of the microsystem and what I say matters. This is evident through staffing, education and training, workload, and professional growth.	☐ Can't Rate
	Education and Training: All clinical Microsystems have responsibility for the ongoing education and training of staff and for aligning daily work roles with training competencies.	☐ Training is accomplished in disciplinary silos, eg, nurses train nurses, physicians train residents, etc. The educational efforts are not aligned with the flow of patient care, so that education becomes an "add on" to what we do.	☐ We recognize that our training could be different to reflect the needs of our microsystem, but we haven't made many changes yet. Some continuing education is available to everyone.	☐ There is a team approach to training, whether we are training staff, nurses or students. Education and patient care are integrated into the flow of work ina way that benefits both from the available resources. Continuing education for all staff is recognized as vital to our continued success.	☐ Can't Rate
	Interdependence: The interaction of staff is characterized by trust, collaboration, willingness to help each other, appreciation of complementary roles, respect and recognition that all contribute individually to a shared purpose.	☐ I work independently and I am responsible for my own part of the work. There is a lack of collaboration and a lack of appreciation for the importance of complementary roles.	☐ The care approach is interdisciplinary but we are not always available to work together as an effective team.	☐ Care provided by a interdisciplinary team characterized by trust, collaboration, appreciation of complementary roles, and a recognition that all contribute individually to a shared purpose.	☐ Can't Rate

	Characteristic	Descriptions			
Patient	***Patient Focus:*** The primary concern is to meet all patient needs—caring, listening, educating, and responding to special requests, innovating to meet patient needs and smooth service flow.	☐ Most of us, including our patients, would agree that we do not always provide patient centered care. We are not always clear about what patients want and need.	☐ We are actively working to provide patient centered care and we are making progress toward more effectively and consistently learning about and meeting patient needs.	☐ We are effective in learning about and meeting patient needs—caring, listening, educating, and responding to special requests and smooth service flow.	☐ Can't Rate
Patient	***Community and Market Focus:*** The microsystem is a resource for the community; the community is a resource to the microsystem; the microsystem establishes excellent and innovative relationships with the community.	☐ We focus on the patients who come to our unit. We haven't implemented any outreach programs in our community. Patients and their families often make their own connections to the community resources they need.	☐ We have tried a few outreach programs and have had some success, but it is not the norm for us to go out into the community or actively connect patients to the community resources that are available to them.	☐ We are doing everything we can to understand our community. We actively employ resources to help us with the community. We add to the community and we draw on resource from the community to meet patient needs	☐ Can't Rate
Performance	***Performance Results:*** Performance focuses on patient outcomes, avoidable costs, streamlining delivery, using data feedback, promoting positive competition, and frank discussions about performance.	☐ We don't routinely collect data on the process or outcomes of the care we provide.	☐ We often collect data on the outcomes of the care we provide and on some processes of care.	☐ Outcomes (clinical, satisfaction, financial, technical and safety) are routinely measured, we feed data back to staff and we make changes based on data.	☐ Can't Rate
Performance	***Process Improvement:*** An atmosphere for learning and redesign is supported by the continuous monitoring of care, use of benchmarking, frequent tests of change and a staff that has been empowered to innovate.	☐ The resource required (in the form of training, financial, support, and time) are rarely available to support improvement work. Any improvement activities we do are in addition to our daily work.	☐ Some resources are available to support improvement work, but we don't use them as often as we could. Change ideas are implemented without much discipline.	☐ There are ample resources to support continual improvement work. Studying, measuring, and improving care in a scientific way are essential parts of our daily work.	☐ Can't Rate
Information/Info Technology	***Information and Information Technology:*** Information is THE connector—Staff to patients, staff to staff, needs with actions to meet needs. Technology facilitates effective communication and multiple formal and informal channels are used to keep everyone informed all the time, list to everyone's ideas and ensure that everyone is connected on important topics. Given the complexity of information and the use of technology in the microsystem, assess your microsystem on the following three characteristics: A. Integration of information with patients B. Integration of information with providers and staff C. Integration of information with technology	A ☐ Patients have access to some standard information that is available to all patients. B ☐ I am always tracking down the information I need to do my work. C ☐ The technology I need to facilitate and enhance my work is either not available to me or it is available but not effective. The technology we currently have does not make my job easier.	☐ Patients have access to standard information that is available to all patients. We've started to think about how to improve the information they are given to better meet their needs. ☐ Most of the time, I have the information I need, but sometimes essential information is missing and I have to track it down. ☐ I have access to technology that will enhance my work, but it is not easy to use and seems to be cumbersome and time consuming.	☐ Patients have a variety of ways to get the information they need and it can be customized to meet their individual learning styles. We routinely ask patients for feedback about how to improve the information we give them. ☐ The information I need to do my work is available when I need it. Technology facilitates a smooth linkage between information and patient care by providing timely, effective access to a rich information environment. The information environment has been designed to support the work of the clinical unit.	☐ Can't Rate ☐ Can't Rate ☐ Can't Rate

From Nelson EC, et al. Microsystems in health care: learning from high-performing front-line clinical units. *Joint Commission Journal on Quality and Safety* 2002;28(9). Reprinted with permission.

Available at: http://www.clinicalmicrosystem.org/actionGuide.htm.

Appendix 102-2. NQF-Endorsed Set of Safe Practices

1. Create a healthcare culture of safety.
2. For designated high-risk, elective surgical procedures or other specified care, patients should be clearly informed of the likely reduced risk of an adverse outcome at treatment facilities that have demonstrated superior outcomes and should be referred to such facilities in accordance with the patient's stated preference.
3. Specify an explicit protocol to be used to ensure an adequate level of nursing based on the institution's usual patient mix and the experience and training of its nursing staff.
4. All patients in general intensive care units (both adult and pediatric) should be managed by physicians having specific training and certification in critical care medicine ("critical care certified").
5. Pharmacists should actively participate in the medication-use process, including, at a minimum, being available for consultation with prescribers on medication ordering, interpretation and review of medication orders, preparation of medications, dispensing of medications, and administration and monitoring of medications.
6. Verbal orders should be recorded whenever possible and immediately read back to the prescriber—i.e., a healthcare provider receiving a verbal order should read or repeat back the information that the prescriber conveys in order to verify the accuracy of what was heard.
7. Use only standardized abbreviations and dose designations.
8. Patient care summaries or other similar records should not be prepared from memory.
9. Ensure that care information, especially changes in orders and new diagnostic information, is transmitted in a timely and clearly understandable form to all of the patient's current healthcare providers who need that information to provide care.
10. Ask each patient or legal surrogate to recount what he or she has been told during the informed consent discussion.
11. Ensure that written documentation of the patient's preference for life-sustaining treatments is prominently displayed in his or her chart.
12. Implement a computerized prescriber order entry system.
13. Implement a standardized protocol to prevent the mislabeling of radiographs.
14. Implement standardized protocols to prevent the occurrence of wrong-site procedures or wrong-patient procedures.
15. Evaluate each patient undergoing elective surgery for risk of an acute ischemic cardiac event during surgery, and provide prophylactic treatment of high-risk patients with beta blockers.
16. Evaluate each patient upon admission, and regularly thereafter, for the risk of developing pressure ulcers. This evaluation should be repeated at regular intervals during care. Clinically appropriate preventive methods should be implemented consequent to the evaluation.
17. Evaluate each patient upon admission, and regularly thereafter, for the risk of developing deep vein thrombosis (DVT)/venous thromboembolism (VTE). Utilize clinically appropriate methods to prevent DVT/VTE.
18. Utilize dedicated anti-thrombotic (anti-coagulation) services that facilitate coordinated care management.
19. Upon admission, and regularly thereafter, evaluate each patient for the risk of aspiration.
20. Adhere to effective methods of preventing central venous catheter-associated blood stream infections.
21. Evaluate each pre-operative patient in light of his or her planned surgical procedure for the risk of surgical site infection and implement appropriate antibiotic prophylaxis and other preventive measures based on that evaluation.
22. Utilize validated protocols to evaluate patients who are at risk for contrast media-induced renal failure and utilize a clinically appropriate method for reducing risk of renal injury based on the patient's kidney function evaluation.
23. Evaluate each patient upon admission, and regularly thereafter, for risk of malnutrition. Employ clinically appropriate strategies to prevent malnutrition.
24. Whenever a pneumatic tourniquet is used, evaluate the patient for the risk of an ischemic and/or thrombotic complication and utilize the appropriate prophylactic measures.
25. Decontaminate hands with either a hygienic hand rub or by washing with a disinfectant soap prior to and after direct contact with the patient or objects immediately around the patient.
26. Vaccinate healthcare workers against influenza to protect both them and patients from influenza.
27. Keep workspaces where medications are prepared clean, orderly, well lit, and free of clutter distraction and noise.
28. Standardize the methods for labeling, packaging and storing medications.
29. Identify all "high alert" drugs (eg, intravenous adrenergic agonists and antagonists, chemotherapy agents, anticoagulants and antithrombotics, concentrated parenteral electrolytes, general anesthetics, neuromuscular blockers, insulin and oral hypoglycemics, narcotics and opiates).
30. Dispense medications in unit-dose or, when appropriate, unit-of-use form, whenever possible.

From: National Quality Forum. *Safe Practices for Better Healthcare: A Consensus Report.* Washington, DC: National Quality Forum, 2003.

Available at:
http://www.qualityforum.org/txsafeexecsumm+order6-8-03PUBLIC.pdf

CHAPTER 103

Poison Control

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Annually, it is estimated that there are between 5 and 10 million toxic exposures in the United States. Among children older than one year, accidents cause more deaths than do the five leading fatal diseases combined. Also, among the most common causes of death of preadolescents, adolescents, and adults is suicide. Frequently, accidents and suicides involve poisons. Another important cause of morbidity and mortality, especially among the young, is the deliberate abuse of drugs and chemicals for their effects on the central nervous system. Even though the reporting undoubtedly is incomplete, especially of suicides and abuses, there are known to be more than 10,000 deaths annually in the US attributable to poisoning.

In addition to the fatalities caused by poisoning, there are staggering numbers of nonfatal cases requiring treatment. The toll in terms of manpower, expense, and occupation of medical facilities cannot be estimated but must be tremendous.

In most instances, accidental poisonings should be preventable. This is especially true of accidental poisonings of young children by drugs and chemicals found in the home. This is a problem of great public-health significance, the solution of which requires efforts of individuals in many disciplines. Among these are pharmacists, who can play a key role in preventing or mitigating the consequences of accidental poisonings, especially those caused by drugs.

EPIDEMIOLOGY

Effective preventive measures require a knowledge of who and what are involved, how it happened, and any predisposing or contributory factors. For delineating some of these factors, a description of the experiences of those poison-control centers who report to the Toxic Exposure and Surveillance System (TESS) of the American Association of Poison Control Centers (AAPCC) may be instructive. The TESS of the AAPCC was established in 1983. The data collected by this system constitutes the largest body of data about poisoning exposures in the world. Table 103-1 summarizes the growth of this system. Since its inception in 1983, when it represented approximately 11% of the US population with slightly more than 250,000 reported human exposure cases from 16 reporting centers, the system has grown continually. In 2001, 2,267,979 human exposure cases were reported from 64 centers representing approximately 99% of the US population.

Poisoning exposure calls (Table 103-2) make up approximately 80% of all calls reported to the system. Poison centers also receive calls that are informational in nature in which no poisoning victim is involved. The majority of information calls are toxicology or drug-information requests, but they also include requests for medical and veterinary information. Of the human poisoning exposure cases reported in 2001, 85% were unintentional in nature. Suicidal or intentional poisonings made up 10%, whereas poisonings involving drug abuse amounted to 1%. Environmental or industrial exposures accounted for 4% of the human poisoning exposure cases.

Of the 2, 267,979 exposure cases reported in 2001, 75.8% involved ingestions as the route of exposure. The remainder of exposures were:

Dermal, 7.9%
Ophthalmic, 5.3%
Inhalation, 6.3%
Bites and stings, 3.6%
Parenteral, 0.4%
Miscellaneous or unknown, 0.7%

Children 5 years of age and younger were involved in 51.6% of the cases. Ages 6 through 19 were involved in 14.2%, whereas 33.5% involved adults aged 19 and older. In terms of gender, males and females were represented equally.

In terms of the severity of exposures handled by poison-control centers, 20% had no effect, and 15.5% had only a minor effect. Major toxicity was observed in only 0.6%.

In cases of a poisoning exposure, approximately 75% of poisonings were managed at home or in some other non-health-care facility. Generally, treatment consisted of dilution, irrigation, or rarely emesis. Of the remaining exposure cases, 22% were managed in a health-care facility, and 3.5% either refused referral to a health care facility or the situation was unknown (Tables 103-3 to 103-6).

In the AAPCC database, the substances most frequently involved in human poisoning exposures were over-the-counter and prescription analgesics, cleaning substances, cosmetics and personal care products, foreign bodies, plants, sedatives-hypnotics, antipsychotics, over-the-counter and prescription cough and cold preparations, topical preparations, bites or envenomations, antidepressants, pesticides, foods, antihistamines, alcohols, oral antimicrobials, hydrocarbons, and chemicals (Table 103-7). A wide variety of agents made up the remaining cases. In contrast, the most frequent category of toxic substances involved in reported fatalities was over-the-counter and prescription analgesics, followed by sedatives-hypnotics-antipsychotics, antidepressants, stimulants and street drugs, cardiovascular drugs, alcohols, chemicals, anticonvulsants, gases and fumes, antihistamines, muscle relaxants, hormone and hormone antagonists, cleaning substances, automotive products, asthma therapies, and pesticides. Among those categories causing the most fatalities, there is a wide variation in the percentage of fatalities with respect to all exposures in that category.

Table 103-1. Growth of the AAPCC Toxic Exposure Surveillance System

YEAR	NUMBER OF POISON CENTERS	POPULATION (MILLIONS)	NUMBER OF HUMAN EXPOSURES
1983	16	43.1	251,012
1984	47	99.8	730,224
1985	56	113.6	900,513
1986	57	132.1	1,098,894
1987	63	137.5	1,166,940
1988	64	155.7	1,368,748
1989	70	182.4	1,581,540
1990	72	191.7	1,713,462
1991	73	200.7	1,837,939
1992	68	196.7	1,864,188
1993	64	181.3	1,751,476
1994	65	215.9	1,926,438
1995	67	218.5	2,023,089
1996	67	232.3	2,155,952
1997	66	250.1	2,192,088
1998	65	257.5	2,241,082
1999	64	260.9	2,201,156
2000	63	270.6	2,168,248
2001	64	281.3	2,267,979

Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

Therapeutic overdosage has important preventive implications for the pharmacist. It is not uncommon for a parent who has never been told of the toxic potential of such a common drug as acetaminophen to administer several times the safe dose to a small infant over a period of several days. In fact, such unintentional overdoses are responsible for many of the most serious cases of poisoning.

Particularly tragic are accidental poisonings caused by materials that are either outmoded, excessively toxic for their intended use, or for which there is only questionable rationale. Also, household chemicals, solvents, cleaners, and some pesticides, although valuable to the professional user, are excessively toxic for routine household use. There is little reason for employing highly dangerous materials such as arsenic, phosphorus, or strychnine as rodenticides when warfarin-type compounds, which possess very low acute human toxicity, work equally well.

Table 103-2. Typical Pattern of Human Poison Exposure Cases Reported to AAPCC

TYPE OF POISONING	NUMBER OF CASES	TOTAL %
Unintentional	1,931,841	85.2
General	1,455,602	64.2
Therapeutic error	167,014	7.4
Bite/sting	85,713	3.8
Misuse	82,867	3.7
Environmental	57,209	2.5
Food poisoning	41,319	1.8
Occupational	35,472	1.6
Unknown	6,645	0.3
Intentional	262,703	11.6
Suicidal	176,221	7.8
Abuse	38,640	1.7
Misuse	37,078	1.6
Unknown	10,764	0.5
Adverse Reaction	49,198	2.2
Drug	35,646	1.6
Other	9,519	0.4
Food	4,033	0.2
Unknown	7,986	0.4
Total	2,267,979	100

Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

Table 103-3. Distribution of Human Poison Exposure Cases by Route of Exposure

ROUTE	NUMBER OF CASES	%	NUMBER OF FATALITIES	%
Ingestion	1,807,448	75.8	893	77.1
Dermal	188,620	7.9	12	1.0
Inhalation	149,812	6.3	109	9.4
Ocular	126,117	5.3	0	0.0
Bites/stings	85,627	3.6	3	0.3
Parenteral	9,658	0.4	58	5.0
Otic	2,336	0.1	0	0.0
Aspiration	1,404	0.1	15	1.3
Rectal	900	0.0	2	0.2
Vaginal	800	0.0	0	0.0
Other	2,851	0.1	3	0.3
Unknown	8,025	0.3	63	5.4

Multiple routes of exposure were observed in many poison-exposure victims. Percentage is based on the total number of exposure routes (1,932,106) for all patients, 822 for fatal cases, rather than the total number of human exposures (1,837,939) or fatalities (764).
Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

Influential Factors

Several factors are important in the consideration of poisoning risk and in poison prevention.

AGE—Approximately two-thirds of poisonings occur in children and are accidental, whereas a large portion of the poisonings in adolescents and adults represent suicide attempts. Poisonings do occur in adults from the inadvertent ingestion of some material other than the intended medication or accidental overdosage of proper medication. Although these accidents are rare, people should be cautioned to carefully read labels before taking medications, not to take medications in the dark, not to transfer medications from their original containers, to protect medication labels against destruction, and to follow the recommended dosage schedules carefully.

Accidental poisoning is less common in children older than 5 years of age. The most critical age period is between 1 and 3 years, where nearly one-half of poisonings occur. Poisoning is among the most common reasons to bring a child to the hospital for emergency treatment. The reasons for the high incidence in that age range relate to certain characteristics of child development. During these early years the youngster is inquisi-

Table 103-4. Distribution of Human Poison Exposure Cases by Age of Victim

AGE (YR)	% OF CASES	AGE (YR)	% OF CASES
<1	6.1	30–39	7.9
1	16.7	40–49	6.0
2	16.2	50–59	3.5
3	7.1	60–69	1.9
4	3.3	70–79	1.4
5	1.9	80–89	0.8
6–12	6.9	90–99	0.1
13–19	7.3	Unknown adult	3.9
Child, unknown age	0.4	Unknown age	0.5
20–29	7.9	Total	100.0

Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

Table 103-5. Medical Outcome of Human Exposure Cases

OUTCOME	NUMBER	%
No effect	453,975	20.0
Minor effect	351,191	15.5
Moderate effect	102,540	4.5
Major effect	13,918	0.6
Death	1,074	0.0
No follow-up, nontoxic	405,568	17.9
No follow-up, minimally toxic	776,728	34.2
No follow-up, potentially toxic[a]	99,294	4.4
Unrelated effect	63,691	2.8
Total	2,267,979	100.0

[a] Patient lost to follow-up. Exposure was assessed as potentially toxic.
Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

tive. By one year of age, the child also usually can either crawl or walk, yet is too young to recognize danger. It is to be expected that attempts will be made to mouth or ingest any substance left within reach.

No matter how distasteful a product may be, a child still will make an initial attempt to eat or taste it. Although pleasant flavoring may be influential in a child's ingesting a larger dose, it has little bearing on whether or not an initial attempt to ingest the material will be made. During the first 2 to 3 years of life, texture is at least as important as flavor in determining acceptability of something to be ingested. The young child may ingest materials that would readily gag or dissuade an older individual. At this age, children ingest even highly caustic substances such as acids and alkalis without hesitation.

Children younger than one year old may be given a toxic material by an older sibling. Thus, it is important to keep potentially toxic materials inaccessible to young children and also to their older brothers and sisters. In addition, children should be educated not to give things to the baby without parental permission. Preschool education programs teach children these principles to reinforce parents' instructions.

Among children older than 3 years of age, ingestions may occur as group activities. Occasionally, two or more children share the material in some form of play, where they might otherwise be unlikely to ingest it by themselves. Again, at this age, children are more educable than earlier, so instruction to avoid potentially toxic nonfood substances (eg, cleaning products, personal care products, plants) should be given in the home and in the educational environment.

Some of the supposedly accidental poisonings in teenage and younger children are actually suicide attempts or gestures, or attempts at drug abuse. It is important to realize that serious suicide attempts may occur as young as 9 or 10 years of age. Among the adolescent population, suicidal attempts or gestures are not uncommon and also occur several years immediately before and after this important transitional stage of life.

Table 103-6. Management Site of Human Poisoning Exposure Cases[a]

MANAGEMENT SITE	NUMBER	%
Non-health facility	1,689,907	74.5
Health-care facility	498,524	22.0
Refused referral	46,103	2.0
Other	21,017	0.9
Unknown	12,428	0.5
Total	1,837,939	100

Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

Table 103-7. Substances Most Frequently Involved in Human Poison Exposures

SUBSTANCE	NUMBER	%[A]
Analgesics	240,757	10.6
Cleaning substances	216,102	9.5
Cosmetics/personal care products	208,171	9.2
Foreign bodies	115,320	5.1
Plants	105,560	4.7
Sedatives/hypnotics/antipsychotics	100,141	4.4
Cough and cold preparations	97,710	4.3
Topicals	95,854	4.2
Bites/envenomations	93,821	4.1
Antidepressants	92,675	4.1
Pesticides (includes rodenticides)	90,010	4.0
Food products, food poisoning	67,149	3.0
Antihistamines	67,053	3.0
Alcohols	64,462	2.8
Antimicrobials	61,357	2.7
Hydrocarbons	59,738	2.6
Chemicals	56,381	2.5

[a] Percentages are based on total number of known ingested substances rather than the total number of human exposures cases.
Note: Despite a high frequency of involvement, these substances are not necessarily the most toxic, but rather reflect only ready availability.
Adapted from Litovitz TL et al. 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2002; 20:391.

ACCIDENT PRONENESS—Only a small number of patients treated for poisoning have had a history of having been involved in similar accidents. Thus, although some children may be involved in repetitive episodes, they account for a small percentage of these cases. Nonetheless, a child who has ingested something once, especially if some effort was required in the act, may be at greater future risk and should be treated accordingly. The idea that there are accident-prone children probably is less valid than the fact that there are accident-prone situations and surroundings. Parental education about poison-prevention techniques and what to do in case of a poisoning should be considered part of the routine follow-up in all childhood poisoning episodes.

LOCATION—The majority of childhood accidental poisonings occur in the home. At the time they were ingested, materials that become involved in accidental childhood poisoning usually have been left out after being used rather than being returned to their usual place of storage. The most common areas for poisoning within the home are the kitchen, bathroom, and bedroom.

The highest incidence of accidental childhood poisoning is in the late afternoon and around the dinner hour or in the early-morning hours. However, poisonings occur with regular consistency during a child's waking hours. Poisonings in the late-morning hours often occur in the kitchen, and the substances most frequently involved are common household products (eg, cleaning agents, polishes, and other materials commonly kept in the kitchen). Poisonings that occur in the bedroom may involve cosmetics and, to a lesser extent, medications. Bathroom incidents usually involve either medications or topical antiseptics. The more often a consumer product is used and stored in the home, the more likely it is to be involved in an accidental poisoning exposure.

Among cases that occur outside the home, the garage and automobile are common sites of accidental poisoning in young children. Medications found either in the glove compartment or in mother's purse are most frequently involved in the automobile. Pesticides, petroleum products, cleaning agents, and paint products are often stored in the garage and thus involved in poisoning. An increasing percentage of cases occurring inside or outside the home involve plants kept for decorative purposes or those growing in the yard or wild in the fields. Parents should be reminded that children may be poisoned when they visit the

homes of others (especially grandparents) who leave medications and household items within reach because they are not accustomed to having children about.

ACCESSIBILITY—Poison-prevention campaigns often focus on the provision of a locked medicine cabinet. The availability of a safe storage place for medicines is desirable, but this probably would prevent less than one-half the cases of accidental childhood poisoning.

In up to 75% of accidental childhood poisoning cases, the materials involved has been left within reach of a child. In many instances, ingestion occurs when the individual responsible for the care of a child is interrupted during his or her use of the material in question.

People must be instructed to provide a secure storage place for potentially toxic materials and to return these materials immediately after use.

THE CONTAINER—Removal of potentially toxic materials from their original containers is a significant factor in increasing risk of accidental poisoning, especially with certain compounds. The common practice, for example, of storing a small quantity of gasoline or solvents in a soft-drink bottle is especially hazardous. Other hazardous materials where this approach is employed are automobile products, paint products, cleaning solutions, and pesticides. Sometimes the container used to transfer the offending substance is a drinking glass or dish. In all such instances, toxic substances are easily confused as food or other edible items. In addition, transfer of materials from their original containers creates problems of accurate identification when a poisoning does occur. A similar problem exists when materials, particularly medications, are not identified properly in their original containers. All prescription containers should identify the contents on the label accurately.

SUPERVISION—Many children are under the supervision of one or both parents at the time an accidental poisoning occurs. However, usual adult supervision is not adequate to prevent poisoning accidents in young children. This may, in part, be because parents underestimate the child's ability to move quickly and ingest a potentially toxic material. A common error is to leave medications on a bedside stand after administering them. The child for whom it was intended or a sibling may ingest a portion or the entire contents.

A significant number of childhood poisonings occur when there is a disruption in the normal household routine. Times of moving, painting, holidays, visits by friends or relatives, or death or illness in the family are occasions when increased caution should be exercised. Other circumstances that invite unsupervised access of children to potentially toxic materials are when items are sent through the mail or have been discarded into a waste container.

When deteriorated or unwanted materials are to be discarded, the safest procedure for potentially toxic liquids or powders is either to pour them down a drain or flush them down a toilet. With some highly concentrated, toxic materials, such as pesticide concentrates, even the amount remaining in an *empty* bottle may be sufficient to cause serious poisoning. Those containers should be rinsed thoroughly before being discarded and placed carefully in closed waste containers as far from normal access of children as possible.

Optimal supervision also involves attention to detail in the legitimate use of potentially hazardous materials. As previously noted, drug labels should always be examined carefully to ensure accurate identification before a medication is administered or taken. Self-medication, use of another individual's medications for the "same problem," and unsupervised self-diagnosis and prescription of a child's treatment by the parents should only be encouraged with appropriate education and potential for consumer understanding.

There is a tendency for many to believe that if a material were significantly hazardous it would not be available for over-the-counter (OTC) sales, but this is untrue. Frequently, parents may overmedicate a child, either because they underestimate the potential hazard or are given inadequate instructions. It is important that physicians who order and pharmacists who dispense or recommend over-the-counter medications provide and emphasize specific instructions concerning proper use. The pharmacist plays a key role in patient education, even if the intervention is only a minute or two.

Although seemingly unlikely, it is not uncommon for a patient who has been advised to take or administer "some aspirin every once in a while" to use two or three times the safe dose every few hours for several days or to take concurrent medications containing salicylates until serious intoxication occurs. Instructions on the label are meaningful to the cautious and the concerned, but they are rarely the people who become poisoned. Person-to-person discussion is far more effective and can easily take place at the time a material is prescribed or dispensed.

TREATMENT

The most important treatment measure for poisoning is prevention. Once a poisoning occurs, it is important to be able to provide highly skilled supportive medical care. It is insufficient to focus only on simple first-aid measures, antidotal therapy, or home remedies.

Actually, there are few poisons for which there are effective antidotes. Even in the instances in which antidotes are available, supportive care is equally as important; indeed, the best antidote in the world is of little value without good supportive care. Most of the home remedies that have been recommended from time to time are actually of little value or are even potentially dangerous. Most tend to waste valuable time that could better be devoted to proper treatment under adequate medical supervision.

Unfortunately, many lay publications, including first-aid texts, are outmoded in this respect and continue to recommend all sorts of elaborate but ineffective procedures to be carried out in the home. The same criticism can be leveled at the instructions provided on the many rather complicated antidote lists and first-aid treatment charts that are disseminated for use by the public, often by well-meaning professional organizations.

FIRST-AID PRINCIPLES

The cardinal rule for first-aid treatment of poisoning is to remove the poison from contact with the patient (unless such removal is contraindicated) and to obtain further definitive medical care at the earliest possible moment if warranted.

The more simplified instructions for home treatment are, the more likely they will be followed and the less likely they are to either delay or be substituted for proper care by a physician. Thus, general procedures that are simple and applicable regardless of the nature of the poison are to be recommended until medical help can be obtained.

Recommended procedures for lay use in the first-aid treatment of poisoning are outlined in Table 103-8. The principal elements are knowing what to do before you call someone, obtaining medical advice immediately to determine what to do next, and terminating contact of the victim with the poison by dilution, washing or, in increasingly rare instances, through induction of vomiting. In regard to the latter point, note that induction of vomiting with ipecac syrup is the only method of vomiting in use today. Many measures recommended in the past for the induction of vomiting, such as mechanical stimulation of the posterior pharynx or giving mustard water or salt water, appear to be less effective and may be dangerous. The most widely used emetic for first-aid use is ipecac syrup. However, a lack of scientific data demonstrating a positive impact on patient outcome has led to a substantial decline in the use of ipecac syrup.

Activated charcoal is a highly effective adsorbent of many poisons and appears to be more effective than ipecac-induced vomiting at decreasing the absorption of materials from the

gastrointestinal tract. This material adsorbs most organic and inorganic materials. Thus, its routine use in cases of poisoning by ingestion is worthwhile. Remember, however, that if activated charcoal is given before ipecac syrup, it will inactivate the latter. Consequently, if one is going to both induce vomiting and administer activated charcoal, it is advisable to induce vomiting first and then, after the vomiting has subsided, administer the charcoal. As the use of ipecac-induced emesis has declined in popularity, the use of activated charcoal as the sole method of gastrointestinal decontamination has increased substantially. Activated charcoal is worthwhile as a nonspecific antidote for home use and for use in hospitals and in poison treatment centers. It is best given as a slurry in water.

In recent years parents have been encouraged to keep ipecac syrup and activated charcoal in homes where there are children of poisoning-prone age. If such items are to be used, it is important that a prominent part of the label instructions is to call the local poison-control center, an emergency department, or a physician before administering either.

ANTIDOTES—Note that although activated charcoal is an effective, nonspecific adsorbent of many materials, there is no true *universal antidote*. The classic universal antidote, which was in use for a long period, consisted of activated charcoal, tannic acid, or magnesium oxide (or, in the home: burnt toast, strong tea, or milk of magnesia). It now has been established that the last two constituents have no significant efficacy and may actually impede the one active ingredient, activated charcoal. The long-advocated preparation of burnt toast and strong tea in the home has no merit.

Because they are not used often, it is important for information concerning antidotes to be readily available so that they can be used properly and at the earliest possible moment. It is important not to waste time searching for nonexistent antidotes. For a few poisons, there are chemical antidotes that react with the poison in the stomach either to inactivate it or to retard its absorption. Such local antidotes are sufficiently innocuous that they can be administered safely.

The most useful antidotes are those available for systemic administration to counteract the effects of poisons that have been absorbed. Table 103-9 summarizes the use and administration of antidotes that currently are recommended.

OTHER MEASURES—Aside from removal or inactivation of the poison and use of antidotes when available, the treatment of poisoning is supportive. The symptomatic or supportive approach to treatment does not differ significantly from that encountered in other medical problems. Common problems requiring supportive care include coma, respiratory insufficiency, convulsions, shock, vomiting, diarrhea, fluid and electrolyte disturbances, cerebral edema, kidney failure, and damage to other organs.

Additionally, several procedures exist that may be used to hasten elimination of a poison. In some instances, drugs can be eliminated more rapidly with diuresis induced by use of pharmacological or osmotic diuretics along with alkalinization of the urine. With poisons that are dialyzable, extracorporeal hemodialysis (use of artificial kidney) is preferred. Also, charcoal hemoperfusion is effective with many agents. These procedures are indicated when normal excretory processes fail or

Table 103-8. First-Aid Treatment for Poisoning

I. DO THESE THINGS BEFORE YOU CALL SOMEONE
- A. Remove poisons from contact with eyes, skin, or mouth.
  1. Eyes: Gently wash eyes with plenty of water (or milk) for 10 to 15 minutes with the eyelids held open. Remove contact lenses and again wash the eyes. Do not allow victims to rub their eyes.
  2. Skin: Wash poisons off the skin with large amounts of plain water. Then wash the skin with a detergent if it is possible. Remove and discard all contaminated clothing.
  3. Mouth: Look into victim's mouth and remove all tablets, powder, plants, or any other material that is found. Also examine for cuts, burns, or any unusual coloring. Wipe out mouth with a cloth and wash thoroughly with water.
- B. Remove victim from contact with poisonous fumes or gases.
  Get the victim into fresh air.
  Loosen all tight-fitting clothing.
  If the victim is not breathing, one should start artificial respiration immediately. Do not stop until the victim is either breathing well or emergency assistance arrives. Use oxygen if available. Send someone else to call for help.

II. CALL FOR INFORMATION ABOUT WHAT TO DO NEXT:
- A. Call the poison control center or your physician.
  1. Identify yourself and your relationship to the victim.
  2. Describe the victim by name, age, and sex.
  3. Have the package or poison in your hand and identify as best as you can what and how much the victim ingested.
- B. Call for information even if you are unsure. Keep calm. You have enough time to act, but don't delay unnecessarily.

III. IF YOU ARE INSTRUCTED TO INDUCE VOMITING
Never induce vomiting until you are instructed to do so.
- A. If you live more than one hour from the closest medical facility, have syrup of ipecac available to induce vomiting. The use of this drug has declined substantially in recent years, but there still may be instances where the use of ipecac syrup may be suggested. The poison center or your doctor will instruct you in how to administer the ipecac syrup.
- B. Don't waste time trying other ways to make the victim vomit.
  Tickling the back of the throat with your fingers, a spoon, or some other object is not effective. Do not use salt water. It is potentially dangerous.
- C. Never induce vomiting if the patient:
  Is unconscious
  Is having convulsions (seizures)
  Has swallowed strong caustics or corrosives
  Has swallowed petroleum products, cleaning fluids, gasoline, lighter fluid, etc, unless specifically instructed to do so

IV. IF YOU GO TO THE HOSPITAL:
- A. Take with you or send the poison container, poisonous plant, etc
- B. Take any vomitus you collect
- C. Do not administer substances such as coffee, alcohol, stimulants, or drugs to the victim

Table 103-9. Summary of Antidotes and Stocking Levels[a]

GENERIC/BRAND NAME	USE	NOTES	SUGGESTED STOCKING LEVEL
Atropine	Organophosphate/Carbamate insecticide poisoning, bradycardia induced by a variety of toxins	Requires very large amounts in severe organophosphate/ carbamate insecticide poisoning	1,000 mg total Preservative free
Antivenin Crotalidae Polyvalent (equine) Wyeth-Ayerst	Rattlesnake envenomation	Different dosing from Cro-Fab™	20 vials
Antivenin Crotalidae Polyvalent Immune FAB-Ovine/Cro-Fab	Rattlesnake envenomation	Different dosing from Wyeth-Ayerst polyvalent antivenin	18 vials
Antivenin, Black Widow Spider/Antivenin (Latrodectus Mactans)	Black Widow spider envenomation		1 × 6000u vial
BAL (Dimercaprol)/BAL in oil 10%	Heavy metal poisoning		4 × 3ml 10% in oil amps
Calcium chloride injection	Calcium channel blocker poisoning		20 × 10ml 10% vials
Calcium gluconate powder	Hydrofluoric acid skin exposures	For compounding topical gel	1 × 100gm powder bottle
Calcium gluconate injection	Calcium channel blocker poisoning, hydrofluoric acid poisoning or skin exposure, toxin-induced hypocalcemia		20 × 10ml 10% vials
Cyanide Antidote Kit/Taylor Cyanide Antidote Kit	Cyanide poisoning		2 kits
Deferoxamine/Desferal	Iron poisoning		12 × 500mg vials (6 grams total)
Digoxin Immune FAB (ovine)/ Digibind, DigiFab	Digitalis glycoside poisoning		20 vials
DMSA (Succimer)/Chemet	Heavy metal poisoning		1 × 100 capsule bottle
EDTA, Calcium/Versenate	Heavy metal poisoning		18 × 1000mg/5ml amps
Ethanol IV 10%	Ethylene glycol, methanol poisoning		3 × 1000ml (10%) bottles in 5% dextrose
Flumazenil/ Romazicon	Benzodiazepine poisoning		5 × 0.5mg/ml vial
Fomepizole (4-MP)/Antizol	Ethylene glycol, methanol poisoning		4 × 1.5ml (1gm/ml) vials
Glucagon	Beta blocker, calcium channel blocker poisoning		100 × 1mg vials
Methylene Blue	Methemoglobinemia		5 × 10ml 1% amps
N-Acetylcysteine (NAC)/ Mucomyst	Acetaminophen poisoning	Use orally. Dilute (at least by a 3:1 ratio) in juice or soda to increase palatability	7 × 30ml 20% vials
Naloxone/ Narcan	Narcotic overdose		20 × 0.4mg/2ml amps
Octreotide acetate/ Sandostatin	Sulfonylurea poisoning		2 × 1ml (0.1mg/ml) amp or 1 × 5ml (.2mg/ml) MDV
Physostygmine/Antilerium	Anticholinergic poisoning		10 × 2ml 1mg/ml vials
Pralidoxine (2-PAM)/ Protopam	Organophosphate pesticide poisoning		12 × 1gm 20ml vials
Pyridoxine (Vitamin B_6)/ Beesix	Isoniazid (INH) poisoning	Very large amounts needed (20 grams total)	20 × 10ml (100mg/ml) vials
Vitamin K_1 (Phytonadione)/ Mephyton, AquaMephyton	Warfarin and super-warfarin (rodenticide) anticoagulant poisoning		100 × 5mg tabs 10 × 10mg/ml amps

[a] Based on dose to treat a 70-kg patient for 24 hours.
Adapted from California Poison Control System Antidote Chart, California Poison Control System, University of California San Francisco, School of Pharmacy, 2002.

prove to be inadequate or when the degree of poisoning portends a fatal outcome unless the level of poison in the body is rapidly reduced.

Centers that are likely to be called on to treat cases of poisoning generally have the necessary supplies and equipment for performance of peritoneal dialysis, hemodialysis, and hemoperfusion. If such is not available in a given hospital, the poison center should have information concerning the nearest location of such equipment.

PREVENTION

Many preventive measures have been suggested or alluded to previously. Total prevention through education is an ideal worth striving to accomplish. To date, educational programs have eliminated only a portion of the problem. One concern is that educational efforts may be too general, so the public does not know precisely what it should do and has no specific actions to implement. Instruction is most effective when it includes

specific directions that can and should be followed. For instance, announcing to parents that they should "keep things out of the reach of small children" helps little until they are told what to keep out of reach.

It is not uncommon in cases of childhood poisoning that parents are unaware that the material was potentially poisonous, that they took no special precautions because their child had been no problem previously, or that they thought the material was inaccessible to the child. Aiming educational efforts at specific actions (see below) has far more chance of being effective. General admonitions about preventing poisoning are much less likely to be effective.

Consonant with the theory of specific instruction is the need to provide specific directions with individual products. This is an important role for the pharmacist. There is a tendency for precautionary labeling to be ignored until after an accident. Labels may be effective in directing individuals to proper treatment, but their preventive value depends on the consumer's interest and concern in reading the label in the first place. Person-to-person instruction by the physician or the dispensing pharmacist is much more effective.

Limiting the availability of highly toxic materials or directing the consumer to the least toxic material that will serve the intended purpose are of potential value. Outmoded materials that have higher degrees of toxicity should be eliminated as safer substitutes become available. Pharmacists should be in a position to advise about comparative safety as well as efficacy of the products that they dispense or sell.

THE *POISON PREVENTION PACKAGING ACT*— Enacted in 1970, this legislation (PL 91-601; 16CFR 1700) calls for the packaging of specified potentially hazardous household chemicals and drugs in *safety* containers. The latter include safety-capped vials or bottles or *strip*, *blister*, or other unit packaging. Child-resistant packaging must be demonstrated through the use of standardized tests in target-age populations to resist opening by children but not by adults. Such testing demonstrates the particularly effective barrier these packages provide to the poison-prone-age child. Drugs designated thus far as requiring such packaging include, with certain specific exemptions, aspirin-containing preparations, those containing high concentrations of methyl salicylate, prescription drugs, caustics, petroleum distillates, glycols, alcohols, acetaminophen, and iron. Additional drugs may be regulated similarly by the time of this publication. For the benefit of the elderly and infirm, the law provides that a single size of regulated products may, at the request of the consumer or prescribing physician, be packaged in conventional containers that are labeled as being intended for households without young children.

Although the manufacturer provides the safety packaging for over-the-counter drugs, the pharmacist is responsible for complying with the regulations for prescription products that are repackaged and plays a key role in implementation of this important poisoning-prevention measure. The pharmacist is the person to select and employ appropriate packaging for prescription items and is in an excellent position to promote the effectiveness of the Act. The Act can succeed only to the extent that purchasing adults accept and use the special packaging. The pharmacist should assure that people are aware of the availability of such packaging for regulated products, that they are instructed as to its importance and proper use, and that substitutions of conventional packaging are restricted to legitimate and informed requests. This is particularly important as long as reversible or dual function closures are used because their comparative safety has yet to be demonstrated.

POISON-CONTROL CENTERS

The poison-control concept was initiated in Chicago in 1953. After the impetus of local health officials, pediatricians, and other interested physicians, a single center for collecting product data was established. The idea soon caught on and numerous other centers were established. To provide a coordinating agency for these centers, the then Bureau of Product Safety in the Food and Drug Administration (FDA) established the National Clearinghouse for Poison Control Centers. This clearinghouse served as a center for collecting and standardizing product toxicology data and for distributing this data in the form of 5- by 8-inch index cards to recognized poison-control centers. State health departments were given the responsibility for identifying poison centers within their states. The great interest in poison control eventually resulted in more than 580 officially recognized poison-control centers and numerous additional unofficial centers, including drug-information services, bringing the total to well over 600. Unfortunately, many poison centers have had little if any capability for providing sophisticated information or treatment for poisoning, because they handle as few as one call per week.

From the beginning, studies of poison-control center operations demonstrated a wide variability in the manner by which services were provided. Some centers provided information solely to physicians or health-care facilities, whereas others provided information to the public or both. Staffing of poison-control centers likewise was variable. The staff of a poison center may have consisted only of full- or part-time clerks, nurses, or pharmacists without any direct medical supervision, or they have consisted of a full-time clinical toxicologist-medical director and specially trained, full-time professional staff, such as clinical pharmacists or nurses. Other centers have included pharmacologists, emergency room physicians, ambulatory pediatricians, or other scientifically trained personnel as staff or consultants.

The questions facing the poison-control center movement, now in the sixth decade after its inception, are to whom to provide services, how best to provide services, how to improve services, how to standardize or monitor services, and how to organize such services on a regional or a national basis. The question of how to organize these services has been resolved to a great degree over these past several years. Consolidation of manpower and resources into centralized or regional services is crucial. In centralized or regional poison-control centers, sophisticated information can be provided to health professionals and the public. Treatment facilities are generally an integral part of the regional poison-control center, and the staff, particularly the medical staff, can provide the treatment for poisoning victims. In addition, active supervision and even bedside consultation of poisoning cases admitted to other health-care facilities ought to be provided.

Optimally, there should be 50 to 60 regional programs in the US. A regional poison-control center should be one that, in less densely populated areas, serves a single or multistate region or that, in heavily populated areas, serves a portion of a state. Generally, a regional center serves no fewer than one million people, but could serve as many as 5 to 10 million people in areas of high-population density. A regional center would provide:

Comprehensive poison information, both to health professionals and consumers
Comprehensive poisoning treatment services
A toll-free communication system
Access to a full range of analytical toxicological services
Access to transportation facilities for critically ill patients
Professional and public education programs
Collection and dissemination of poisoning experience data

In essence, these regional centers are capable of assuming ultimate responsibility, which includes the functions mentioned above, for the provision of poisoning consultations and patient care for all poisonings brought to its attention within its region. The AAPCC has developed standards for regional poison control centers and provides a process to evaluate a poison center's capabilities and to designate centers as *regional poison centers*. The types of services and equipment recommended for various

types of centers are described in more detail in references noted in the *Bibliography*.

NATIONAL POISON PREVENTION WEEK

Since 1962 the third week of March has been designated National Poison Prevention Week. In addition to giving annual emphasis to the problem of poison control, this week provides an opportunity for concentrated educational efforts directed to the public. Pharmacists should play an active role in the activities of this period. Special displays in pharmacies have been one type of effective strategy. Other worthwhile activities have included television or radio messages, special meetings, and newspaper articles, all of which can be made more effective by involved pharmacists. By joining forces with the regional or local poison-control centers, this week can be used to highlight the year-round educational activities of the center and the community.

ROLE OF THE PHARMACIST

There is much that a pharmacist can do to help prevent poisoning and to improve the treatment thereof. Pharmacists direct and staff many regional poison centers. They actively provide consultation to physicians treating poisoned patients to assure quality care.

Undoubtedly, the most important role played by a pharmacist is in the area of prevention. This role, relative to poison-prevention packaging of prescription drugs, was mentioned previously. However, the role of the pharmacist is particularly critical with regard to nonprescription or OTC items. With prescription medications, there is involvement of a physician who may provide instructions and precautionary advice. However, with over-the-counter products, the pharmacist is often the only person who is in a position to serve these functions.

The pharmacist can and should provide, explain, and amplify directions for proper use of potentially toxic materials, bearing in mind that the concern is for the safety of the patient and for other household individuals. Thus, the dispensing of a toxic medication provides an opportunity to warn the buyer about the hazards of leaving the material within reach of unsuspecting children.

In some instances, it is desirable to affix warning labels on the products that a pharmacist dispenses or to hand out patient information materials. The dispensing of a drug also provides an opportunity to inquire and give advice about facilities for safe storage. Because of this contact, the pharmacist can play a personalized role in cautioning about prescription and commercial products.

The pharmacist can do much to reduce the aforementioned limitations of labeling. Although the public often may not read or appreciate precautions on labels, the effectiveness of the latter are increased significantly if a pharmacist takes time to explain them. The pharmacist also has a unique role to play in detecting product or labeling defects and an obligation to call to the attention of appropriate manufacturers or regulatory agencies potential labeling or product defects.

There has been a tendency in the past for the development of too many small and ineffectual poison centers, the activities of which could be carried out more effectively and efficiently if they were amalgamated with others in the same area. Local pharmacy associations should support the trend toward centralization and regionalization of poison information and treatment facilities.

Finally, pharmacists can assist greatly in the educational efforts of a community by distributing literature and by providing space for displays related to poisoning prevention.

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CHAPTER 104

Drug Interactions

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Although some drug-related problems develop unexpectedly and cannot be predicted, many are related to known properties and actions of the drugs and reasonably can be anticipated. However, as drug therapy becomes more complex and because many patients are being treated with two or more drugs, the ability to predict the magnitude of a specific action of any given drug diminishes. These circumstances point to a need not only for maintenance of complete and current medication records for patients but also for closer monitoring and supervision of drug therapy so that problems can be prevented or detected at an early stage in their development. The pharmacist is in a unique position to meet these needs, and opportunities exist for greater involvement in, and contribution to, provision of drug therapy that is both efficacious and safe.

Many drug-related problems are caused by drug interactions. As a basis for this discussion a drug interaction may be considered a situation in which the effects of one drug are altered by prior or concurrent administration of another drug (ie, drug-drug interactions). The concept of drug interaction often is extended to include situations in which

1. Food or certain dietary items influence the activity of a drug (ie, drug-food interactions) or
2. Herbs or other natural products influence the activity of a drug or
3. Environmental chemicals or smoking influences the activity of a drug or
4. A drug causes alterations of laboratory test results (ie, drug-laboratory test interactions) or
5. A drug causes undesired effects in patients with certain disease states (ie, drug-disease interactions).

Considerable attention has been focused on the subject of drug interaction, and information pertaining to these occurrences has been widely publicized. Several comprehensive references, such as *Drug Interaction Facts* (Tatro DS, ed. St Louis: Facts and Comparisons, 2005) and *Drug Interactions Analysis and Management* (Hansten PD, Horn JR, eds. St Louis: Facts and Comparisons, 2005) deal exclusively with this subject, while other references give extensive attention to it. Computerized databases that provide drug interaction information are also widely used.

Problems that may result from drug interactions also have been publicized to the public. In addition to cautions given to patients by physicians and pharmacists, articles on the subject have appeared in many publications widely read by the public. Many have observed that drug interactions are an important cause of concern for consumers as reflected, in part, by the number of inquiries regarding these drug-related problems initiated to Internet and other drug information sources.

One of the most important consequences of a drug interaction is an excessive response to one or more of the agents being used. For example, a significantly enhanced effect of agents like digoxin and warfarin can result in serious adverse events. Not as well recognized, but also very important, are those interactions in which drug activity is decreased, resulting in a loss of efficacy. These interactions are especially difficult to detect, since they may be mistaken for therapeutic failure or progression of the disease.

Some drug interactions continue to occur even though they are well documented and recognized. Digoxin and a diuretic often are given concurrently, and rationally so, in treating patients with congestive heart failure. It is well known that most diuretics can cause potassium depletion that if uncorrected could become excessive and lead to an increased action of digoxin and adverse events. Yet problems continue to occur as a result of this interaction.

Even with the extensive publicity that drug interactions have received, it is still often difficult to determine their incidence or clinical significance. However, numerous studies have demonstrated that many patients receive multiple drug therapy with agents of recognized potential for interaction. As the number of drugs in a patient's therapeutic regimen increases, the greater is the risk of occurrence of a drug interaction. Although there are only limited data regarding many of the potential drug interactions that have been suggested, considerable progress has been made in defining the level of risk attending the use of a number of combinations of drugs. Indeed, the risk of serious interactions involving the use of terfenadine, astemizole, cisapride, and mibefradil was sufficiently important for these drugs to be withdrawn from the market in the US.

FACTORS CONTRIBUTING TO THE OCCURRENCE OF DRUG INTERACTIONS

A number of factors contribute to the occurrence of drug interactions.

MULTIPLE PHARMACOLOGICAL EFFECTS—Most drugs used in current therapy have the capacity to influence many physiological systems. Therefore, two drugs concomitantly administered will often affect some of the same systems. When considering the potential for interactions between drugs there often is a tendency only to be concerned with the primary effects of the drugs involved and to overlook the secondary activities they possess. Combined therapy with a phenothiazine antipsychotic (eg, chlorpromazine), a tricyclic antidepressant (eg, amitriptyline), and an antiparkinson agent (eg, tri-

hexyphenidyl) is employed in some patients. Each of these agents has a considerably different primary effect; however, all three possess anticholinergic activity. Even though the anticholinergic effect of any one of the drugs may be slight, the additive effects of the three agents may be significant.

MULTIPLE PRESCRIBERS—It is necessary for some individuals to see more than one physician, and it is very common for a patient to be seeing one or more specialists in addition to a family physician. Some individuals also are seeing other health professionals (eg, dentists, podiatrists) who may prescribe medication. It frequently is difficult for one prescriber to be aware of all the medications that have been prescribed by others for a particular patient, and difficulties could arise from such situations. For example, one physician may prescribe a medication capable of causing tiredness/sleepiness (eg, certain antihistamines, opioid analgesics) for a patient for whom another physician has prescribed an antianxiety agent, with the possible consequence of an excessive depressant effect.

Even though the patient is seeing different physicians, he or she often will have the prescriptions dispensed by the same pharmacy. Therefore, the pharmacist has an important role in the detection and prevention of drug-related problems.

USE OF NONPRESCRIPTION PRODUCTS—Many reports of drug interactions have involved the concurrent use of a prescription drug with a nonprescription drug (eg, aspirin, antacids, decongestants) or herbal (St John's wort) or other natural product. When a physician questions patients about medications that they are taking, the patients often will neglect to mention the nonprescription products that they have purchased. Many patients have been taking preparations such as antacids, analgesics, laxatives, dietary supplements, and herbal products for such long periods and in such a routine manner that they do not consider them to be drugs or to be important with respect to the effectiveness and safety of medications. This information often may be missed in questioning a patient, and some physicians and pharmacists prefer to use a list of symptoms that might ordinarily be treated with nonprescription products in trying to obtain this information from the patient.

Interactions also may result from the concurrent use of two or more products available without a prescription. In some situations two nonprescription products promoted for different purposes contain the same active ingredient(s), increasing the risk of an excessive response to these agents. Diphenhydramine is included in many products for its antihistaminic action but also is included for its sedative effect in many nonprescription sleep-aid formulations. Patients often are unaware that products they purchase for different conditions may contain the same active ingredients and that they, therefore, are at increased risk of problems with the use of products they might assume to be safe because they do not require a prescription.

Although many individuals will have their prescriptions dispensed in their local pharmacy, they often purchase nonprescription drugs elsewhere, thus making identification of potential problems extremely difficult for the pharmacist as well as the physician. For this reason, patients should be encouraged to obtain both their prescription and nonprescription medications at a pharmacy. Such advice is justified, however, only when the pharmacist personally supervises the sale of nonprescription medications with which problems may develop.

The precautions observed with respect to potential interactions involving products that are typically designated as nonprescription drugs also apply to the use of herbal products, dietary supplements, and other related products that are available without a prescription. Although much is still to be learned about the properties of these products, many appear to have a potential to interact with prescription medications, and patients should be asked whether they are using such products.

PATIENT NONCOMPLIANCE—For a variety of reasons many patients do not take medication in the manner intended by the prescriber. Some have not received adequate instruction from the prescriber and pharmacist as to how and when to take their medication. In other situations, particularly involving patients who are taking several medications, confusion about the instructions may develop even though the patient may have understood them initially. It is understandable that older patients who may be taking five or six medications several times a day at different times can become confused or forget to take their medication, although these occurrences are by no means unique to the geriatric population.

Although the situations involving noncompliance usually would result in a patient not taking enough medication, some circumstances could lead to excessive use of certain medications, thereby increasing the possibility of drug interaction. For example, some patients if they realize they have forgotten a dose of medication, double the next dose to make up for it. Some other patients may act on an assumption that if the one tablet-dose that has been prescribed provides partial, but not complete relief of symptoms, a two-tablet dose will be even more effective.

DRUG ABUSE—The tendencies of some individuals to abuse or deliberately misuse drugs also may lead to an increased incidence of drug interactions. The antianxiety agents, opioid analgesics, and amphetamines are among the agents most often abused, and the inappropriate use of these drugs can result in a number of problems, including an increased potential for drug interaction.

Many interactions that occur are undetected or unreported. Koch-Weser (*Drug Inform J* 1972; 6: 42) observed that detection of drug interactions by clinicians is inefficient and cited six reasons for existence of this situation. Although initially noted in 1972, many of these observations are just as valid today.

1. In most cases the clinical situation is too complex to allow recognition of an unexpected event in a patient's course as related to his or her drug therapy.
2. With few exceptions, the intensity of action of drugs in the therapeutic setting cannot be quantitated accurately.

One reason for the many reports of interactions involving anticoagulants, antidiabetic agents, and antihypertensive agents is that there are specific parameters such as prothrombin time, blood glucose concentrations, and blood pressure that can be measured and provide a quantitative indication of drug activity. Therefore, any change in these values that may be caused by introducing another drug into therapy can be measured with relative ease. In contrast, when one considers drugs like the antipsychotic agents and analgesics with which it is far more difficult to measure degree of activity, it becomes increasingly difficult to observe and measure the effect of other drugs on their activity.

3. Even when a deficient, excessive, or abnormal response to one or both drugs is recognized clearly during concomitant administration, it is attributed usually to factors other than drug interaction.

When an unexpected response to a drug develops, it often is attributed to something other than a drug interaction, such as patient idiosyncrasy in the case of an excessive response, or tolerance in the case of a deficient response.

4. The index of suspicion of most clinicians concerning drug interactions is quite low, and many practicing physicians are hardly aware of the phenomenon.
5. Practicing physicians tend to doubt their observations concerning drug interactions unless the same interaction has been reported previously.

Although physicians are now well aware of the occurrence of drug interactions, there are situations in which a drug interaction may be occurring but there are other factors that also could contribute to the altered response noted. Therefore, physicians often accept a reasonable explanation, albeit incomplete, based on information with which they are familiar, rather than suspect a possibility that has not been reported previously. Although many interactions that have been reported via case reports have not been confirmed by other observations or additional study, many single-case reports have served as the

stimulus for additional study that has resulted in warnings about potentially dangerous interactions.

6. Physicians frequently fail to report drug interactions even when they have unequivocally recognized them.

Several factors, no doubt, contribute to this situation. The time it would take to write up a case report to submit to a journal is a deterrent to many physicians and pharmacists. Also, since drug interactions often represent an undesirable experience for the patient, health professionals often are reluctant to expose themselves to possible criticism, or even liability, regarding the therapy. However, it is important that health professionals communicate information that will be useful to others or will help others to avoid the same problems.

USING DRUG-INTERACTION INFORMATION

Although there has been considerable progress in identifying drug interactions, a careful analysis of the literature reveals that some of the information is conflicting, incomplete, and misleading. Too frequently, the suggested clinical importance of an alleged drug interaction is greatly overstated and publicized.

The use of some of this information unfortunately has led, in some situations, to an undue degree of alarm characterized by some observers as *drug-interaction hysteria* or a *drug-interaction anxiety syndrome*. Caution is needed, therefore, in evaluating and using the information available, because by overreacting to a possible problem, a more difficult situation may result than might have occurred if nothing were done. In some situations patients have been deprived unnecessarily of therapy from which they could benefit as a result of concern about a potential interaction with other medication they are taking. Conversely, some health-care practitioners have found so many of the reports and commentaries regarding drug interactions to be lacking in clinical relevance that their skepticism has precluded adequate attention to those interactions that are clinically important. Recognition of the importance of exercising the appropriate clinical perspective is essential if optimal therapy is to be achieved.

In using the literature on drug interactions and deciding what action is appropriate, a number of factors should be kept in mind.

INTERACTING DRUGS USUALLY CAN BE USED TOGETHER—In most cases, two drugs that are known to interact can be administered concurrently so long as adequate precautions are taken (eg, closer monitoring of therapy, dosage adjustments to compensate for the altered response). Although there are some situations in which the use of one drug usually is contraindicated while another is being given, such combinations are not likely to be employed frequently, and there may even be exceptions to the contraindication under certain circumstances. In those situations, though, where another agent with similar therapeutic properties and a lesser risk of interacting could be used, such a course of action would be preferable.

Serious reactions have been reported to occur following the concurrent use of a monoamine oxidase inhibitor (MAOI) (eg, tranylcypromine) with a tricyclic antidepressant (eg, amitriptyline), and the literature for most of these products warns that use of such combinations is contraindicated. However, it has been indicated by some that such reactions do not occur commonly and that these combinations, when used under close supervision, may be of benefit in some patients when conventional drug therapy has failed. The fact that these combinations may be used beneficially in some patients does not excuse the pharmacist from responsibility in checking the therapy with the physician. However, the pharmacist should be aware that certain circumstances may justify the concomitant use of even *contraindicated* drugs.

BENEFICIAL INTERACTIONS—It should be recognized that sometimes a second drug is prescribed intentionally to modify the effects of another. Such an approach might be used in an effort to enhance the effectiveness or to reduce the adverse effects of the primary agent. In these situations the efficacy and/or safety of a drug is increased, indicating that interactions are not always harmful as frequently thought, but also can be beneficial.

The ability of probenecid to increase the serum concentrations and prolong the activity of penicillin derivatives has been known for many years, and this interaction has been used to therapeutic advantage in certain infections. Probenecid also is used to reduce the risk of toxicity to certain agents such as cidofovir. By inhibiting the renal tubular secretion of cidofovir, probenecid reduces its renal clearance as well as the risk of nephrotoxicity. For this reason orally administered probenecid must accompany each IV infusion of cidofovir.

Another example of a situation in which one drug is given to minimize the undesirable effects of another is seen with the use of an antiparkinson drug with an antipsychotic agent in an effort to reduce the extrapyramidal effects of the latter.

By inhibiting the metabolism of levodopa in the peripheral tissues, carbidopa and entacapone have been used to both increase the effectiveness and reduce the occurrence of adverse events of levodopa.

NATURE OF REPORTS—Reports and reviews of interactions sometimes attach importance to isolated observations of problems in one patient or a limited number of patients. On several occasions a suspected interaction that was observed in a single patient has been reported in a number of reviews, tables, and computer databases without qualification as to the nature of the report or the possible significance of the interaction. The fact that such an interaction now is included in a number of references can result in an impression that the problem is well documented and clinically significant.

DEPTH OF INFORMATION—Many of the charts, tables, and computer databases of drug interactions do not provide detailed information about specific situations. The mere mention of an increased or decreased effect of one drug in the presence of another is not enough to form a judgment as to the clinical importance and potential severity of the situation. Because of this, most references of this type should be used only to screen initially for possible interactions, and more comprehensive reference sources should be consulted for further information.

CURRENT LITERATURE—It is important to review the current literature constantly, since new information may change the significance of earlier reports. The existence of conflicting reports regarding some interactions also will become evident as the literature is carefully searched. Although there is no assurance that more-recent information is more accurate or pertinent, the date of publication of a particular reference should be noted, and, when appropriate, more current references consulted. The importance of having access to the current literature is reflected in the decisions of the publishers of the most widely used comprehensive drug-interaction references to issue updates at frequent intervals (eg, four times a year).

It is also important to be aware of warnings about medications that are issued by the FDA and pharmaceutical manufacturers as well as pertinent revisions in product labeling. Several warnings regarding drug interactions involving terfenadine and mibefradil preceded the withdrawal of these drugs from the market.

RECOMMENDATIONS AND THERAPEUTIC ALTERNATIVES—There is not enough information available on many reported interactions to permit the development of specific guidelines to govern such combination therapy. When

such guidelines are presented they can be extremely helpful, and there is an increasing number of such statements in the package inserts for various products. Where possible, the pharmacist should not only identify a potential problem but also be prepared to make a recommendation to the physician and/or patient as to how problems best can be avoided or minimized.

For example, it is known that aspirin may enhance the anticoagulant activity of warfarin. Although many patients taking the two drugs concurrently will not experience a problem, acetaminophen usually would be preferred to aspirin for use as an analgesic in patients on anticoagulant therapy because it is not likely to alter the activity of agents such as warfarin. However, before making a recommendation that a patient on anticoagulant therapy use acetaminophen instead of aspirin, there should be an awareness of the purpose for which the aspirin is to be used. Although acetaminophen is comparable to aspirin with regard to analgesic and antipyretic activity, it possesses little anti-inflammatory activity and, unlike aspirin, has not been shown to reduce the risk of problems such as transient ischemic attacks and myocardial infarction. Therefore, it should not be used as an alternative to aspirin in the conditions in which one of these actions is needed.

The use of tetracycline by a patient also taking antacids provides an example of a situation in which a specific recommendation can be made to avoid a problem. If taken at the same time, the antacid can decrease the absorption and effectiveness of the tetracycline. However, if the two agents are given at least 1 hr apart, the problem should be avoided.

VIEWING INTERACTIONS IN PERSPECTIVE—Even after the previously discussed factors have been considered and the data have been analyzed critically, the possibility of interactions developing must be viewed in perspective. Although an altered response appears likely, it might not be clinically significant in many patients. In these situations a patient should not be deprived of needed therapy because of the possibility of an interaction, but such therapy should be monitored closely.

Most health-care practitioners do not have rapid access to a large number of primary literature sources. Therefore, the use of an authoritative and comprehensive reference source such as *Drug Interaction Facts* or *Drug Interactions Analysis and Management* is recommended, and these references can be very helpful in identifying potential problems and in making judgments as to their clinical importance and therapeutic alternatives. However, even though certain interactions are well documented, it often is difficult, if not impossible, to predict the severity of an interaction, if indeed it does develop. The many variables that may influence the activity of a drug and its ability to interact with other agents contribute to the existing uncertainty. Many of these variables pertain to the drugs being used and include dosage, route of administration, time of administration, sequence of administration, and duration of therapy, whereas other variables, which are considered in the following discussion, pertain to the patient.

PATIENT VARIABLES

There are many factors that influence the response to a drug in man. A number of reports have indicated how these factors may predispose a patient to the development of adverse events to a drug, and it can be anticipated that many of these considerations also apply to the development of drug interactions.

AGE—When considering the risk of drug-related problems, age is an important factor. Studies indicate that there is an increased incidence of adverse drug events in both young and geriatric patients, and it is reasonable to expect that the occurrence of drug interactions also is highest in these patient groups.

Drug-related problems in young patients are encountered most frequently in newborn infants. Newborn infants do not have fully developed enzyme systems that are involved in the metabolism of certain drugs, and they also have immature renal function.

Several factors point to an increased risk of interactions in the elderly. Most elderly patients have at least one chronic illness (eg, hypertension, diabetes), and this is reflected in the prescribing of a larger number of medications for this patient group. The types of diseases more frequently experienced by elderly patients (eg, renal disorders) may contribute to an altered drug response, and there appears to be an increased sensitivity to the action of certain drugs with advancing age. In addition, there may be aging-related changes in the absorption, distribution, metabolism, and excretion of certain drugs, which increase the possibility of adverse events and drug interactions. Accordingly, drug therapy in elderly patients must be monitored especially closely.

GENETIC FACTORS—These may be responsible for the development of an unexpected drug response in a particular patient. Isoniazid is metabolized by an acetylation process, the rate of which appears to be under genetic control. Some individuals metabolize isoniazid rapidly, whereas others metabolize it slowly, thus necessitating careful dosage adjustment, as the dose that provides satisfactory concentrations in rapid acetylators may cause toxicity in slow acetylators. For example, isoniazid causes peripheral neuritis in a number of patients, and this effect has been noted most frequently in slow acetylators.

It has been observed that isoniazid may inhibit the metabolism of phenytoin, possibly resulting in the development of adverse events (nystagmus, ataxia, lethargy) of the latter. However, studies have indicated that those patients who developed phenytoin toxicity when also receiving isoniazid were slow acetylators of isoniazid. It is likely that this interaction will be of significance only in patients who metabolize isoniazid at a very slow rate.

DISEASE STATES—A number of disease states, other than the one for which a particular drug is being used, may influence patient response to a drug. Impaired renal and hepatic function are the most important conditions that may alter drug activity. However, other disorders also may bring about a change in the activity of a drug. Since many drugs are bound extensively to plasma proteins and only the unbound fraction of the drug is active, a decreased concentration or amount of protein conceivably could change the availability of drugs and, thus, their activity. This possibility must be recognized in patients with conditions that may be associated with hypoalbuminemia.

RENAL FUNCTION—Renal function is one of the most important determinants of drug activity. The patient's renal status should be known, particularly when drugs that are excreted primarily in an active form by the kidney are to be used for long periods of time. If there is renal impairment and the usual dose of a drug that is excreted by the kidney is given, there can be an increased and prolonged effect, since it is not being excreted at the normal rate. As additional doses are given, serum concentrations will increase, possibly resulting in toxicity. Therefore, a need exists for careful dosage adjustment and particular caution when other potentially interacting drugs are added to the therapeutic regimen.

The alteration of renal excretion as a mechanism by which a number of drug interactions develop is considered later, and the status of the patient's renal function is an important determinant of the rate of excretion of the drugs involved and the occurrence of interactions.

HEPATIC FUNCTION—Many drugs are metabolized in the liver by a number of mechanisms. Therefore, when there is

hepatic damage, these drugs may be metabolized at a slower rate and exhibit a prolonged effect. Although each situation should be evaluated to determine whether a reduction in dosage is necessary, it should be recognized that some drugs will be metabolized at the normal rate even though hepatic function is impaired. A number of studies of drug metabolism in patients with liver disease have been conducted. However, the results vary considerably, and it is difficult to predict with certainty whether the rate of metabolism will be altered in a given patient.

Many therapeutic agents are metabolized by hepatic enzymes. If other drugs alter the amount and/or activity of these enzymes, a modified response to the drugs that depend on these enzymes for their metabolism might occur. For example, many agents (eg, barbiturates, rifampin) are known to stimulate the activity of hepatic enzymes (enzyme induction). The result would be a more rapid metabolism and excretion of concurrently administered agents that are metabolized by these enzymes. This mechanism of drug interaction is discussed in greater detail later as are the situations in which the action of hepatic enzymes is inhibited.

ALCOHOL CONSUMPTION—Several studies have shown that chronic use of alcoholic beverages may increase the rate of metabolism of drugs such as warfarin and phenytoin, probably by increasing the activity of hepatic enzymes. However, in contrast, acute use of alcohol by nonalcoholic individuals may cause an inhibition of hepatic enzymes.

Concurrent use of alcoholic beverages with sedatives and other depressant drugs could result in an excessive depressant response. The fact that the use of such combinations is commonplace cannot be cause for failing to exercise the caution that must be observed if problems are to be averted.

SMOKING—A number of investigations have suggested that smoking increases the activity of drug-metabolizing enzymes in the liver, with the result that certain therapeutic agents (eg, diazepam, propoxyphene, theophylline, olanzapine) are metabolized more rapidly, and their effect is decreased.

DIET—Food often may affect the rate and extent of absorption of drugs from the gastrointestinal (GI) tract. For example, many antibiotics should be given at least 1 hr before or 2 hr after meals to achieve optimal absorption.

The type of food may be important with regard to the absorption of concurrently administered drugs. For example, dietary items such as milk and other dairy products that contain calcium may decrease the absorption of tetracycline and fluoroquinolone derivatives by forming a complex with them in the GI tract that is absorbed poorly.

Some dietary items, such as certain cheeses and alcoholic beverages, have a relatively high content of the pressor amine tyramine. Tyramine is metabolized by MAO, and normally these enzymes in the intestinal wall and liver protect against the pressor actions of amines in foods. However, if these enzymes were to be inhibited by an MAOI, large quantities of unmetabolized tyramine could accumulate, which could lead to the development of a severe hypertensive reaction.

Certain dietary items contain an appreciable amount of vitamin K. A change in dietary habits that would significantly alter the intake of these foods could cause problems in patients on warfarin therapy.

Diet also may influence urinary pH values. One study has compared the excretion of amphetamine in two groups of patients maintained on different diets. One group was placed on a balanced protein diet that provided an acidic urine (average pH of 5.9), whereas the other group was put on a low-protein diet that provided an alkaline urine (average pH of 7.5). Each group was given a dose of amphetamine, and those with the acidic urine excreted 23 to 56% of unchanged amphetamine in the first 8 hr and 5 to 13% in the next 8 hr. In comparison, in those with an alkalinized urine, there was a 2 to 6% excretion in the first 8 hr, followed by a 0.5 to 3% excretion in the next 8 hr.

INDIVIDUAL VARIATION—Even after the preceding factors have been considered, wide variations in the response of patients to drugs will be seen that are often difficult to explain. Plasma concentrations of certain drugs may vary widely among individuals using the same dosage regimen over the same time period. When recognition is taken of the difficulty in predicting the response to many therapeutic agents when they are given alone, the challenge and limitations in endeavoring to anticipate the response with a multiple-drug regimen clearly become apparent.

MECHANISMS OF DRUG INTERACTION

An understanding of the mechanisms by which drug interactions develop will be valuable in anticipating such situations and dealing with problems that do develop. Although the circumstances surrounding the development of some drug interactions are complex and poorly understood, the mechanisms by which most interactions develop are well documented and relate to the basic processes by which a drug acts and is acted upon in the body.

These mechanisms often are categorized generally as being pharmacokinetic or pharmacodynamic types. *Pharmacokinetic interactions* are those in which one agent (designated by some as the *precipitant drug*) alters the absorption, distribution, metabolism, or excretion (ADME) of a second agent (the *object drug*), with a resultant change in the plasma concentration of the latter agent. Included among the *pharmacodynamic interactions* are those in which drugs having similar (or opposing) pharmacological effects are administered concurrently and situations in which the sensitivity or responsiveness of the tissues to one drug is altered by another. Pharmacodynamic interactions also have been viewed as situations in which there is a change in drug effect without a change in drug plasma concentration.

Although the pharmacokinetic interactions often present challenging clinical problems that have been publicized widely, the pharmacodynamic interactions are encountered more frequently. It also should be recognized that several mechanisms may be involved in the development of certain interactions.

Pharmacokinetic Interactions

ALTERATION OF GI ABSORPTION

Interactions that involve a change in the absorption of a drug from the GI tract may develop through different mechanisms and be of varying clinical importance. In some situations the absorption of the drug may be reduced, and its therapeutic activity compromised. In others, absorption may be delayed, but the same amount of drug is absorbed eventually. A delay in drug absorption can be undesirable when a rapid effect is needed to relieve acute symptoms, such as pain. The slower absorption rate also may prolong the effects of a drug and may present difficulty. For example, if the effects of a hypnotic agent are prolonged, the patient may experience excessive residual sedation or *hangover* in the morning. A slower rate of absorption may preclude achievement of effective plasma and tissue concentrations of drugs that are metabolized rapidly and excreted.

Conversely, a delay in drug absorption may not be clinically significant; this is usually the case when a drug is being used on a chronic basis and therapeutic concentrations in the body have already been achieved.

As a general guideline, it is the drugs that are not absorbed completely under *optimum* circumstances that are most susceptible to alterations of GI absorption.

ALTERATION OF PH

Since many drugs are weak acids or weak bases, the pH of the GI contents may influence the extent of absorption. It is recognized that the nonionized form of a drug (the more lipid-soluble form) will be absorbed more readily than the ionized form. Acidic drugs exist primarily in the nonionized form in the upper region of the GI tract (having a lower pH). If a drug such as an antacid is ingested, which will raise the pH of the GI contents, it is possible that the absorption of such acidic drugs can be delayed and/or inhibited partially.

Although changes in absorption might be predicted for many acidic and basic drugs on a theoretical basis, it would appear that clinically important interactions are likely to occur in only a few situations, and factors other than pH seem to be more important determinants of GI absorption.

KETOCONAZOLE–ANTACIDS—An acidic medium is required to achieve dissolution of ketoconazole following oral administration. Therefore, an antacid, a histamine H_2-receptor antagonist (eg, cimetidine, ranitidine), or a proton pump inhibitor (eg, lansoprazole, omeprazole) is likely to reduce the dissolution, absorption, and effectiveness of the antifungal agent. An antacid should be administered at least 2 hr after ketoconazole; the concurrent use of ketoconazole and a histamine H_2-receptor antagonist or proton pump inhibitor is best avoided, and alternative agents having a lesser potential for interaction should be considered.

BISACODYL–ANTACIDS—A change in the pH of the GI contents also may cause another type of problem. For example, oral dosage forms of the laxative bisacodyl are enteric-coated because the drug can be extremely irritating. It has been suggested that this agent should not be given orally within an hour of antacid therapy or ingestion of milk because an increase in the pH of the GI contents may cause disintegration of the enteric coating in the stomach, resulting in release of the drug in this area, which could cause irritation and vomiting.

Antacids also may alter the GI absorption of drugs through other mechanisms, and additional examples are considered in the following discussion.

Complexation and Adsorption

TETRACYCLINES–METALS—The interaction between tetracycline derivatives and certain metal ions is well known. Tetracycline can combine with metal ions such as calcium, magnesium, aluminum, iron, bismuth, and zinc in the GI tract to form complexes that are absorbed poorly. Thus, the simultaneous administration of certain dietary items (eg, milk, other products containing calcium) or drugs (eg, antacids, iron preparations, products containing calcium salts) with tetracycline could result in a significant decrease in the amount of antibiotic absorbed.

The absorption of doxycycline and minocycline is influenced to a lesser extent by simultaneous ingestion of food or milk. However, the concurrent administration of aluminum hydroxide gel will decrease absorption of these analogs, as is seen with other tetracyclines.

When two drugs are recognized as having a potential to interact there is often a tendency to believe that one of them should be discontinued. In the case of the antacid-tetracycline interaction, problems can be avoided by allowing an appropriate interval of time to separate administration of the two agents. This interval should be as long as possible, but a minimum period of 1 hr should elapse between administration of the drugs.

The interaction between doxycycline and iron salts calls attention to another factor that must be considered, as the results of one study suggest that the interaction cannot be avoided completely by allowing an interval of 3 hr (or even a longer period) to separate administration of the two drugs. It is noted that a significant amount of doxycycline is transported back to the GI tract via the enterohepatic circulation, and the unabsorbed iron still present in the GI tract prevents reabsorption of the antibiotic.

FLUOROQUINOLONES–METALS—Aluminum- and magnesium-containing antacids, as well as certain dietary items (eg, milk, yogurt), have been reported to reduce markedly the absorption and serum concentrations of fluoroquinolones, probably as a result of the metal ions complexing with the antiinfective agent. Even allowing a long interval to separate the administration of the two drugs may not be sufficient to avoid the interaction, and as long an interval as possible should separate the administration of the fluoroquinolone and metal-containing product. For example, in the product labeling for moxifloxacin, it is recommended that this antibacterial agent be taken at least 4 hours before or 8 hours after antacids containing magnesium or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc.

CHOLESTYRAMINE AND COLESTIPOL—Other interactions involving complexation might be anticipated when the drugs cholestyramine and colestipol are used. These resinous materials, which are not absorbed from the GI tract, bind with bile acids and prevent their reabsorption. In addition to binding with bile acids, cholestyramine and colestipol can bind with drugs that are present in the GI tract, and these agents may reduce the absorption of drugs such as thyroid hormone, warfarin, digoxin, and thiazide diuretics. To reduce the possibility of an interaction, the interval between the administration of cholestyramine or colestipol and another drug should be as long as possible.

The naturally occurring human bile acid, ursodiol, is used in the dissolution of gallstones composed primarily of cholesterol. Because of the affinity of cholestyramine and colestipol for bile acids, the administration of these agents should be separated by as long an interval as possible.

It also should be recognized that prolonged administration of cholestyramine and colestipol can decrease the absorption of fat-soluble vitamins such as vitamin K. This could lead to increased bleeding tendencies in some patients if the vitamin K intake is not increased. When cholestyramine or colestipol is administered to a patient on warfarin therapy, it is understandably difficult to predict the eventual response, since conceivably the absorption of both the anticoagulant and its antagonist, vitamin K, could be reduced.

A newer bile acid-binding agent, colesevelam, appears less likely than cholestyramine and colestipol to interact with other medications or fat-soluble vitamins. Accordingly, colesevelam would be preferred to the other agents in situations in which the potential exists for these interactions.

An interesting application of this interaction is seen with the use of leflunomide in the treatment of rheumatoid arthritis. Leflunomide can cause fetal harm if administered during pregnancy, and it has an active metabolite that can persist in the system for up to 2 years. If a woman of childbearing potential discontinues use of leflunomide, it is recommended that cholestyramine (8 g, three times a day, for 11 days) be used to accelerate the elimination of the drug and its active metabolite.

PENICILLAMINE–METALS—Aluminum and iron salts have been reported to reduce the absorption of penicillamine significantly, probably through chelation and/or adsorption mechanisms. An interval of at least 2 hr should separate the administration of an antacid or iron salt and penicillamine. Food also will decrease the absorption of penicillamine, and the drug should be administered apart from meals.

Alteration of Motility/Rate of Gastric Emptying

CATHARTICS—A cathartic, by increasing GI motility, may increase the rate at which another drug passes through the GI tract. This could result in a decreased absorption of certain drugs, particularly those that normally are absorbed slowly and require prolonged contact with the absorbing surface or those that are absorbed only at a particular site along the GI tract. Similar problems might be noted with enteric-coated and controlled-release formulations.

ANTICHOLINERGICS—Anticholinergics, by decreasing GI motility, also may influence drug absorption. The effect may be one of *decreased* absorption, since the reduced peristalsis may retard dissolution and the slowing of gastric emptying may delay absorption from the small intestine, or *increased* absorption if a drug is retained for a longer period of time in the area from which it is optimally absorbed.

METOCLOPRAMIDE—Because metoclopramide increases motility of the upper GI tract, it should be anticipated that it may influence the absorption of other drugs administered concurrently.

The Effect of Food

It is known that food can influence the absorption of a number of drugs. In some situations, absorption may be delayed but not reduced, whereas in other circumstances the total amount of drug absorbed may be reduced. The effect of food in influencing drug absorption sometimes is due to its action in slowing gastric emptying. However, food also may affect absorption by binding with drugs, decreasing the access of drugs to sites of absorption, altering the dissolution rate of drugs, or altering the pH of the GI contents. The drug-administration time schedules used in many hospitals and long-term care facilities may correspond closely to the times at which meals are served. It is important that a specific dosage schedule be established for those drugs that should be administered apart from meals or with food.

ANTI-INFECTIVE AGENTS–FOOD—The presence of food in the GI tract will reduce the absorption of many anti-infective agents. Although there are some exceptions (eg, penicillin V, amoxicillin, doxycycline, minocycline), it generally is recommended that the penicillin and tetracycline derivatives as well as certain other anti-infective agents be given at least 1 hr before meals or 2 hr after meals, to achieve optimum absorption.

Erythromycin stearate formulations should be administered at least 1 hr before meals or 2 hr after a meal, whereas formulations of erythromycin ethylsuccinate may be given without regard to meals.

The formulations of erythromycin base should be considered on an individual basis because the information for some products indicates they may be given without regard to meals, whereas for other products it is noted that optimum absorption is achieved when given apart from meals.

THEOPHYLLINE–FOOD—It generally has been felt that food does not alter the activity of theophylline significantly when the drug is administered in an immediate-release formulation (ie, those formulations that are not controlled-release).

However, considerable variation is seen among the controlled-release formulations of theophylline with respect to their potential to interact with food. If data are insufficient to assess the potential for a particular theophylline formulation to interact with food, the medication preferably should be administered apart from meals.

CAPTOPRIL–FOOD—The presence of food in the GI tract has been reported to reduce the absorption of captopril by 30 to 40%. Although more-recent investigations suggest that food is unlikely to alter significantly the effects of captopril, it is advisable to administer the drug 1 hr before meals. Food does not appear to alter the absorption of most of the other angiotensin-converting enzyme inhibitors (eg, enalapril, lisinopril).

ALENDRONATE AND RISEDRONATE–FOOD—Food and even orange juice, coffee, and mineral water may markedly reduce the bioavailability of alendronate and risedronate, and it is recommended that these drugs be administered soon after arising at least 1/2 hr before any food, beverage, or medication, with plain water only.

ACARBOSE AND MIGLITOL–FOOD—In some situations it is important that a medication be administered with food to obtain optimum benefit. Acarbose and miglitol are effective in the treatment of diabetes mellitus because they delay the digestion of ingested carbohydrates and reduce the elevation of blood glucose concentrations following meals. Maximum effectiveness is attained when doses are administered at the start (with the first bite) of each main meal.

Alteration of Metabolism in the GI Tract

The absorption of certain agents is influenced by the extent to which they are metabolized in the GI tract.

MAOIs–TYRAMINE—There have been reports of serious reactions (hypertensive crisis) occurring in people being treated with an MAOI (eg, isocarboxazid, phenelzine, tranylcypromine) following ingestion of certain foods with a high content of pressor substances, such as tyramine.

Tyramine is metabolized by MAO, and normally these enzymes in the intestinal wall and in the liver protect against the pressor actions of amines in foods. However, when these enzymes are inhibited, large quantities of unmetabolized tyramine can accumulate and act to release norepinephrine from adrenergic neurons where greater-than-usual stores of this catecholamine are concentrated as a result of MAO inhibition. Among the foods having the highest tyramine content are aged cheeses (eg, cheddar; in contrast, cottage and cream cheeses contain little or no tyramine and need not be restricted), certain alcoholic beverages (eg, Chianti wine), pickled fish (eg, herring), concentrated yeast extracts, and broad-bean pods (also known as fava beans or Italian green beans).

The pharmaceutical companies that market the MAOIs have developed lists of dietary items that patients taking one of these agents should avoid. This information should be provided to, and discussed with, each patient for whom an MAOI is prescribed.

GRAPEFRUIT JUICE—The consumption of grapefruit juice has been reported to increase the serum concentration and activity of a number of medications such as certain calcium channel blockers (eg, amlodipine, felodipine, nisoldipine), certain HMG-CoA reductase inhibitors (eg, lovastatin), and cyclosporine. The bioavailability of most of these agents is generally low, primarily as a result of extensive first-pass metabolism. It has been suggested that components of grapefruit juice reduce the activity of the cytochrome P-450 enzymes (primarily CYP3A4) in the gut wall that are involved in the metabolism of these agents. As a result, larger amounts of unmetabolized drug is absorbed, and serum concentrations are increased.

Alteration of GI Flora

Changes in the microbial flora of the GI tract caused by antibiotics may alter the production or metabolism of certain agents, with a resultant change in the amount of agent being absorbed and available to produce a clinical response.

ANTICOAGULANTS–ANTIBIOTICS—A number of anti-infective agents have been reported to enhance the effect of concurrently administered anticoagulants. It has been suggested that this effect develops, in part, as a result of interference by the anti-infective agent with production of vitamin K by microorganisms in the GI tract. Broad-spectrum antibiotics such as the tetracyclines are most likely to cause problems of this type, although similar effects also may be seen with other antibiotics. The clinical importance of this mechanism has been questioned, and if it is a factor, it is likely that problems will occur only in patients who have a low dietary intake of vitamin K.

It is also probable that other mechanisms may be involved in some of these interactions. For example, the increased anticoagulant effect noted when sulfonamides and anticoagulants are given concurrently may be due, in part, to displacement of the anticoagulant from protein-binding sites and/or inhibition of its hepatic metabolism.

DIGOXIN–ANTIBIOTICS—It is estimated that approximately 10% of patients being treated with digoxin convert a significant portion of the parent compound to inactive reduction metabolites in the GI tract. The bacterial flora of the intestine contributes to this metabolic process. Elevated serum digoxin concentrations have been observed in patients receiving erythromycin or tetracycline concurrently, and it is suggested that

these antibiotics, by reducing the bacterial flora, decrease the extent to which digoxin is metabolized in the GI tract, resulting in the higher serum concentrations of the cardiac glycoside.

ORAL CONTRACEPTIVES–ANTIBIOTICS—Several antibiotics (eg, ampicillin) have been suggested to decrease the effectiveness of oral contraceptives. The estrogen component of the contraceptive formulation is conjugated to a large extent in the liver and excreted in the bile. Bacteria in the intestine hydrolyze the conjugated form of the estrogen, permitting the free drug to be reabsorbed, and contribute to the serum concentration of the estrogen. Antibiotics, by reducing the bacterial flora, may interrupt the enterohepatic circulation, with a resultant reduction in serum estrogen concentrations.

Although questions have been raised regarding the significance of this interaction, it would be desirable for patients to use supplementary contraceptive measures in addition to the oral contraceptive, during cycles in which antibiotics are used.

Malabsorption States

Certain drugs, such as laxatives, colchicine, cholestyramine, and colestipol, have been reported to cause malabsorption problems that result in decreased absorption of vitamins and nutrients from the GI tract. It should be recognized that these agents may alter absorption of other drugs that are administered simultaneously, and several examples with cholestyramine already have been considered.

ALTERATION OF DISTRIBUTION

Displacement from Protein-Binding Sites

An interaction of this type may occur when two drugs that are capable of binding to proteins are administered concurrently. Although they may bind at different sites on the protein, the binding characteristics of one of the drugs may be altered (noncompetitive displacement). Probably more significant are situations in which two drugs are capable of binding to the same sites on the protein (competitive displacement). Since there are only a limited number of protein-binding sites, competition will exist, and the drug with the greater affinity for the binding sites will displace the other from plasma or tissue proteins. It is recognized that the protein-bound fraction of a drug in the body is not pharmacologically active. However, an equilibrium exists between bound and unbound fractions, and as the unbound or *free* form of the drug is metabolized and excreted, bound drug is released gradually to maintain the equilibrium and pharmacological response.

The binding of acidic drugs to serum albumin represents the type of drug-protein binding that has been studied most extensively. The binding to albumin is readily reversible, and the albumin-drug complex essentially serves as a reservoir that releases more drug as the free drug is metabolized and/or excreted. The importance of the binding of basic drugs (eg, propranolol, lidocaine) to α_1-acid glycoprotein (AAG) also has been recognized. Even small increases in the reactant protein concentration, such as might be associated with infection and inflammation, can result in significant changes in the concentration of free drug.

The risk of an interaction occurring is greatest with drugs that are highly protein-bound (more than 90%) and also have a small apparent volume of distribution. Since only a small fraction of the drug ordinarily would be available in the *free* form, the displacement of even a small percentage of the amount that is bound to proteins could produce a considerable increase in activity.

The risk of interactions resulting from protein displacement appears to be greatest during the first several days of concurrent therapy. It has been suggested that drugs having the greatest capability of displacing a highly bound drug such as warfarin can increase the anticoagulant response within 24 hr and exhibit maximum potentiation in 3 to 5 days. After this period the effect levels off, since the drug, as a result of greater amounts being available in the unbound form, also is being metabolized more rapidly and excreted. Therefore, the anticoagulant usually has a shorter half-life when a displacing agent is given concurrently.

METHOTREXATE—Methotrexate is highly bound to plasma proteins, and it has been suggested that agents such as the salicylates may be capable of displacing it from binding sites. Studies also indicate that salicylates may increase the action of methotrexate by inhibiting its renal excretion. Although data pertaining to this interaction are limited, the potential for toxicity with methotrexate dictates extreme caution in any situation in which it is used.

PHENYTOIN–VALPROIC ACID—Valproic acid has been reported to displace phenytoin from plasma protein–binding sites, and some studies suggest it also may inhibit the metabolism of phenytoin. In some patients the result may be significantly increased free phenytoin concentrations and the occurrence of adverse events, even when the total phenytoin serum concentrations are within what would ordinarily be considered the desired therapeutic range. The evaluation of the potential for these agents to interact is made even more complex by reports that phenytoin may decrease valproic acid plasma concentrations. Combination therapy with these agents should be monitored closely, with dosage adjustments made as needed, in an effort to achieve effective control of the disorders for which they have been prescribed with as low a risk of adverse events as possible.

REDUCED ALBUMIN CONCENTRATIONS—Because many drugs are bound extensively to plasma proteins, a decreased concentration or amount of protein could change the availability of drugs and thus their activity. Although the type and incidence of clinical problems have not been determined conclusively, several reports suggest that the incidence of adverse events with certain drugs may be higher in patients with conditions associated with hypoalbuminemia (eg, renal, hepatic, and GI diseases).

A relationship between prednisone dosage, frequency of adverse events, and serum albumin concentrations has been shown in one study. When the serum albumin concentration is less than 2.5 g/100 mL, the frequency of prednisone adverse events is almost doubled, and this is attributed to an increased concentration of prednisolone, an active metabolite of prednisone.

In another study it was noted that the incidence of adverse events to phenytoin was greater in patients with low serum albumin concentrations. It is suggested that the higher incidence of adverse events in the hypoalbuminemic patients is probably due to increased circulating concentrations of unbound phenytoin.

STIMULATION OF METABOLISM

Drug metabolism occurs primarily in the liver and most commonly involves oxidation, reduction, hydrolysis, and conjugation (eg, with glucuronic acid) reactions. Quantitatively, the most important hepatic enzymes are the cytochrome P-450 enzymes, which have been divided into families and subfamilies (eg, CYP3A4) on the basis of the similarity of their amino acid sequences. These enzymes are responsible for the oxidation—often, hydroxylation—of a large number of drugs (Table 104-1). Several comprehensive reviews of the clinically significant cytochrome P-450 drug interactions have been developed (Michalets EL. *Pharmacotherapy* 1998; 18:84; Flockhart DA. www.drug-interactions.com).

Many drug interactions have resulted from the ability of one drug to stimulate the metabolism of another, most often by increasing the activity of hepatic enzymes that are involved in the metabolism of numerous therapeutic agents. The increased activity probably is due to enhanced enzyme synthesis, resulting in increased amounts of drug-metabolizing enzymes, an effect fre-

Table 104-1. Examples of Substrates, Inhibitors, and Inducers of Certain Cytochrome P450 Enzymes

CYP ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	caffeine clozapine olanzapine theophylline	cimetidine ciprofloxacin	cigarette smoke
CYP2C9	celecoxib ibuprofen losartan phenytoin warfarin	fluconazole fluoxetine	rifampin
CYP2C19	diazepam	cimetidine fluoxetine omeprazole	rifampin
CYP2D6	amitriptyline codeine imipramine metoprolol mexiletine propafenone propranolol risperidone tramadol	cimetidine fluoxetine paroxetine quinidine	
CYP3A4	atorvastatin carbamazepine cyclosporine dexamethasone diltiazem felodipine HIV protease inhibitors lovastatin midazolam nifedipine quinidine sildenafil simvastatin tacrolimus tadalafil triazolam vardenafil	amiodarone clarithromycin erythromycin fluconazole grapefruit juice HIV protease inhibitors (eg, indinavir, ritonavir) itraconazole ketoconazole	carbamazepine efavirenz phenobarbital phenytoin rifampin St John's wort

quently referred to as *enzyme induction*. These situations have been documented well, with barbiturates, phenytoin, carbamazepine, and rifampin being among the agents best recognized as causing enzyme induction. The ability of the herbal product St John's wort to cause enzyme induction is also well documented.

In most situations, drugs are converted to less active, water-soluble metabolites, and enzyme induction usually will result in an increased metabolism and excretion and a reduced pharmacological action of the agent being metabolized by hepatic enzymes. Less frequently, a drug may be converted to a metabolite that is more active than the parent compound, and there may be an enhanced response. However, the initially increased effect may subsequently diminish, since the drug will be excreted more rapidly and have a shorter duration of action.

The stimulation of hepatic enzyme activity is not only a factor in the development of drug interactions, but also may be responsible for a drug (eg, carbamazepine) stimulating its own metabolism. With continued use, the half-life of the drug will decrease, possibly resulting in a need to increase the dosage.

WARFARIN–PHENOBARBITAL—By causing enzyme induction, phenobarbital can increase the rate of metabolism of warfarin. The result of this interaction is a decreased response to the anticoagulant since it is being more rapidly metabolized and excreted, possibly leading to an increased risk of thrombus formation if the interaction is not recognized. To compensate for this loss of effect, the dose of warfarin would have to be increased until the desired activity was obtained. If the dose of warfarin has been increased to compensate for loss of activity, it will have to be reduced when phenobarbital is discontinued. Otherwise, the readjusted higher dosage that was necessary when phenobarbital was given concurrently may be excessive when it is withdrawn and possibly result in hemorrhaging.

It is probable that all barbiturates have the ability to cause enzyme induction, although phenobarbital may be a more potent inducing agent than analogs having a shorter duration of action. Several studies indicate that the effect of barbiturates in decreasing anticoagulant activity is evident within 2 to 5 days, and it is suggested that the administration of a barbiturate for a week or longer is likely to produce this effect in most patients. There have been varying reports as to how rapidly enzyme activity returns to pretreatment levels when the barbiturate is discontinued. However, it is probable that in most situations normal enzyme activity will be restored in 2 to 3 weeks.

Although close monitoring of combined barbiturate-anticoagulant therapy usually will prevent problems from developing, it would seem unwise to expose the patient unnecessarily to the risk of an interaction when therapeutic alternatives are available. The benzodiazepines (eg, diazepam, temazepam) are not likely to interact with warfarin and one of these agents might be useful as an alternative to a barbiturate. These alternatives apply to the use of a barbiturate as a sedative-hypnotic. Although some benzodiazepines have been used in certain types of seizure disorders, they would not be adequate alternatives to phenobarbital when the latter is used in the treatment of these conditions.

ORAL CONTRACEPTIVES—Phenobarbital, rifampin, and other drugs are known to increase the metabolism of steroid hormones, including estrogens and progestins that are used in oral contraceptive formulations. The high rate of effectiveness of oral contraceptives may suggest that other agents are not likely to reduce their effect significantly. However, there is concern that agents capable of causing enzyme induction indeed may reduce the effectiveness of oral contraceptives, possibly resulting in an unplanned pregnancy. This possibility takes on increased significance in view of the fact that the dosages of the hormones included in these products have been decreased in the interest of minimizing the risk of adverse events. It is possible that the lower dosages of the hormones used in certain products could be approaching the minimum effective concentration and that addition of another agent that can reduce their action is sufficient to compromise their effectiveness. Although the potential for such an interaction is low, the importance of the possible consequences warrants extra caution, and additional contraceptive measures should be used during the period of time that the enzyme- inducing drug is used.

HIV PROTEASE INHIBITORS—All of the HIV protease inhibitors (eg, amprenavir, atazanavir, lopinavir, nelfinavir) are extensively metabolized via CYP3A/3A4 pathways, and the concurrent use of an enzyme inducer could reduce their action and compromise the effectiveness of the antiretroviral regimen for HIV infection/AIDS of which they are a component. Rifampin is such a strong enzyme inducer that its concurrent use with most of the HIV protease inhibitors is contraindicated.

SMOKING—A number of studies have indicated that the effects of certain drugs may be decreased in individuals who are heavy smokers, presumably because of increased hepatic enzyme activity resulting from the action of polycyclic hydrocarbons that are present in cigarette smoke. Among the drugs whose metabolism is increased and therapeutic activity likely to be reduced are diazepam, propoxyphene, theophylline, pentazocine, and olanzapine. In addition to careful monitoring of therapy with drugs that are metabolized by hepatic enzyme systems in patients who are moderate or heavy smokers, caution also must be exercised if a patient treated with such a medication discontinues smoking. For example, if therapy with olanzapine is initiated in a patient who is a heavy smoker, the maintenance dosage will be determined during the time period in which the enzyme-inducing action of smoking is decreasing

the effect of the medication. If the patient stops smoking and is still taking the medication, the dosage that had been appropriate is now likely to be excessive and will have to be reduced.

In the examples noted, the effect of smoking is to increase the rate of metabolism of other agents being used, and a decreased response to these agents can be anticipated. In contrast, a significant risk of toxicity exists when oral contraceptives are used by women who smoke, as it has been noted that smoking markedly increases the risk of serious cardiovascular effects (eg, myocardial infarction), especially in women over 35 years of age.

ALCOHOL—Alcohol may either stimulate or inhibit the activity of hepatic enzymes, depending on the circumstances of use. An increased rate of metabolism of warfarin and phenytoin has been reported in alcoholic patients. This was attributed to increased liver enzyme activity caused by chronic administration of alcohol.

In contrast, acute use of alcohol by nonalcoholic individuals may cause inhibition of hepatic enzymes. This may decrease the rate of metabolism, thereby increasing the effect of other agents administered concurrently, and may be responsible, at least in part, for the enhanced sedation experienced when alcoholic beverages and sedative drugs are taken together by individuals who are not alcoholics. The extent to which the mechanisms of enzyme inhibition and central nervous system (CNS) summation or synergism are involved in this interaction remains to be clarified.

LEVODOPA–PYRIDOXINE—Pyridoxine has been shown to reduce the action of levodopa by accelerating its decarboxylation to dopamine in the peripheral tissues. Consequently, less levodopa reaches and crosses the blood-brain barrier, with the result that less dopamine is formed in the brain and the therapeutic effect is diminished. Doses of pyridoxine of 10 to 25 mg have been reported to rapidly reverse the effect of the antiparkinson drug.

The combination product *Sinemet* contains both levodopa and carbidopa, the latter agent acting as an inhibitor of decarboxylase enzymes. When administered with levodopa, carbidopa permits the use of significantly lower doses of the former, since it now is metabolized to a lesser extent in the peripheral tissues. The decrease in dosage often is accompanied by a decreased incidence of adverse effects. Since carbidopa does not cross the blood-brain barrier, it will not hinder the conversion of levodopa to dopamine in the brain.

Levodopa is metabolized also in the peripheral tissues in a pathway that is catalyzed by catechol-*O*-methyltransferase (COMT). When the decarboxylation pathway is inhibited by carbidopa, the *O*-methylation pathway becomes the primary pathway through which levodopa is metabolized in the peripheral tissues. The COMT inhibitor entacapone was developed to inhibit this metabolic pathway and has been used in conjunction with levodopa and carbidopa. A combination product (Stalevo) that includes these three agents has been recently marketed.

INHIBITION OF METABOLISM

A number of situations have been reported in which one drug has inhibited the metabolism of another, usually resulting in a prolonged and intensified activity of the latter (Table 104-1).

ALCOHOL–DISULFIRAM—A well-known example of inhibition of metabolism that has been used to advantage is the use of disulfiram in the treatment of alcoholism. Disulfiram inhibits the activity of aldehyde dehydrogenase, thus inhibiting oxidation of acetaldehyde, an oxidation product of alcohol. This results in accumulation of excessive quantities of acetaldehyde and development of the unpleasant effects characteristic of the disulfiram reaction. A similar noteworthy reaction occurs between metronidazole and alcohol.

Disulfiram is not a selective inhibitor of aldehyde dehydrogenase but exhibits several inhibitory actions that can result in the development of drug interactions. It has been reported that it can enhance the activity of warfarin and phenytoin, presumably by inhibiting their metabolism.

MERCAPTOPURINE OR AZATHIOPRINE–ALLOPURINOL—Allopurinol, by inhibiting the enzyme xanthine oxidase, reduces production of uric acid, which is the basis for its use in the treatment of gout. Xanthine oxidase also has an important role in the metabolism of such potentially toxic drugs as mercaptopurine and azathioprine, and when this enzyme is inhibited by allopurinol, the effect of the latter agents can be increased markedly. When allopurinol is given in doses of 300 to 600 mg/day concurrently with either of these drugs, it is advised that the dose of mercaptopurine or azathioprine be reduced to about 1/3 to 1/4 the usual dose.

CIMETIDINE—Because cimetidine is known to inhibit hepatic oxidative enzyme systems, it should be anticipated that the action of other agents that are metabolized extensively via these pathways will be increased. There have been reports of such interactions with carbamazepine, diazepam, phenytoin, theophylline, warfarin, and other agents, and it may be necessary to reduce the dosage of these agents when cimetidine is included in the therapeutic regimen. Although ranitidine also binds to a limited extent to the cytochrome P-450 enzymes involved in the metabolism of these agents, it appears to have a lesser affinity for the enzymes than does cimetidine. Consequently, clinically significant interactions are less likely to occur with ranitidine. Studies of the other histamine H_2-receptor antagonists (famotidine and nizatidine) suggest that they are not likely to inhibit oxidative metabolic pathways and to interact with other drugs via this mechanism.

THEOPHYLLINE–MACROLIDE ANTIBIOTICS—Erythromycin has been reported to increase significantly serum theophylline concentrations by inhibiting its hepatic metabolism. Patients receiving high doses of theophylline or who are otherwise predisposed to theophylline toxicity should be monitored closely if erythromycin is administered concurrently. It also should be anticipated that clarithromycin and telithromycin will inhibit the metabolism of theophylline, whereas azithromycin is unlikely to interact.

THEOPHYLLINE–FLUOROQUINOLONES—Ciprofloxacin has been reported to increase the plasma concentrations and activity of theophylline markedly, presumably by inhibiting its hepatic metabolism, and concurrent use is best avoided. Certain other fluoroquinolones, such as levofloxacin, are not likely to inhibit hepatic enzyme systems and interact with theophylline.

MAOIs—There have been many reports of drug interactions involving use of an MAOI with another drug or with certain dietary items. It is likely that MAOIs enhance the effect of drugs such as the barbiturates and opioid analgesics by inhibiting hepatic enzyme systems involved in their metabolism. However, other mechanisms are involved in some of the more publicized problems with these compounds and are considered elsewhere in this chapter.

CALCIUM CHANNEL BLOCKING AGENTS—The calcium channel blocking agents (eg, diltiazem, nifedipine, verapamil) have been reported to interact with a number of drugs, although the mechanisms through which these interactions occur are not completely defined. It has been suggested that verapamil and diltiazem may inhibit the hepatic metabolism of carbamazepine, thereby increasing the activity of the latter agent. Because the calcium channel blocking agents are metabolized themselves in the liver, they may interact with certain drugs because they are competing for the same metabolic pathways.

ALTERATION OF EXCRETION

Although some therapeutic agents are eliminated via other mechanisms, most drugs and their metabolites are excreted, at least in part, via the kidneys. The most important clinical implications of altering renal excretion involve the use of drugs that are excreted in their unchanged form or in the form of an active metabolite. Thus, substances with pharmacological activity are being reabsorbed or excreted to a greater extent when renal excretion is altered. In contrast, when only inactive

metabolites are being excreted, changes in therapeutic activity are less likely to be associated with the use of other drugs that can influence renal excretory pathways.

Alteration of Urinary pH

SALICYLATES–ACIDIFYING AND ALKALINIZING AGENTS—A change in urinary pH will influence the ionization of weak acids and weak bases and thus affect the extent to which these agents are reabsorbed and excreted. When a drug is in its nonionized form it will diffuse more readily from urine back into blood. Therefore, for an acidic drug, there will be a larger proportion of drug in the nonionized form in an acid urine than in an alkaline urine—where it will exist primarily as an ionized salt. The result is that from an acid urine more of an acidic drug will diffuse back into the blood and produce a prolonged, and perhaps intensified, activity. In one study it was noted that a salicylate dosage regimen that provided a serum concentration of 20 to 30 μg/mL in a patient when the urinary pH was approximately 6.5 produced serum concentrations that were approximately twice as high when the urinary pH was decreased to 5.5. The risk of a significant interaction is greatest in patients who are taking large doses of salicylates (eg, for arthritis).

AMPHETAMINES–ALKALINIZING AGENTS—Converse effects will be seen for a basic drug like dextroamphetamine. In one investigation the excretion of a dose of dextroamphetamine at urinary pH values of approximately 5 and 8 was studied. When the urinary pH was maintained at approximately 5, 54.5% of the dose of dextroamphetamine was excreted within 16 hr, compared with a 2.9% excretion in the same period when the urinary pH was maintained at approximately 8.

Similar observations have been made with other basic drugs. One report calls attention to the possible development of quinidine toxicity when urine becomes alkaline, since excretion of quinidine was shown to decrease considerably as urinary pH was raised. In another investigation, when the urinary pH was increased to about 8 with sodium bicarbonate, the plasma half-life of pseudoephedrine was approximately double that in normal subjects. When urinary pH in the same subjects was decreased to 5.2, using ammonium chloride, the plasma half-life decreased markedly from control values.

Alteration of Active Transport

PENICILLINS–PROBENECID—A number of organic acids undergo active transport from the blood into the tubular urine and *vice versa*. In some situations these agents interfere with the excretion of each other. It is well-recognized that probenecid can increase serum concentrations and prolong activity of penicillin derivatives by blocking their tubular secretion. Often there will be a 2-fold to 4-fold elevation of serum penicillin concentrations, although the degree to which these concentrations are increased and the duration of activity prolonged depend on a number of factors.

Probenecid also has been reported to decrease renal excretion of other agents, including methotrexate.

METHOTREXATE–NONSTEROIDAL ANTI-INFLAMMATORY DRUGS—A number of nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to increase the activity and toxicity of methotrexate. There have been several reports of fatal methotrexate toxicity in patients also receiving ketoprofen, and it has been suggested that ketoprofen inhibited the active renal tubular secretion of methotrexate. However, other mechanisms probably also contribute to an increase in serum methotrexate concentrations. Most of the patients in whom these interactions have been reported were receiving high-dose methotrexate therapy for neoplastic disorders. However, caution also should be exercised in patients receiving lower doses, particularly since low-dose methotrexate regimens are used in patients with rheumatoid arthritis who also are taking an NSAID.

LITHIUM–NONSTEROIDAL ANTI-INFLAMMATORY DRUGS—The serum concentrations and incidence of adverse effects of lithium salts have been reported to be increased by the concurrent administration of anti-inflammatory agents such as ibuprofen, indomethacin, and piroxicam. It is suggested that the renal clearance of lithium is reduced as a result of the action of these anti-inflammatory agents to inhibit renal prostaglandin synthesis. This interaction should be anticipated when any NSAID is administered concurrently with a lithium salt.

ALTERATION OF DRUG TRANSPORT

There has been increased recognition of the importance of P-glycoprotein in the absorption, distribution, metabolism, and excretion of certain drugs. P-glycoprotein functions as a transport system that may act as a barrier for certain agents and as a pump that facilitates the transport of certain agents across membranes. For example, it limits cellular uptake of certain drugs from the blood into the brain and from the intestinal lumen into epithelial cells. The role of P-glycoprotein in the overall absorption of a drug that is administered orally in high milligram doses is not likely to be clinically important because this transport system is quickly saturated by the high concentrations of drug in the intestinal lumen. However, its role may be important in the absorption of drugs that are administered orally in very small doses (eg, digoxin). Numerous medications have been shown to be substrates for P-glycoprotein including agents such as cyclosporine, digoxin, diltiazem, verapamil, atorvastatin, lovastatin, simvastatin, doxorubicin, paclitaxel, HIV protease inhibitors, and loperamide.

There is overlapping substrate specificity between P-glycoprotein and CYP3A4, and many of the drugs that inhibit or induce CYP3A4 also inhibit or induce P-glycoprotein. Therefore, drug interactions that result from inhibition or induction of CYP3A4 often also involve inhibition or induction of P-glycoprotein. Inhibitors of P-glycoprotein include agents such as clarithromycin, erythromycin, itraconazole, ketoconazole, quinidine, and verapamil. Inducers include such agents as rifampin and St John's wort.

DIGOXIN–QUINIDINE OR VERAPAMIL—The concurrent use of quinidine or verapamil with digoxin has resulted in significantly greater serum digoxin concentrations. Both quinidine and verapamil are inhibitors of P-glycoprotein and it is thought that this action results in increased absorption, decreased elimination, and higher concentrations of digoxin. Conversely, inducers of P-glycoprotein such as rifampin and St John's wort would be expected to decrease serum concentrations of digoxin.

LOPERAMIDE–P-GLYCOPROTEIN—The antidiarrheal agent loperamide is very unlikely to cause central nervous system adverse events, in part because P-glycoprotein prevents it from crossing the blood-brain barrier and gaining access to the central nervous system. However, if a patient using loperamide is also treated with a P-glycoprotein inhibitor, CNS effects that are characteristic of the opioids may be experienced.

Pharmacodynamic Interactions

Although pharmacokinetic interactions often present challenging clinical problems and are publicized widely, pharmacodynamic interactions are the type that occur most frequently.

DRUGS HAVING OPPOSING PHARMACOLOGICAL EFFECTS

Interactions resulting from the use of two drugs with opposing effects should be among the easiest to detect. However, these sometimes are due to the secondary effects of certain drugs and this and other factors may preclude early identification of such situations.

DIURETICS—The ability of the thiazides and certain other diuretics to elevate blood glucose concentrations is well known. When the diuretic is prescribed for a diabetic patient being treated with insulin or one of the oral antidiabetic agents, this action may partially counteract the glucose-lowering action of the antidiabetic drug, necessitating an adjustment in dosage. Similarly, many diuretics may produce a hyperuricemic effect. Therapy in patients with gout should be monitored closely, as the hyperuricemic action of a diuretic may necessitate an adjustment in dosage of the agent being used in the treatment of gout.

DRUGS HAVING SIMILAR PHARMACOLOGICAL EFFECTS

An excessive response attributable to the concurrent use of drugs having similar actions is the type of interaction that occurs most often, and these potential problems warrant particular attention.

CNS DEPRESSANTS—An excessive CNS depressant effect resulting from the concurrent use of two or more drugs exhibiting a depressant action represents one of the most dangerous drug-related problems. Older patients should be viewed as being especially susceptible to this type of response, and patients experiencing effects such as sedation and dizziness are at increased risk of falls and injuries, such as hip fractures. Patients also must be advised of the risks of operating motor vehicles or machinery. In considering multiple drug regimens, recognition must be taken of the large number of agents (eg, sedative-hypnotics, antipsychotics, tricyclic antidepressants, opioid analgesics, and most antihistamines) that can exhibit a depressant effect that will be at least additive to the effect contributed by other drugs. If it is considered necessary to use agents with a CNS depressant action concurrently, it should be anticipated that a lower dosage of at least one of the agents should be used.

ALCOHOL–OTHER CNS DEPRESSANTS—The increased CNS depressant effect that is experienced by individuals being treated with depressant drugs when they consume alcoholic beverages is among the best-known interactions. However, this interaction also illustrates the difficulties in trying to predict the magnitude of the response that will be experienced by a particular patient, as the response will depend on many variables, including the patient's tolerance to alcohol. How then should the patient be instructed when he or she is to take a depressant medication? Certainly it would be most desirable not to consume alcoholic beverages during the period the medication is being taken. However, there should be a realistic recognition that many patients if faced with a mandate not to drink while on drug therapy will decide not to take the drug. Every patient should be alerted to the fact that the depressant effect of the drug prescribed may be increased by alcohol. If it is anticipated that a patient would not completely avoid alcoholic beverages, that patient should be urged to use them in moderation, particularly when therapy is initiated or the dosage is increased, and cautioned to observe his or her own tolerance when such combinations are employed. The fact that many individuals can take depressant drugs and consume relatively large amounts of alcoholic beverages with no apparent difficulty should not be cause to forget that such combinations have been lethal in some individuals and the cause of injury in others. Thus, there is an important need to caution all patients for whom such drugs are prescribed.

DRUGS HAVING ANTICHOLINERGIC ACTIVITY—Drugs that differ considerably in their primary pharmacological actions may exhibit the same secondary effects. Some patients being treated with antipsychotic agents such as chlorpromazine also are given an antiparkinson agent such as trihexyphenidyl to control the extrapyramidal effects of the former. In addition, a number of these patients experience symptoms of depression, and a tricyclic antidepressant such as amitriptyline might be added to the therapy. Each of these three agents possesses anticholinergic activity, and the additive effect could result in side effects such as dryness of the mouth, blurred vision, urinary retention, constipation, and elevation of intraocular pressure.

Even an effect such as dryness of the mouth, which most health professionals would consider as a minor problem, could be troublesome in certain patients. For example, persistent dryness of the mouth could make the use of dentures more difficult and also cause other dental complications. In addition, there may be increased difficulty in chewing and swallowing, an important factor with respect to the problem of malnutrition in many elderly individuals. Dryness of the mouth also may result in other problems as illustrated by a case report of a patient treated with imipramine. The patient experienced persistent dryness of the mouth and when nitroglycerin tablets were administered sublingually for the management of exertional angina, the relief of the symptoms was delayed because of the slower dissolution of the sublingual tablets.

It has been observed that an excessive anticholinergic effect can cause an atropine-like delirium, particularly in geriatric patients. This effect could be misinterpreted as an increase in psychiatric symptoms, which might be treated by increasing the dosage of the therapeutic agents that are actually responsible for causing the problem. This example points out the difficulty that often can exist in distinguishing between the symptoms of the condition(s) being treated and the effects of the drug(s) being employed as therapy.

Several studies call attention to other potential problems associated with the use of drugs having anticholinergic activity. In one investigation using volunteers aged 60 to 72, trihexyphenidyl was found to cause substantial memory impairment. In another study of 22 demented nursing-home patients, it was noted that those with high serum anticholinergic concentrations had greater impairment in self-care capacity than patients with low concentrations.

The blurring of vision, which also may be associated with the use of drugs having anticholinergic activity, may be especially distressing for older patients, particularly those whose physical activities may be limited and for whom reading is a favorite activity.

Several reports have described the development of severe hyperpyrexia in patients taking phenothiazine–antiparkinson combinations who were exposed to high environmental temperature and humidity. These investigators call attention to the ability of these combinations to interfere with the thermoregulatory system of the body and recommend that physicians treating patients in hot and humid climates should minimize outdoor exposure of patients receiving high doses of these agents.

DRUGS EXHIBITING HYPOTENSIVE EFFECTS—Certain antihypertensive drugs as well as some other classes of medications (eg, tricyclic antidepressants) can cause orthostatic hypotension, resulting in symptoms such as dizziness, lightheadedness, and, in more severe cases, syncope. Older patients are more susceptible to this type of response and the associated risks such as falls and injuries, and appropriate precautions should be exercised whether these agents are given alone or in combination.

The use of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction is contraindicated in patients treated with nitrates because these agents may potentiate the hypotensive effect of the nitrates.

NSAIDs—Several situations exist in which a patient unknowingly may be taking several different products that contain the same NSAID. An arthritic patient whose condition has been managed with ibuprofen obtained via prescription (often at dosage levels at or near the recommended maximum) may purchase an ibuprofen product available without a prescription for pain/discomfort not associated with the arthritis, without recognizing that the two products contain the same drug and that there is an increased risk of adverse effects.

ALTERATION OF ELECTROLYTE CONCENTRATIONS

Several important drug interactions occur as a result of the ability of certain therapeutic agents to alter the concentration of electrolytes such as potassium and sodium. When these drugs are included in a therapeutic regimen, it is important that electrolyte concentrations be monitored periodically.

DIGOXIN–DIURETICS—One of the problems associated with the use of most of the commonly employed diuretics (eg, the thiazide derivatives) is that they can cause an excessive loss of potassium. Particular caution is necessary in patients also being treated with digoxin, many of whom would be candidates for diuretic therapy. If potassium depletion remains uncorrected, the heart may become more sensitive to the effects of the cardiac glycoside and arrhythmia may result.

Although potassium supplementation will be necessary in many individuals being treated with a potassium-depleting diuretic, the initiation of therapy with such a diuretic must not be viewed as a mandate also to provide potassium supplementation. This decision should be based on a consideration of the individual patient situation, and the appropriate parameters should be monitored periodically. It must be recognized that dangers also exist if hyperkalemia occurs as a result of excessive supplementation. This risk of such complications is greatest in patients with diminished renal function.

In addition to the diuretics, other agents also can cause potassium depletion. Prolonged therapy with cathartics and corticosteroids may cause potassium depletion, although this is not likely to occur as quickly or to the same extent as with diuretics.

Interest has developed also in the clinical implications of magnesium depletion. Concern has been expressed that this condition occurs much more commonly than is recognized and that some clinical problems may continue or worsen despite seemingly adequate electrolyte therapy because magnesium deficiency has not been identified and corrected.

Diuretic therapy may lead to development of magnesium depletion, and as observed when potassium is depleted, the activity of digoxin may be increased and possibly result in toxicity. In some patients with digoxin toxicity, low serum-magnesium concentrations may coexist with normal potassium values.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS–POTASSIUM-SPARING DIURETICS—The angiotensin-converting enzyme (ACE) inhibitors (eg, enalapril, lisinopril, ramipril) may cause an elevation of serum potassium concentrations. Potassium-sparing diuretics (amiloride, spironolactone, and triamterene) or potassium supplements should be used concurrently with caution, because of the risk of hyperkalemia and associated complications. Salt substitutes containing potassium also should be used with caution.

LITHIUM–DIURETICS—Sodium depletion is known to increase lithium toxicity, for which reason it generally has been recommended that lithium salts should not be used in patients on diuretic therapy or on a sodium-restricted diet. Even protracted sweating or diarrhea can cause sufficient depletion of sodium to result in decreased tolerance to lithium.

The sodium depletion caused by diuretics reduces the renal clearance and increases the activity of lithium. However, if preferable therapeutic alternatives are not available, concurrent therapy need not be contraindicated so long as the interaction is recognized and steps are taken to monitor therapy and adjust dosage.

INTERACTIONS AT RECEPTOR SITES

MAOIs–SYMPATHOMIMETIC AGENTS—MAO functions to break down catecholamines such as norepinephrine. When the enzyme is inhibited, the concentrations of norepinephrine within adrenergic neurons increase, and a drug that can stimulate its release can bring about an exaggerated response. It is by this mechanism that interactions between MAOIs and indirectly acting sympathomimetic amines (eg, amphetamine) develop. Thus, if amphetamine is administered to patients whose stores of norepinephrine have been increased by MAO inhibition, they may experience severe headache, hypertension (possibly a hypertensive crisis), and cardiac arrhythmias. The serious consequences associated with these interactions contraindicate use of these agents in combination.

Although most sympathomimetic amines, such as amphetamine, are available only by prescription, others such as phenylephrine, which also has been reported to interact similarly with MAOIs, are found in many nonprescription cold and allergy preparations. It is important that patients being treated with MAOIs avoid using products containing these agents.

MAOIs–TRICYCLIC ANTIDEPRESSANTS—Cautions in the product literature, as well as case reports, warn against concurrent use of an MAOI with a tricyclic antidepressant (eg, amitriptyline, imipramine) because severe atropine-like reactions, tremors, convulsions, hyperthermia, and vascular collapse have been reported to result from such use. It is recommended in the labeling for most of these products that therapy with an MAOI or a tricyclic antidepressant should not be initiated until at least 7 to 14 days after therapy with the other has been discontinued.

Although the labeling for most MAOIs and tricyclic antidepressants notes that concurrent use is contraindicated, there is debate as to the degree of risk involved. Several studies of the combined use of these agents have revealed little evidence of interaction, and the growing impression that serious interactions are uncommon, coupled with the reports of favorable results with such combinations in selected patients who did not respond to either agent given alone, have led some to conclude that these combinations can be employed cautiously. In patients who are refractory to single antidepressants and who are not candidates for alternative therapeutic approaches, the potential benefits of combination therapy may outweigh the risks. However, such therapy should be undertaken only by those who are thoroughly familiar with the risks involved and under circumstances in which therapy can be monitored closely.

MAOIs–SELECTIVE SEROTONIN REUPTAKE INHIBITORS—Serious consequences may result from the combined use of an MAOI and a selective serotonin reuptake inhibitor (SSRI, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertaline), and concurrent use or use within 14 days before or after most of these agents is contraindicated.

There have been several reports of deaths of patients in whom therapy with an MAOI was initiated shortly after discontinuation of fluoxetine. Because of the long half-lives of fluoxetine and its active metabolite, it is recommended that at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of therapy with an MAOI.

It should be noted that the antineoplastic procarbazine and the anti-infectives furazolidone and linezolid, also can inhibit MAO enzymes, and warnings applying to the use of other MAOIs should be heeded for these drugs also.

GUANETHIDINE–TRICYCLIC ANTIDEPRESSANTS—Guanethidine is transported to its site of action within adrenergic neurons by a transport system that also is responsible for uptake of norepinephrine, as well as several indirectly acting sympathomimetic amines such as ephedrine and the amphetamines. Concentration of guanethidine in these neurons is necessary for its antihypertensive action. Tricyclic antidepressants can inhibit uptake of guanethidine into the neuron terminal, thereby preventing its concentration at these sites and reducing its activity. Other studies suggest that antipsychotic agents such as chlorpromazine and haloperidol can act similarly to the tricyclic antidepressants in reducing the antihypertensive effect of this agent.

Although other mechanisms may be involved in the development of drug interactions, the ones cited are the most important. As often stated, more than one mechanism may be responsible

for certain interactions; these mechanisms may work in concert or in opposition as determinants of the resulting effect. Still other drug interactions develop by mechanisms yet to be identified.

However, an awareness of the factors predisposing to the development of drug interactions, as well as the mechanisms by which many of them occur, will be of value in the identification and prevention of potential problems.

It is evident that significant limitations still exist in trying to predict the results of combination therapy. In the following section, guidelines are provided to reduce the risk of the occurrence of drug interactions.

REDUCING THE RISK OF DRUG INTERACTION

The reduction of the risk of drug interactions is a challenge that embraces a number of considerations. Although they could be applied to drug therapy in general, the following guidelines to reduce and manage drug interactions are offered to assist health professionals who have the responsibility of selecting and monitoring therapeutic regimens.

Identify the Patient Risk Factors Factors such as age, the nature of the patient's medical problems (eg, impaired renal function), dietary habits, smoking, and problems like alcoholism will influence the effect of certain drugs and should be considered during the initial patient interview.

Take a Thorough Drug History An accurate and complete record of the prescription and nonprescription medications a patient is taking as well as products such as herbal products and dietary supplements must be obtained. Numerous interactions have resulted from a lack of awareness of prescription products prescribed by another physician or nonprescription medications the patient did not consider important enough to mention.

Be Knowledgeable about the Actions of the Drugs Being Used The knowledge of the properties and the primary and secondary pharmacological actions of each of the agents used or being considered for use is essential if the interaction potential is to be assessed accurately.

Consider Therapeutic Alternatives In most cases, two drugs that are known to interact can be administered concurrently as long as adequate precautions are taken (eg, closer monitoring of therapy or dosage adjustments to compensate for the altered response). However, in those situations in which another agent with similar therapeutic properties and a lesser risk of interacting is available, it should be used.

Avoid Complex Therapeutic Regimens When Possible The number of medications used should be kept to a minimum. In addition, the use of medications or dosage regimens that permit less-frequent administration may help avoid interactions that result from an alteration of absorption (eg, when a drug is administered in close proximity to meals).

Educate the Patient Patients often know little about their illnesses, let alone the benefits and problems that could result from drug therapy. Individuals who are aware of, and understand, this information can be expected to be in greater compliance with the instructions for administering medications and more attentive to the development of symptoms that could be early indicators of drug-related problems. Patients should be encouraged to ask questions about their therapy and to report any excessive or unexpected responses. There should be no uncertainty on the part of patients as to how to use their medications in the most effective and safest way.

Monitor Therapy The risk of drug-related problems warrants close monitoring, not only for the possible occurrence of drug interactions but also for adverse events occurring with individual agents and noncompliance. Any change in patient behavior should be suspected as being drug-related until that possibility is excluded.

Individualize Therapy Although the development of a therapeutic regimen that meets the specific needs of individual patients is inherent in many of the above guidelines, the importance of individualization of therapy cannot be emphasized too strongly. Wide variations in the response of patients to the same dose of certain individual drugs is well-recognized. It is difficult to predict the response of many therapeutic agents when they are given alone; the challenge and limitations in anticipating the response with a multiple-drug regimen are even greater. Therefore, priority should be assigned to the needs and clinical response of the individual patient, rather than to the usual dosage recommendations and standard treatment and monitoring guidelines.

The pharmacist will be involved actively in the observance of the guidelines described above. In addition, the need to not only maintain complete and current patient medication records, but also to supervise and monitor drug therapy more closely, places the pharmacist in a strategic position to detect and prevent drug interactions. By observing the preceding guidelines and recommendations and by strengthening communication with patients and other health professionals, the pharmacist has a valuable opportunity to make a significant contribution toward the further enhancement of the efficacy and safety of drug therapy.

CHAPTER 105

Extemporaneous Prescription Compounding

Loyd V Allen, Jr, PhD

Historically, *pharmaceutical compounding* has been an integral part of pharmacy practice as shown by some definitions and references to pharmacy, such as

> Pharmacy is the art or practice of preparing and preserving drugs and of compounding and dispensing medicines according to the prescriptions of physicians.[1]

> Pharmacy is (1) the art or practice of preparing, preserving, *compounding,* and dispensing drugs or (2) a place where medicines are *compounded* or dispensed.[2]

> Pharmacy is the science, art, and practice of preparing, preserving, *compounding*, and dispensing medicinal drugs and giving instructions for their use.[3]

> And thou shalt make it an oil of holy ointment, an ointment *compounded* after the art of the apothecary; it shall be an anointing oil.[4]

Compounding is a professional prerogative that pharmacists have performed since the beginning of the profession. Even today, the definitions of pharmacy include the *preparation of drugs*.[5,6]

The heritage of pharmacy, spanning some 5000 years, has centered around the provision of pharmaceutical products for patients. Pharmacists are the only health care professionals that possess the knowledge and skill required for compounding and preparing medications to meet the unique needs of patients. The responsibility of extemporaneously compounding safe, effective prescription products for patients who require special care is fundamental to the pharmacy profession.

The 19th century did not see an end to the art of compounding, but the art did give way, however grudgingly, to new technology. In the 20th century, it has been estimated that a *broad knowledge of compounding* was still essential for 80% of the prescriptions dispensed in the 1920s. Although pharmacists increasingly relied on chemicals purchased from the manufacturer to make up prescriptions, there still remained much to be done *secundum artem*.[1]

Pharmaceutical industry began to take over the production of most medications used by the medical profession. In many ways this has provided superior service, new methods, and a vast array of innovative products that could not have been provided in a one-on-one basis. Research and development have been the hallmarks of the pharmaceutical manufacturers. However, the very nature of providing millions of doses of a product requires that the dosage forms (eg, capsules, tablets, suppositories) and doses (individual strengths of each dose) be limited and results in a one-sided approach to therapy. In the 21st century, it is simply not economical for a pharmaceutical company to produce a product in 10 different conceivable doses or in 5 different dosage forms to meet the needs of the entire range of individuals receiving therapy. Windows of activity are determined that meet the majority of patient needs, but the very nature of the process cannot meet all patient needs.

We also must recognize that some individuals and their health care needs do not fall in the windows of theoretical dosage strength and dosage forms and that large-scale manufacturers cannot tailor-make a medication for a handful of patients and do so cost effectively and meet the ever-changing needs of a given patient or institution. The skills of pharmacists in practicing their art of compounding fills in this gap to meet individualized needs. By this assessment the pharmacist may, through understanding of the principals of compounding and recognition of their skill level in working secundum artem, recommend that therapy be provided that is not provided by pharmaceutical industry but that is individualized for a specific patients' needs at a specific time.

Compounding has always been a basic part of pharmacy practice; the drugs, dosage forms, and equipment or techniques used are the variables. Pharmacists possess knowledge and skills that are unique and are not duplicated by any other profession. Pharmacy activities to individualize patient therapy include compounding and clinical functions. Either function in the absence of the other results in placing pharmacy in a disadvantaged position. It is important to use a pharmacist's expertise to adjust dosage quantities, frequencies, and even dosage forms for enhanced compliance. All pharmacists should understand the options presented by compounding.

Pharmaceutical compounding is increasing for a number of reasons, including the availability of a limited number of dosage forms for most drugs, a limited number of strengths of most drugs, home health care, hospice, the non-availability of drug products/combinations, discontinued drugs, drug shortages, orphan drugs, new therapeutic approaches and special patient populations (pediatrics, geriatrics, bioidentical hormone replacement therapy for postmenopausal women, pain management, dental patients, environmentally and cosmetic sensitive patients, sports injuries and veterinary compounding, including small, large, herd, exotic, and companion animals).

Newly evolving dosage forms and therapeutic approaches suggest that compounding of pharmaceuticals and related products specifically for individual patients will become more common in pharmacy practice. Compounding pharmacy is unique as it allows one to use much of their scientific, math, and technology background to a fuller extent than some of the other types of practices. Compounding pharmacists develop a special and unique relationship with the patients they serve. They work hand in hand with physicians to solve problems not addressed by commercially available dosage forms.

In the hospital and home health-care environments, there has been a noticeable increase in the *batch production* of sterile products. Reasons for this increase may include the changing patterns of drug therapy, such as home parenteral therapy and patient-controlled parenteral administration and the use of noncommercially available injectable drug products in hospi-

tals to meet individual patient needs or prescriber's clinical investigational protocols.

THE COMPOUNDING PHARMACIST—Pharmacists are unique professionals: well trained in the natural, physical, and medical sciences and sensitized to the potential tragedy that may result from a single mistake that may occur in the daily practice of their profession. Pharmacists have developed the reputation of being available in the local community to interact with patients, provide needed medications, and work with patients to regain or maintain a certain standard or quality of health and of just being there in time of need.

Pharmacy is a complex mixture of different practices and practice sites. No longer is pharmacy simply community pharmacy or hospital pharmacy. Pharmacy is diverse and offers many opportunities for those willing to look around, find their niche and practice pharmacy to meet the needs of their own community of patients. Most compounding pharmacists appear to be interested and excited about their practices. In fact, many pharmacists intimately involved in pharmaceutical care have now realized the importance of providing *individualized patient care* through the preparation of *patient-specific products*. Compounding pharmacy is not for everyone, but as it grows, it will provide an increasingly significant number of pharmacists the excitement and fulfillment of using their innovative and creative skills to solve patient problems. This is compounding pharmacy.

As mentioned, pharmaceutical compounding requires the use of one's training in mathematics, science, and technology more than some of the other practices of pharmacy. It has been stated:

"The sciences are what support pharmacy's expertise in drug distribution and drug use. Recent history leads one to question whether we in the profession, and some in pharmaceutical education, recognize and appreciate the contribution that the pharmaceutical sciences have made and continue to make to the pharmacy profession and health care. The pharmaceutical sciences are what make us unique. They provide us the special value that we bring to the bedside. No other health professional is capable of bringing to the pharmacotherapeutic decision-making table such concepts as pH, particle size, partition coefficient, protein binding, structure-activity relationships, economics, and epidemiology. The pharmaceutical sciences, combined with pharmacy's infrastructure, including pharmaceutical education, are what make the pharmacist an indispensable participant on the health care team."[7]

And what area of pharmacy practice has the opportunity of using the scientific education and training as much as pharmacists involved in individualizing patient care through extemporaneous compounding? The pharmaceutical sciences, especially chemistry and pharmaceutics, serve as the foundation for pharmacists' ability to formulate specific dosage forms to meet patients' needs.

DEFINITIONS—Pharmacy is united in the sense that pharmacists have a responsibility to serve their patients and compound an appropriately prescribed product in the course of their professional practice. It is the right and responsibility of pharmacists to compound medications to meet the specific needs of patients. Pharmacists are ultimately responsible for the integrity of the finished product prepared under their immediate supervision.

Compounding has been defined by the National Association of Boards of Pharmacy:

"Compounding means the preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice, or (ii) for the purpose of, as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed patterns."[8]

Compounding may hold different meanings to different pharmacists. It may mean the preparation of oral liquids, topical creams/ointments, suppositories; the conversion of one dose or dosage form into another; the preparation of select dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting.

There are different types of compounded prescriptions, including the isolated, routine and batch prepared. The *isolated* prescription is one the pharmacist is not expecting to receive nor expecting to receive it again. The *routine* prescription is one the pharmacist may expect to receive in the future on a routine basis, and there may be some benefits to product quality to *standardize* preparations like this (ie, preparation protocols on file). The *batch-prepared* prescription is one in which multiple identical units are prepared as a single operation *in anticipation* of the receipt of prescriptions.

EVALUATING THE NEED—When considering whether to compound a prescription, one might wish to consider the following questions:

1. Is the product commercially available in the exact dosage form, strength, and packaging?
2. Is the prescription rational concerning the ingredients, intended use, dosage, and method of administration?
3. Am I qualified to prepare this prescription by education, skill development, and expertise?
4. Do I have the proper equipment, supplies, and chemicals or drugs?
5. Is there documentation for assigning a *beyond-use* date for the prescription, or do I use the guidelines delineated in US Pharmacopeia (USP) Chapters <795> and <797>, *Pharmacy Compounding-Nonsterile Preparations and Pharmacy Compounding-Sterile Preparations,* respectively?
6. Is there an alternative by which the patient will receive a benefit?
7. Will this compounded product satisfy the intent of the prescribing physician and meet the needs of the patient?
8. Is there a bona fide prescriber–pharmacist–patient relationship?
9. Does the patient have the necessary storage facility, if required, to assure potency of the product until its beyond-use date?
10. Can I perform the necessary calculations to prepare the product?
11. Am I willing to complete the necessary documentation to prepare the product?
12. Is there a literature reference that might provide information on use, preparation, stability, administration, etc?
13. How long will the patient be using the product and is the expected duration of therapy consistent with an appropriate beyond-use date? Alternatively, should the product be prepared in small quantities and dispensed to the patient in short intervals?
14. Can I do some basic quality control to check the product prior to dispensing (eg, capsule weight variation, pH, visual observations)?
15. Am I assured of ingredient identity, quality, and purity?
16. What procedures do I have for investigating and correcting failures?
17. Are the physical, chemical and therapeutic properties of the individual ingredients consistent with the expected properties of the ordered drug product?[9]

Evaluating the Feasibility of Batch Compounding

The following questions may be considered prior to batch compounding activities:

1. Will the processes, procedures, compounding environment, and equipment used to prepare this batch produce the expected qualities in the finished product?
2. Will all the critical processes and procedures be carried out exactly as intended for every batch of the prepared product to produce the same high-quality product in every batch?
3. Will the finished product have all the qualities as specified, on completion of the preparation and packaging of each batch?
4. Will each batch retain all the qualities within the specified limits until the end of the labeled beyond-use date?
5. Can I monitor and trace the history of each batch, identify potential sources of problems and institute appropriate corrective measures to minimize the likelihood of their occurrence?[9]

Pharmacists who perform batch compounding should be capable and willing to do it properly, particularly when sterile drug

products are involved. Trends indicate that more batch compounding may be occurring in more pharmacies in the future.

ECONOMIC CONSIDERATIONS—There are at least two different economic considerations in making the decision to compound prescriptions; these include (1) pharmacist compensation and (2) health-care costs.

Pharmaceutical compounding is a cognitive service, hence cognitive services reimbursement is justified. As a surgeon uses both cognitive and technical, manipulative skills, so does the pharmacist use cognitive, technical, and manipulative skills in extemporaneous compounding to meet individualized patient needs. The pricing of a compounded prescription should include consideration for pharmacodynamic and pharmacotherapeutic decision making, formulation expertise, time, and reimbursement of materials. Compounding prescriptions can be attractive professionally and financially. Historically, it has been said that compounding is an act whereby the professional and scientific knowledge of a pharmacist can find its expression. For those pharmacists dedicated to doing a quality job in compounding, the professional, psychological, and financial rewards can be substantial.

Compounding prescriptions can be a way of lowering the cost of drug therapy. In some cases, it is less expensive for the pharmacist to prepare a specific prescription for the patient, which may mean the difference between the patient actually obtaining the drug or doing without it. If compounding a prescription results in a patient being able to afford the drug therapy, it must be considered.

Another example concerns the economic use of expensive drug products. Some drug products are expensive and may have short shelf lives. If a patient does not need the entire contents of a vial or dosage unit, in many cases, the remaining drug product is discarded and wasted. However, there are numerous instances in which the pharmacist can divide the commercial product into smaller, usable units, store it properly and dispense the required quantity on individual prescriptions.

Another obliquely related economic question can also be addressed about the commercialization of compounded products. Over the years it has been interesting to note that many compounded products eventually become commercially available products. Examples include:

Fentanyl Lozenges
Minoxidil Topical Solution
Nystatin Lozenges
Clindamycin Topical Solution
Tetracaine-Adrenalin-Cocaine (TAC) Solution
Dihydroergotamine Mesylate Nasal Spray
Buprenorphine Nasal Spray
Buffered Hypertonic Saline Solution
Erythromycin Topical Solution

as well as numerous other dermatological and pediatric oral liquids and some premixed intravenous solutions. It is inevitable that a product will be manufactured when a product becomes economically profitable for a pharmaceutical manufacturer to produce it.

COMPOUNDING FACTORS

STABILITY—One key factor in compounding prescriptions is stability. The more common types of stability of which compounding pharmacists should be aware include chemical, physical, and microbiological. Whereas commercially manufactured products are required to possess an *expiration date*, compounded products are assigned a *beyond-use date*. There are numerous sources of information that can be used for determining an appropriate beyond-use date, such as chemical companies, manufacturers literature, laboratory data, journals, and published books on the subject. Generally, most pharmacists prepare or dispense small quantities of compounded products; recommend storage at room, cool, or cold temperatures; and use a conservative beyond-use date.

The guidelines published in the USP 26/NF 21 Section <795>, *Pharmacy Compounding*, state that

"In the absence of stability information that is applicable to a specific drug and preparation, the following maximum beyond-use dates are recommended for non-sterile compounded drug precautions that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated."

For nonaqueous liquids and solid formulations (for which the manufactured drug product is the source of active ingredient)—The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

A USP or NF substance is the source of active ingredient—The beyond-use date is not later than 6 months.

For water-containing formulations (prepared from ingredients in solid form)—The beyond-use date is not later than 14 days when stored at cold temperatures.

For all other formulations—The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.

These beyond-use date limits may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation (ie, the *same* drug concentration range, pH, excipients, vehicle, water content).[10]

QUALITY CONTROL—One of the fastest growing and most important areas of pharmaceutical compounding is that of quality control. Quality must be built-in to the preparation from the beginning steps to evaluating the final preparation. There are several quality control tests that can be done within the pharmacy and others can be sent to a contract laboratory. The following quality control tests can be considered for the respective dosage forms.

1. Oral and topical liquids (solutions, suspensions, emulsions): Weight/volume, pH, specific gravity, active drug assay, globule size range, rheological properties/pourability, physical observation (color, clarity), physical stability (discoloration, foreign materials, gas formation, mold growth).
2. Hard Gelatin Capsules: Weight-overall average weight, weight-individual weight variation, dissolution of capsule shell, disintegration and/or dissolution of capsule contents, active-drug assay, physical appearance (color, uniformity, extent of fill, locked), physical stability (discoloration, changes in appearance).
3. Ointments, Creams and Gels: Theoretical weight compared to actual weight, pH, specific gravity, active drug assay, physical observations (color, clarity, texture-surface, texture-spatula spread, appearance, feel) and rheological properties.
4. Suppositories, Troches, Lollipops and Sticks: Weight, specific gravity, active drug assay, physical observation (color, clarity, texture of surface, appearance, feel), melting test, dissolution test, physical stability.
5. Parenteral preparations: Weight/volume, physical observation, pH, specific gravity, osmolality, assay, color, clarity, particulate matter, sterility, pyrogenicity.

COMPOUNDING SUPPORT—Numerous agencies, companies, organizations, etc, are available to assist pharmacists in compounding. Information, chemicals, supplies, and equipment are readily available. Chemical and supply companies have increased in size and number in recent years and many provide information on compounding, incompatibilities, and stability. Specialty compounding organizations have developed over recent years and generally provide full-line services and products to the compounding pharmacist. Many national organizations provide continuing professional education programs in both non-sterile and sterile compounding.

These entities provide services to compounding pharmacists ranging from selling only compounding aids to providing only chemicals. Others offer additional services to include formulas as well as consulting expertise by telephone or via the internet. This service can assist in the process of compounding a particular product that may be difficult.

TRAINING AND EXPERIENCE—Pharmacists involved in upgrading and increasing the traditional aspects of extemporaneous compounding need to keep current with all the new

tools of their trade, retrieve the old from storage, and put in a bit of practice using their scientific background and their art before they will be comfortable in exhibiting their skills. When considering providing additional services of compounding in an institution, pharmacists should not expect that this will change a great deal of their practice in time consumed for compounding. The majority of the time, pharmaceutical manufacturers do provide what patients need. They do an excellent job, as they have invested money and effort into research and development, and are entitled to the sales of products that they are approved to produce. The extemporaneous compounding by pharmacists meets the additional needs of patients that traditionally manufactured products do not meet.

Because there is an expectation that pharmacists can compound, there is a need that pharmacists be able to compound. Because of the decrease in instruction in compounding pharmacy in colleges of pharmacy, graduating pharmacists may not feel comfortable in their ability to compound. They can be advised to seek training if their practice may encompass compounding activities. The need for compounding training and experience is addressed by short courses, continuing education, increased curricular requirements, and apprenticeships. Additional training areas for compounding are needed to provide the experience needed to compound prescriptions accurately and safely. Many pharmacists who compound become actively involved in the practicums and rotations of the colleges of pharmacy in their respective states.

Only properly educated pharmacists should be involved in pharmaceutical compounding. If pharmacists wish to compound, but do not possess the required techniques or skills, they should participate in continuing professional education programs that have been designed to train them properly, including the scientific basis and practical skills necessary for sound, contemporary compounding.

EQUIPMENT—The equipment needed will be determined by the type and extent of the services one chooses to provide. Many pharmacies already have clean air environments (eg, laminar air flow hoods, isolation barrier systems) where aseptic compounding of sterile solutions is performed. These same units can be used to compound other sterile preparations such as eye drops. A balance, preferably electronic, is essential. Ointment slabs (ie, pill tiles), along with spatulas of different types and materials, should be purchased. A few mortars and pestles (ie, glass, ceramic, plastic) and some glassware should be secured. It may not be necessary to buy a roomful of equipment, but one should purchase what is needed to start the service and should build on it as the service grows and expands to different arenas.

Much of the equipment used today in compounding has changed. Today, electronic balances are used more often than torsion balances; micropipets are commonplace; and ultrafreezers are sometimes required in addition to standard refrigerator freezers. This area is constantly changing and the compounding pharmacist should be aware of the available technology to prepare accurate and effective prescriptions. Becoming acquainted with the local representative for a laboratory supply company is helpful.

ENVIRONMENT—A separate area for traditional compounding is recommended, rather than simply cleaning off a small area of the dispensing counter. The compounding pharmacist needs a clean, neat, well-lit and quiet working area. If aseptic compounding is considered, a clean air environment (e.g., laminar air flow hood, isolation barrier system) should be used. The actual facility to be used depends on the level and volume of compounding to be done.

FORMULAS—Consistency of the compounded product is important. Formulas should be developed or obtained and tried to assure that each time an extemporaneous product is prepared, the methods used, ingredients added, and the order of steps is documented. This accomplishes three things. First, it provides the methodology for each person involved or requested to provide such service the information necessary to do so properly. Second, it provides consistency from batch to batch. Third, if the product does not turn out the way expected, a stepwise methodology exists for reviewing and determining what happened and if revisions and improvements are needed.

CHEMICALS AND SUPPLIES—If one is going to prepare a topical product, a vehicle (eg, cream, ointment, gel) and the active ingredients (eg, either finely ground product from an available tablet or injection or pharmaceutical-grade chemicals) would be required. One needs proper dispensing containers for the medication. In short, a relationship with providers that carry chemicals and supplies is important.

Pharmacists have been using chemicals and other materials for prescription compounding throughout history. In the past, these chemicals and materials have been obtained from natural products, raw materials, and household ingredients. Today, compounding pharmacists use chemicals from various reliable commercial sources, depending on their availability.

Some chemical companies place a disclaimer on their chemicals for various reasons, including, but not necessarily limited to

1. The companies do not want to be required to provide complete labeling of the materials as required by the *Food Drug and Cosmetic (FD&C) Act*; consequently, they state they are not to be used as drugs. This exempts the companies from having to comply with the FD&C regulations.
2. The source of the chemicals may not be companies meeting current Good Manufacturing Practices; consequently, when the drugs are repackaged, only selected information concerning the level of potency, impurities, and other miscellaneous characterization data is provided.
3. The disclaimer is to protect the companies from the use of their products without the full safety and effectiveness testing as required by the Food and Drug Administration (FDA) for drug products for manufacturing.

Historically, the *FD&C Act* has not applied to chemicals used for pharmaceutical compounding, but it does apply to chemicals used for manufacturing. The selection of the chemical source for compounding is a judgment call on the part of pharmacists. When selecting a supplier of compounding chemicals, certificates of analysis should be obtained and reviewed for purity, impurities, etc, as part of the decision-making process.

Chapter <795>, *Pharmacy Compounding*, in the USP 26/NF 21 is reprinted here as follows[10]:

"A USP or NF grade drug substance is the preferred source of ingredients for compounding all drug preparations. If that is not available, the use of another high-quality source, such as analytical reagent (AR) or certified American Chemical Society (ACS) grade, is an option for professional judgment. If the substance is not an official preparation or substance, additional information, such as a certificate of analysis, needs to be obtained by the pharmacist to ensure its suitability."

A manufactured drug product may be a source of active ingredient. Only manufactured drugs from containers labeled with a batch control number and a future expiration date are acceptable as a potential source of active ingredients. When compounding with manufactured drug products, the pharmacist must consider all ingredients present in the drug product relative to the intended use of the compounded preparation.

In summary, it is the responsibility of the pharmacist to select the *most-appropriate* quality of chemical for compounding, beginning with the USP/NF as the first choice and, if this is not available, then descending the list of purity grades (Table 105-1) using professional judgment and discretion. A certificate of analysis for the chemicals should be obtained and kept on file in the pharmacy for these selected chemicals.[10,11]

COMPOUNDING INFORMATION SOURCES

Numerous sources are now available for compounding information, including books, journals, pamphlets, brochures and elec-

Table 105-1. Description of Chemical Grades

GRADE	DESCRIPTION
Technical or commercial	Indeterminate quality
CP (chemically pure)	More refined, but still of unknown quality
USP/NF	Meets minimum purity standards; conforms to tolerances set by the SP/NF for contaminants dangerous to health
ACS reagent	High purity; conforms to minimum specifications set by the Reagent Chemicals Committee of the American Chemical Society
Analytical reagent	Very high purity
HPLC	Solvents purified for use in high-performance liquid chromatography (HPLC); very high purity
Spectroscopic grade	Very high purity
Primary standard	Highest purity; required for accurate volumetric analysis) (for standard solutions)

tronic media. Some of these reference sources should be accessible by compounding pharmacies, including the following:

1. **Pharmacy and medical libraries**
2. **References**
   Allen Jr LV. The Art, Science and Technology of Pharmaceutical Compounding, 2nd ed. Washington DC: American Pharmaceutical Association; 2002.
   Allen Jr LV, Popovich NG, Ansel HC. Pharmaceutical Dosage Forms and Drug Delivery Systems. Media, PA: Lippincott Williams & Wilkins, 2004.
   Merck Index. 13th ed. Whitehouse Station, NJ: Merck & Co, 2001.
   Remington: The Science and Practice of Pharmacy. 21st ed. Lippincott Williams and Wilkins, 2004.
   Trissel LA. Trissel's Stability of Compounded Formulations, 2nd ed. Washington DC: American Pharmaceutical Association; 2000.
   Trissel LA. Handbook on Injectable Drugs. Bethesda, MD: American Society of Health-Systems Pharmacists.
   United States Pharmacopeia 26/National Formulary 21. United States Pharmacopeial Convention, Rockville, MD, 2003.
3. **Journals**
   International Journal of Pharmaceutical Compounding
   Journal of the American Society of Health-System Pharmacists
   Lippincott's Hospital Pharmacy
   Pharmacy Times
   US Pharmacist
4. **Package insert information from pharmaceutical manufacturers**

COMPOUNDING TYPES

AMBULATORY-CARE COMPOUNDING—If individuals can walk, they are considered mobile or ambulatory (ie, they are not bedridden). Consequently, most pharmacists are involved in ambulatory care, and most ambulatory patients are *outpatients*. Actually, the term can also be applied to home-care patients and even institutionalized patients who are mobile. One general characteristic of ambulatory patients is that they are generally responsible for obtaining their own medication, storing it, preparing it (if necessary), and taking it.[12] It seems almost incongruous that in health care today as we become more aware that patients are *individuals*, respond as *individuals,* and must be treated as *individuals* that some health-care providers appear to be grouping patients into *categories*. They are grouped in categories for treatment, for reimbursement from a third party, or for determining levels of care in managed-care organizations and using *fixed-dose products* provided by pharmaceutical manufacturers that are available because the marketing demand is sufficiently high to justify their manufacture and production. Why should the availability or the lack of availability of a specific economically profitable commercially available product dictate the therapy of a patient?

Pharmacists have an opportunity to extend their activities in patient care as the emphasis continues to shift from inpatient care to ambulatory care. Ambulatory care, however, is so diverse and involves so many disciplines that sometimes it is difficult to understand it; and, it changes rapidly. Also, ambulatory care could generally encourage a team approach to health improvement, prevention, health maintenance, risk assessment, early detection, management, curative therapy, and rehabilitation.[13] Ambulatory care offers various opportunities for individualizing patient care through pharmaceutical compounding. In fact, it is the area where most compounding pharmacists practice.

Pharmacists' roles in ambulatory care patients can include, among others

1. Dispensing
2. Compounding
3. Counseling
4. Minimizing medication errors
5. Compliance enhancement
6. Therapeutic drug monitoring
7. Minimizing expenditures[12–14]

Most reimbursement for ambulatory patients comes from the dispensing or the compounding process. Little financial consideration is given to counseling, minimizing medication errors, compliance enhancement and therapeutic monitoring. However, these activities are important and should be performed. Because of the unique nature of compounded medications, counseling is an absolute must for these patients.

From the above discussion of the activities of ambulatory care pharmacists, it should be evident that extemporaneous compounding can be vitally important in ambulatory patient care.

HOSPITAL PHARMACY COMPOUNDING—The ever-present responsibility of the health-care industry is to provide the best available care for the patient, using the best means to do so, and providing that care in a conducive environment. This must be sufficiently economical to not put the institution in jeopardy of being unable to continue to provide the services to the community they serve. This requires cooperation on the part of the hospital administration, the medical staff, and the employees (nurses and pharmacists in particular as regards to medication usage) and must involve the patient. One of the effective means by which hospitals, and therefore hospital pharmacies, can meet these challenges is to consider expanding extemporaneous compounding services within the hospital pharmacy. Pharmaceutical care and pharmaceutical compounding can provide cost savings to the hospital while providing needed options to the physician through problem-solving approaches and stimulating the hospital pharmacist through new challenges that allow the expression of both their skills and their art.

Hospital pharmacists have always been actively involved in compounding, or producing medications for the patient. Daily intravenous (IV) therapy is provided through compounding of medications. Antibiotic piggybacks, total parenteral nutrition (TPN) solutions, IV additives, and many others are daily calculated, compounded, dispensed, and then generally administered by the nursing staff. The preparation of pediatric dosage forms has also been an area of extensive activity in some hospitals.

To assist hospital administrators in supporting the provision of extemporaneous compounding services, they should be aware that[15]

1. The patients' needs are better served
2. The economic implication is favorable to the institution, or at least no less favorable than other alternatives
3. The provision of such alternative care improves and does not detract from the image of the institution for the purpose of public relations

4. Making such services available enhances the abilities of the physician to meet the patients' specific needs
5. The services fall within regulatory guidelines
6. The pharmacy staff is capable of performing such services

Members of the hospital staff are constantly reading journal articles and are generally aware of innovative thought and practice by their peers. When physicians become aware of the skill, availability, and awareness of pharmaceutical compounding and that they can literally have almost any medication they need, in the form and strength they need for a specific situation, they generally request it more often. As the hospital pharmacy staff demonstrates their expertise and problem-solving skills, the medical staff consistently depends upon them.

Guidelines are essential in determining any changes that go on within a hospital pharmacy. Policies and procedures must be written to indicate the types of services that are made available. The two most important aspects to consider when making both the decision and the guidelines are[15]:

1. Keep intact the triad relationship. The medical staff (physician), the hospital staff (pharmacist and nurse), and the patient should all be informed of the decision to approach patient care by the use of institutionally compounded products. The patient is already aware that much of this occurs in the preparation of their TPN solutions or their IV antibiotic piggybacks. Patient awareness that the institution has recognized a special need they might have and that the institution is going the extra mile to meet those needs enhances public relations. The patient, recognizing that they are being treated as an individual, is receiving treatment benefit that may have a placebo effect in enhancing their improvement, especially when handled in a caring manner.
2. Do not overstep one's bounds. When products are commercially available to meet the needs of the institution, the patient, and the physician use them. When the physician desires a product that is different for any number of reasons than anything commercially available, then one should consider extemporaneous compounding.

In consideration of meeting patient specific needs, the hospital pharmacist must look at various modalities as potential solutions. When traditional hospital processes and procedures are not meeting the patient's need, extemporaneous compounding should be a consideration. Improving outcomes, getting patients well and out of the hospital as quickly as possible, should be the end goal. Individualized dosage forms, dosage strengths, and alternative routes of administration can often help attain these goals. There are many easily accessible organizations specializing in helping meet these needs. The public relations aspect of meeting these needs may enhance community support. Improving outcomes assists the medical staff by allowing them to spend their time dealing with new problems as hospital pharmacy meets the challenge of past problems. Nursing and pharmacy have the enhanced opportunity to use the skills they have developed and to provide opportunities for pharmacy to have more patient involvement and job satisfaction.

VETERINARY COMPOUNDING—The first symposium on veterinary compounding was a significant forum for discussion by experts and was a pivotal point in the history of veterinary compounding, occurring in September 1993.[16] The meeting was important because it assembled an impressive group of experts on veterinary compounding, who then set about explaining and defining the roles of the veterinarian and the pharmacist.

The FDA's interest in compounding by veterinarians dates back to the beginning of the1990s. The avowed purpose of the symposium was to provide a forum for a comprehensive, public debate in response to the American Veterinary Medical Association (AVMA) position on compounding prior to the issuance of the FDA *Compliance Policy Guide* on veterinary compounding. Numerous speakers presented views on (1) compounding by veterinarians, and (2) compounding for veterinarians by pharmacists. Topics such as conflicts of interest, lack of compounding training by veterinarians, the *new-drug* issue, and bioequivalency standards were discussed in detail.[16]

Veterinary compounding is necessary for many reasons. For example, with multiple species ranging from small to large it would be impossible to practice effective medicine without compounded products! Do we simply refuse to treat exotic species or small animals? Do we abandon oncology in veterinary medicine?

Also commented on was a more specific area of need: the lack of an ideal anesthetic drug, which has led veterinarians to devise anesthetic combinations inducing good-quality anesthesia, with minimal risk to the animal. Compounding is essential for safe and effective veterinary anesthetic practice. Veterinarians need to administer anesthetic drugs to a wide variety of animals with a wide variety of temperaments in settings that are less than ideal. They are called on to anesthetize elephants, gorillas, tigers, ostriches, sharks, horses, cows, and poisonous snakes, among others.

Other reasons why veterinary compounding is necessary included:

The necessity for multiple injections in the absence of a compounded multi-ingredient product
Rapid changes in management and disease problems in veterinary medicine
Problems associated with the treatment of large numbers of animals with several drugs within a short period
Cost-prohibitive factors associated with the large volume of some large-volume parenterals required for animals
The need for previously prepared antidotes for use in cases of animal poisoning

There are unique considerations involved with veterinary compounding compared with compounding for human patients. A few examples follow:

1. If compounding for food-producing animals, what is the potential effect on human health? Are appropriate "washout" times established to minimize exposure of the public to any drug residues in the animal?
2. There is a large variability in response to drugs by different animal species. It is sometimes difficult to find dosing information on a mg/kg basis.
3. Some animals cannot metabolize certain chemicals (cats cannot metabolize "benzoates").
4. There is a large difference in animal sizes from small birds to large elephants.
5. Flavoring is a unique problem with some finicky animals (eg, cats).
6. Selection of a dosage form for different animals can sometimes be challenging.
7. A "batch" of a compounded preparation may be 1000 pounds for a herd of animals.

The summarized ideas expressed at the aforementioned veterinary meeting were

- Veterinarians have a definite need for drug compounding
- Drug compounding was reported to be necessary in all areas of veterinary medicine
- The necessity of compounding poisoning antidotes (eg, sodium nitrite, sodium thiosulfate, methylene blue, or CaEDTA) was expressed

Compounding will continue to exist in the future for the same reason as it does now, to fulfill therapeutic needs in veterinary medicine, as well as in medicine for human patients. Difficulties and costs associated with the veterinary drug-approval process make compounding necessary to fulfill therapeutic needs not being met by the introduction of therapeutic agents.

An increasing interdependence between the veterinarian and the pharmacist is developing, resulting in higher standards of veterinary care. As to the future of compounding for veterinary patients, it was reported that

1. It is virtually inconceivable that there will ever be FDA-approved drugs labeled for every therapeutic need in every species of animal.
2. It appears that compounding for veterinary medicine will become more prevalent, as it has in human medicine, especially with the future introduction of biotechnology-derived products with limited stability.[16]

NUCLEAR PHARMACY COMPOUNDING—Nuclear pharmacy is a specialty practice of pharmacy that has been defined as a patient-oriented service that embodies the scientific knowledge and professional judgment required for improving and promoting health through assurance of the safe and efficacious use of radioactive drugs for diagnosis and therapy. Radioactive drugs, commonly referred to as radiopharmaceuticals, are a special class of drugs that are regulated by the FDA. They are unique in that they contain an unstable nuclide (radioactive nuclide) as a part of the compound designed to localize in an organ or tissue. Since radiopharmaceuticals are radioactive, the Nuclear Regulatory Commission or a similar state agency is involved in regulatory matters relevant to radiopharmaceuticals.

A nuclear pharmacist is expert at preparing (compounding) radiopharmaceuticals with Tc-99m sodium pertechnetate and reagent kits. The kits are multidose vials containing the compound to be *labeled* with the radioactive nuclide Tc-99m to create the radiopharmaceutical. The contents within the vial are sterile and pyrogen free as is the Tc-99m sodium pertechnetate. Most radiopharmaceuticals are administered intravenously so a nuclear pharmacist must be proficient at maintaining aseptic conditions during compounding.

The most common setting for the provision of radiopharmaceuticals by nuclear pharmacists is a commercially centralized nuclear pharmacy. Radiopharmaceuticals are generally prepared early in the morning and unit doses delivered to hospitals in the region surrounding the nuclear pharmacy. The nuclear pharmacy provides economic benefit to the hospital by use of all the doses of a radiopharmaceutical produced in a multidose vial plus reduction in space required for radiopharmaceutical preparation and radioactive waste containment. Other benefits include the availability of infrequently used radiopharmaceuticals, specialized products requiring extensive compounding, and the resources of pharmaceutical care available through professionals in nuclear pharmacy. Today there are several hundred commercial centralized nuclear pharmacies providing a significant fraction of radiopharmaceuticals used in nuclear medicine procedures. What started as limited service in large medical centers and universities by a few pharmacists with education beyond the entry-level pharmacy degree has grown to extensive services provided by several hundred first-professional-degree pharmacists. Truly a remarkable change in a time period of 20 to 25 years, resulting from dedicated entrepreneurs working to make a difference in patient care through quality products and pharmaceutical care.[17]

JOB SATISFACTION

Job satisfaction among independent community pharmacists who were classified as compounders and noncompounders has been measured.[18] Two previously validated survey instruments that measured job satisfaction were used with additional questions to determine the volume of compounded prescriptions the respondent dispensed. Questionnaires were mailed to randomly selected independent community pharmacists in the US and Canada with a response rate of 53.4% (n = 391).

The results indicate that pharmacists' job satisfaction levels may be improved if intrinsic factors are satisfied in their job role. Because prescription compounding provides satisfaction with several intrinsic factors such as variety, challenge, and use of skills, independent community pharmacists may improve their job satisfaction levels by providing prescription compounding services.

In the past 25 years, studies on pharmacist job satisfaction have provided descriptive information on job satisfaction or have attempted to assess the relationship between factors and job satisfaction. One factor that studies have shown positively influences pharmacist job satisfaction is the provision of clinical services by the pharmacist. From these clinical services, the following intrinsic job characteristics were identified:

1. Opportunities for self-expression and self-actualization
2. Autonomy
3. Variety
4. Skill
5. Responsibility
6. Feelings of confidence, pride and accomplishment

All of these characteristics can enhance an individual's satisfaction with job situations. Several of these intrinsic job characteristics describe the activities of those pharmacists who do compounding in their daily work tasks, and thus a study into the relation between job satisfaction and prescription compounding seemed warranted.

One of the responsibilities of a compounder requires that the pharmacist become actively engaged in the clinical assessment of a patient to assist the prescriber in determining the customized patient specific formula to be extemporaneously compounded. In addition, this responsibility requires the pharmacist to interact with prescribers and the patient as the customized formulation and dosage form are determined. The use of clinical skills and physician–patient interaction have been identified in previous studies as intrinsic factors that enhance a pharmacist's job satisfaction. Therefore, a compounder using clinical skills and interacting with prescribers and patients may be predisposed to a higher job satisfaction than would be noncompounders whose responsibilities may not require such activities. The objective of the study was to determine and compare the job satisfaction of pharmacists who are classified as compounders and noncompounders.

This study supports findings of earlier studies that show that job satisfaction is influenced by pharmacist activities that include intrinsic job characteristics. Because a compounder is typically required to use his or her professional skills to meet the challenges of preparing a variety of formulations, such intrinsic job characteristics may have a positive influence on job satisfaction of compounders.

The two statistically and probably practical significant differences between compounders and noncompounders was in career satisfaction and overall job satisfaction. The professional challenges of the practice activities of a compounder (ie, prescriber–patient interaction to determine customized dosage form, art, and skill in compounding an elegant dosage form and patient monitoring) are intrinsic factors that may have influenced respondents' opinions.

REGULATIONS AND GUIDELINES[8]

Two documents are of special importance in providing guidelines and standards for pharmaceutical compounding; these include the:

1. *National Association of Boards of Pharmacy Good Compounding Practices Applicable to State Licensed Pharmacies, and*
2. USP 26/NF 21 Chapter <795>, *Pharmacy Compounding-Nonsterile Preparations* and Chapter <797>, *Pharmacy Compounding-Sterile Preparations,*

as well as numerous other portions of the USP/NF. Of these, the National Association of Boards of Pharmacy *Good Compounding Practices Applicable to State Licensed Pharmacies* and a summary of the USP/NF Chapters <795> and <797> will be discussed.

GOOD COMPOUNDING PRACTICES APPLICABLE TO STATE-LICENSED PHARMACIES—The following Good Compounding Practices (GCPs) are meant to apply only to the compounding of drugs by state-licensed pharmacies.

SUBPART A—GENERAL PROVISIONS The recommendations contained herein are considered the minimum current good compounding practices for the preparation of drug products by state-licensed pharmacies for dispensing or administration to humans or animals.

The following definitions from the *NABP Model State Pharmacy Act* apply to these GCPs. States may wish to insert their own definitions to comply with *State Pharmacy Practice Acts*.

Compounding—The preparation, mixing, assembling, packaging, or Labeling of a Drug or Device (i) as the result of a Practitioner's Prescription Drug Order or initiative based on the Practitioner/patient/Pharmacist relationship in the course of professional practice, or (ii) for the purpose of, or as an incident to, research, teaching or chemical analysis and not for sale or Dispensing. Compounding also includes the preparation of Drugs or Devices in anticipation of Prescription Drug Orders based on routine, regularly observed prescribing patterns.

Manufacturing—The production, preparation, propagation, conversion or processing of a Drug or Device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or Labeling or relabeling of its container, and the promotion and marketing of such Drugs or Devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compounds for resale by pharmacies, Practitioners, or other Persons.

Component—Any ingredient intended for use in the compounding of a drug product, including those that may not appear in such product. Based on the existence of a Pharmacist/patient/Prescriber relationship and the presentation of a valid Prescription, Pharmacists may Compound, in reasonable quantities, Drug products that are commercially available in the marketplace.

Pharmacists shall receive, store, or use drug substances for compounding that have been made in an FDA-approved facility. Pharmacists shall also receive, store, or use drug components in compounding prescriptions that meet official compendia requirements. If neither of these requirements can be met, pharmacists shall use their professional judgment to procure alternatives.

Pharmacists may compound drugs in very limited quantities prior to receiving a valid prescription based on a history of receiving valid prescriptions that have been generated solely within an established pharmacist/patient/prescriber relationship, and provided that they maintain the prescriptions on file for all such products compounded at the pharmacy (as required by State law). The compounding of inordinate amounts of drugs in anticipation of receiving prescriptions without any historical basis is considered manufacturing.

Pharmacists shall not offer compounded drug products to other State-licensed persons or commercial entities for subsequent resale, except in the course of professional practice for a prescriber to administer to an individual patient. Compounding pharmacies/pharmacists may advertise or otherwise promote the fact that they provide prescription compounding services; however, they shall not solicit business (eg, promote, advertise, or use salespersons) to compound specific drug products.

The distribution of inordinate amounts of compounded products pursuant to a legitimate prescription out of state without a prescriber/patient/pharmacist relationship is considered manufacturing. Pharmacists engaged in the compounding of drugs shall operate in conformance with applicable State law regulating the practice of pharmacy.

SUBPART B—ORGANIZATION AND PERSONNEL As in the dispensing of all prescriptions, the pharmacist has the responsibility and authority to inspect and approve or reject all components, drug product containers, closures, in-process materials, labeling and the authority to prepare and review all compounding records to assure that no errors have occurred in the compounding process. The pharmacist is also responsible for the proper maintenance, cleanliness and use of all equipment used in prescription compounding practice.

All pharmacists who engage in compounding of drugs, shall be proficient in the art of compounding and shall maintain that proficiency through current awareness and training. Also, every pharmacist who engages in drug compounding must be aware of and familiar with all details of the Good Compounding Practices.

Personnel engaged in the compounding of drugs shall wear clean clothing appropriate to the operation being performed. Protective apparel, such as a coat/jacket, apron or hand or arm coverings, shall be worn as necessary to protect drug products from contamination.

Only personnel authorized by the responsible pharmacist shall be in the immediate vicinity of the drug compounding operation. Any person shown at any time (either by medical examination or pharmacist determination) to have an apparent illness or open lesion(s) that may adversely affect the safety or quality of a drug product being compounded shall be excluded from direct contact with components, drug product containers, closures, in-process materials and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of the products(s) being compounded. All personnel who normally assist the pharmacist in compounding procedures shall be instructed to report to the pharmacist any health conditions that may have an adverse effect on drug products.

SUBPART C—DRUG COMPOUNDING FACILITIES Pharmacies engaging in compounding shall have a specifically designated and adequate area (space) for the orderly placement of equipment and materials to be used to compound medications. The drug compounding area for sterile products shall be separate and distinct from the area used for the compounding or dispensing of non-sterile drug products. The area(s) used for the compounding of drugs shall be maintained in a good state of repair.

Bulk drugs and other materials used in the compounding of drugs must be stored in adequately labeled containers in a clean, dry area or, if required, under proper refrigeration.

Adequate lighting and ventilation shall be provided in all drug compounding areas. Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any compounded drug product. Adequate washing facilities, easily accessible to the compounding area(s) of the pharmacy, shall be provided. These facilities shall include, but not be limited to, hot and cold water, soap or detergent, and air-driers or single-use towels.

The area(s) used for the compounding of drugs shall be maintained in a clean and sanitary condition. It shall be free of infestation by insects, rodents and other vermin. Trash shall be held and disposed of in a timely and sanitary manner. Sewage, trash and other refuse in and from the pharmacy and immediate drug compounding area(s) shall be disposed of in a safe and sanitary manner.

Sterile Products/Radiopharmaceuticals—If sterile (aseptic) products are being compounded, conditions set forth in the *NABP Model Rules for Sterile Pharmaceuticals* must be followed.

If radiopharmaceuticals are being compounded, conditions set forth in the *NABP Model Rules for Nuclear/Radiologic Pharmacy* must be followed.

Special Precaution Products—If drug products with special precautions for contamination, such as penicillin, are involved in a compounding operation, appropriate measures, including either the dedication of equipment for such operations or the meticulous cleaning of contaminated equipment prior to its return to inventory, must be used in order to prevent cross-contamination.

SUBPART D—EQUIPMENT Equipment used in the compounding of drug products shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance. Equipment used in the compounding of drug products shall be of suitable composition so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond that desired.

Equipment and utensils used for compounding shall be cleaned and sanitized immediately prior to use to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product beyond that desired. In the case of equipment, utensils and containers/closures used in the compounding of sterile drug products, cleaning, sterilization and maintenance procedures as set forth in the *NABP Model Rules for Sterile Pharmaceuticals* must be followed.

Previously cleaned equipment and utensils used for compounding drugs must be protected from contamination prior to use. Immediately prior to the initiation of compounding operations, they must be inspected by the pharmacist and determined to be suitable for use.

Automatic, mechanical or electronic equipment, or other types of equipment or related systems that will perform a function satisfactorily may be used in the compounding of drug products. If such equipment is used, it shall be routinely inspected, calibrated (if necessary) or checked to assure proper performance.

SUBPART E—CONTROL OF COMPONENTS AND DRUG PRODUCT CONTAINERS AND CLOSURES Components, drug product containers and closures, used in the compounding of drugs shall be handled and stored in a manner to prevent contamination. Bagged or boxed components of drug product containers and closures used in the compounding of drugs shall be stored off the floor in such a manner as to permit cleaning and inspection.

Drug product containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the compounded drug beyond the desired result. Components, drug product containers and closures for use in the compounding of drug products shall be rotated so that the oldest stock is used first. Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the compounded drug product. Drug product containers and closures shall be clean and, where indicated by the intended use of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use.

Drug product containers and closures intended for the compounding of sterile products must be handled, sterilized, stored, etc in keeping with the *NABP Model Rules for Sterile Pharmaceuticals*. Methods of

cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures used in the preparation of sterile pharmaceuticals, if these processes are performed by the pharmacist, or under the pharmacist's supervision following *the NABP Model Rules for Sterile Pharmaceuticals*.

SUBPART F—DRUG COMPOUNDING CONTROLS There shall be written procedures for the compounding of drug products to assure that the finished products have the identity, strength, quality and purity they purport or are represented to possess. Such procedures shall include a listing of the components (ingredients), their amounts (in weight or volume), the order of component addition and a description of the compounding process. All equipment and utensils and the container/closure system, relevant to the sterility and stability of the intended use of the drug, shall be listed. These written procedures shall be followed in the execution of the drug compounding procedure.

Components for drug product compounding shall be accurately weighed, measured or subdivided as appropriate. These operations should be checked and rechecked by the compounding pharmacist at each stage of the process to ensure that each weight or measure is correct as stated in the written compounding procedures. If a component is removed from the original container to another (eg, a powder is taken from the original container, weighed, placed in a container and stored in another container) the new container shall be identified with the:

(a) component name, and
(b) weight or measure.

To assure the reasonable uniformity and integrity of compounded drug products, written procedures shall be established and followed that describe the tests or examinations to be conducted on the product being compounded (e.g., compounding of capsules). Such control procedures shall be established to monitor the output and to validate the performance of those compounding processes that may be responsible for causing variability in the final drug product. Such control procedures shall include, but are not limited to, the following (where appropriate):

(a) capsule weight variation;
(b) adequacy of mixing to assure uniformity and homogeneity;
(c) clarity, completeness or pH of solutions.

Appropriate written procedures designed to prevent microbiological contamination of compounded drug products purporting to be sterile shall be established and followed. Such procedures shall include validation of any sterilization process.

SUBPART G—LABELING CONTROL OF EXCESS PRODUCTS In the case where a quantity of a compounded drug product in excess of that to be initially dispensed in accordance with Subpart A is prepared, the excess product shall be labeled or documentation referenced with the complete list of ingredients (components), the preparation date, and the assigned expiration date based upon professional judgment, appropriate testing, or published data. It shall also be stored and accounted for under conditions dictated by its composition and stability characteristics (eg, in a clean, dry place on a shelf or in the refrigerator) to ensure its strength, quality and purity.

At the completion of the drug finishing operation, the product shall be examined for correct labeling.

SUBPART H—RECORDS AND REPORTS Any procedures or other records required to be maintained in compliance with these Good Compounding Practices shall be retained for the same period of time as each State requires for the retention of prescription files.

All records required to be retained under these Good Compounding Practices, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection.

Records required under these Good Compounding Practices may be retained either as the original records or as true copies, such as photocopies, microfilm, microfiche or other accurate reproductions of the original records.

USP 26/NF 21—The following are summaries of Chapters <795>, *P*harmacy Compounding-Nonsterile Preparations[10], and <797>, Pharmacy Compounding-Sterile Preparations[11], in the USP/NF.

Chapter <795>—This material is divided into (1) Compounding Environment, (2) Stability of Compounded Preparations, (3) Definitions, (4) Ingredient Selection and Calculations, (5) Checklist for Acceptable Strength, Quality and Purity, (6) Compounded Preparations, (7) Compounding Process, (8) Compounding Records and documents, (9) Quality Control and (10) Patient Counseling.

The Compounding Environment section discusses the standards for the facility and the equipment that is used. Both should be adequate and appropriate for the compounding activities that will be performed. The area should be separate from other functions that occur in the pharmacy and should be maintained in a clean and sanitary condition.

The Stability of Compounded Preparations section has been previously discussed in this chapter. Special attention is given to the "Beyond-Use Labeling that is required for compounded preparations.

The Definitions include terms such as preparation(s), official substance(s), active ingredient(s) and added substances.

Ingredient Selection and Calculations discuss the sources of the ingredients, a topic that has also been covered in this chapter along with the compounding of non-drug preparations. The calculations area is a brief summary of what is involved to obtain, theoretically, 100% of the amount of each ingredient in compounded preparations.

The Checklist for Acceptable Strength, Quality and Purity emphasizes the USP/NF hallmarks of standards of acceptable Strength, Quality, and Purity and is presented in a series of questions to be answered.

Compounded Preparations discusses examples of compounded dosage forms along with some precautionary statements as appropriate. Some of the dosage forms discussed include tips on compounding procedures.

The Compounding Process section is a step-by-step presentation on the compounding process to ensure uniformity of activities in preparing each formulation.

Compounding Records and Documents describes the *Formulation Record*, the *Compounding Record*, and the *Material Safety Data Sheets* (MSDS) files that should be maintained. The rationale and purpose of the documents is explained.

Quality Control is included to ensure the accuracy and completeness of the compounding process. Compounded preparations must meet the USP/NF standards and the pharmacist should review each procedure in the compounding process as a final check.

The section ends with various aspects for Patient Counseling involving the proper use, storage, and evidence of instability of the compounded preparation(s).

Chapter <797>—involves procedures and requirements for compounding sterile preparations (CSPs). This chapter has been completely revised, formerly known as Chapter <1206> Sterile Drug Products for Home Use. It is divided into the following sections: (1) Introduction, (2) Responsibility of Compounding Personnel, (3) CSP Microbial Contamination Risk Levels, (4) Compounding Accuracy and Sterilization, (5) Personnel Training and Evaluation in Aseptic Manipulation Skills, (6) Environmental Quality and Control, (7) Processing, (8) Verification of Automated Compounding Devices for Parenteral Nutrition Compounding, (9) Finished Preparation Release Checks and Tests, (10) Storage and Beyond-Use Dating, (11) Maintaining Product Quality and Control After the CSP Leaves the Pharmacy, (12) Patient or Caregiver Training, (13) Patient Monitoring and Adverse Events Reporting, and (14) The Quality Assurance Program.

The Introduction discusses the intent and organization of the chapter and emphasizes that it is the ultimate responsibility of all personnel who prepare CSPs to understand these fundamental practices and precautions and to develop and implement appropriate procedures.

The section on the Responsibility of Compounding Personnel discusses the various procedures, requirements, and performance responsibilities of those involved in compounding sterile preparations.

CSP microbial Contamination Risk Levels includes a discussion on the various risk levels determined by the corresponding probability of contaminating a CSP with (1) microbial contamination, and (2) chemical and physical contamination. Three risk levels are identified; Low, Medium and High. The characteristics described for each level are intended as a guide to the breadth and depth of care necessary in compounding. The section discusses the conditions, examples and quality assurance associated with each risk level.

Verification of Compounding Accuracy and Sterilization includes a discussion of the methods of sterilization (filtration, steam) and their characteristics and requirements.

Personnel Training and Evaluation in Aseptic Manipulation Skills describes the requirements for training of the personnel involved as well as how these individuals are validated in aseptic manipulations.

Environmental Quality and Control involves critical site exposure, clean rooms and barrier isolators, environmental controls, the CSP environment, cleaning and sanitizing the workspaces, personnel cleansing and gowning, suggested standard operating procedures and environmental monitoring.

Processing includes a discussion on aseptic technique, components, sterile ingredients and components, nonsterile ingredients and components, and equipment standards.

The compounding of parenteral nutrition preparations often involves automated devices, which are discussed in the Verification of Automated Compounding Devices for Parenteral Nutrition Compounding and includes sections on accuracy and precision.

Finished Preparation Release Checks and Tests describes physical inspection, compounding accuracy checks, sterility testing, bacterial endotoxin (pyrogen) testing and identity and strength verification of ingredients.

Storage and beyond use dating provides information on the determination of beyond-use dates for CSPs. The beyond-use dates for CSPs is associated with the end-product testing for these preparations as well as the monitoring of controlled storage areas.

The section on Maintaining Product Quality and Control After the CSP Leaves the Pharmacy discusses both sterile preparations for institutional use and packing and transporting CSPs. Topics included in these sections include packaging, handling and transportation, administration, education and training and storage in locations outside CSP facilities (in patients homes).

Patient or Caregiver Training provides detailed topics that should be a part of a training program to ensure the patient or caregiver understands and complies with the many special and complex responsibilities involving the storage, handling and administrations of CSPs.

Patient Monitoring and Adverse Events Reporting explains standards for monitoring patients and any adverse events that might occur, including the establishment of standard operating procedures for reporting these events.

The Quality Assurance section describes the standard of a formal program that is intended to provide a mechanism for monitoring, evaluating, correcting and improving the activities and processes involved with CSPs.

There are two additional General Chapters in the USP/NF prepared specifically for pharmacy compounding; <1160> Pharmaceutical Calculations in Prescription Compounding, and <1075> Good Compounding Practices.

USP General Chapter <1160> Pharmaceutical Calculations in Prescription Compounding is provided as a reference and review of pharmaceutical calculations that may be used in compounding pharmacies.[19] It discusses topics such as weighing, buffer solutions, dosage calculations, percentage concentrations, specific gravity, dilution and concentration, potency units, reconstitution, alligation, molar, molal and normal concentrations, milliequivalents and millimoles, isoosmotic solutions, flow rates in intravenous sets, temperature, and others related to pharmaceutical compounding.

USP General Chapter, <1075> Good Compounding Practices is designed to provide compounders with guidance on applying good compounding practices for the preparation of compounded formulations for dispensing and/or administration to humans or animals.[20] It covers definitions, responsibilities, training, procedures and documentation, drug compounding facilities, equipment, packaging and product containers, controls, labeling, records and reports, office-use compounding and the compounding of veterinarian products and pharmacy-generated products.

Numerous other General Chapters in the USP/NF are related to compounding and directly impact it, such as Chapters <1151> Pharmaceutical Dosage Forms, <1176> Prescription Balances and Volumetric Apparatus, <12191> Stability Considerations in Dispensing Practice, and <1231> Water for Pharmaceutical Purposes.

SUMMARY

Pharmacy compounding is providing pharmacists with a unique opportunity to practice their time-honored profession. It will become an even more important part of pharmacy practice in the future, including those involved in community, hospital, nursing home, home health care, veterinary, and other specialty practices. Pharmaceutical compounding is a practice in which the clinical expertise of pharmacists can be merged with the scientific expertise of pharmacists to make pharmaceutical care a reality.

Pharmacists should not hesitate to become involved in pharmacy compounding but should be aware of the requirements and uniqueness of formulating a specific drug product for a specific patient. This is an important component in providing pharmaceutical care. After all, without the pharmaceutical product, there is no pharmaceutical care.

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CHAPTER 106

Nuclear Pharmacy Practice

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Nuclear pharmacy (also referred to as radiopharmacy) is the specialty practice of pharmacy that focuses on the safe and efficacious use of radioactive drugs. Radioactive drugs, usually referred to as radiopharmaceuticals, constitute a special class of drugs according to the Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA), in Title 21 of the Code of Federal Regulations (CFR), defines a radioactive drug as a drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator that is intended to be used in the preparation of any such substance. From this definition, it is apparent that a radiopharmaceutical consists of both a drug component and a radioactive component. The drug component is responsible for localization in specific organs or tissues. The radioactive component is responsible for the emission of gamma rays for external detection in diagnostic imaging and/or particulate radiation for radionuclide therapy. Radioactive *in vitro* diagnostic kits for radioimmunoassays and brachytherapy sources for radiotherapy implants are classified by the FDA as devices, in contradistinction to radiopharmaceuticals which are classified as drugs.

A distinctive feature of radiopharmaceuticals, in contrast to traditional drugs, is their lack of pharmacological effects. Radiopharmaceuticals typically are employed as tracers of physiological functions. Their small amounts of mass produce negligible effects on biological processes, while their radioactivity allows noninvasive external monitoring or targeted therapeutic irradiation.

Some radiopharmaceuticals are simply salts of radioisotopes of elements (eg, I-131 sodium iodide, Tl-201 thallous chloride, Sr-89 strontium chloride[1]), but most radiopharmaceuticals consist of radioactive atoms attached to, or incorporated into, other chemical compounds that serve to carry the radioactive atoms to the intended tissues or organs. Some radiopharmaceuticals are manufactured and commercially marketed by pharmaceutical companies in their final, ready-to-use dosage forms. Because of their short half-lives, however, most radiopharmaceuticals require preparation of the final product either on-site, such as in a hospital, or in a local commercial nuclear pharmacy that then delivers the finished products to surrounding hospitals and clinics.

Radiopharmaceuticals can be categorized as either diagnostic or therapeutic. Diagnostic radiopharmaceuticals are intended for use in the diagnosis and/or monitoring of various disease states. Relatively small radiation doses are delivered, similar in magnitude to radiation doses from diagnostic X-ray procedures. Examples of diagnostic radiopharmaceuticals include Tc-99m diphosphonates for bone imaging procedures, Tc-99m macroaggregated albumin for lung imaging procedures, and Tl-201 thallous chloride for myocardial perfusion imaging procedures. Therapeutic radiopharmaceuticals, on the other hand, are intended for use in the treatment of various disease states. Relatively large radiation doses purposefully are delivered to cause localized radiation damage, similar in magnitude to radiation doses from teletherapy irradiation. A common example of a therapeutic radiopharmaceutical is I-131 sodium iodide for treatment of hyperthyroidism or thyroid cancer.

Radiopharmaceuticals are employed in the discipline termed "nuclear medicine." Nuclear medicine may be a separate unit or found as a part of radiology. In some situations, limited groups of radiopharmaceuticals may also be employed in specialty practices such as radiation oncology, cardiology, or endocrinology. In a diagnostic nuclear medicine procedure, the radiopharmaceutical is administered to the patient most often by IV injection, although sometimes by oral, inhalation, or other routes. The localization, disposition, and/or clearance of the radiopharmaceutical is then determined by detection of the radiation emitted from the radionuclide with a sophisticated instrument termed a "gamma camera." Obviously, the type of radiation detected is gamma, and the data exhibited by the detector will be an image or picture. Quantitative information can be obtained by using computers associated with the radiation detector. Normal versus abnormal images will vary depending upon the procedure. For example, a normal image with a radiopharmaceutical designed to be phagocytized by the liver will appear as a rather uniform uptake and distribution of the radiopharmaceutical throughout the liver. A space-occupying lesion such as a tumor lacks phagocytic cells so does not concentrate the radiopharmaceutical. Thus, the image of the liver will show a *cold* area (ie, an area with less radioactivity than the surrounding liver). The opposite effect will be noted in the case of a radiopharmaceutical designed to localize metastatic lesions in the bone. Excessive amounts of the radioactivity will occur in the area of the metastatic lesion, in comparison to the surrounding normal bone. This is termed a *hot* spot on the image.

The radionuclides typically used for radiopharmaceuticals employed in diagnostic nuclear medicine studies have short physical half-lives. Half-life is defined as the time that it takes for one-half of the radioactive atoms to undergo radioactive decay with emission of their characteristic radiation. For example, technetium Tc-99m has a physical half-life of 6.0 hr, so 100

[1] In practice, most radiopharmaceuticals usually are referred to by common names, such as abbreviated chemical names, rather than by nonproprietary drug names established by the United States Adopted Names Council (USAN).

units of radioactivity initially present would be 50 units of radioactivity 6 hr later. The shorter the half-life, the fewer total number of atoms necessary for the production of a given unit of activity, compared with a longer half-life radionuclide. Simply stated, the atoms for a short-half-life radionuclide do not exist very long before emitting their radiation. This allows a patient to receive fewer total atoms and increases the degree of safety for the patient while allowing the nuclear medicine procedure to be conducted satisfactorily. A rapid rate of decay and, thus, frequent radiation emission is further desirable for the efficient performance of these procedures, since the gamma camera must *see* a certain number of gamma rays to obtain sufficient data to create the desired image.

Because the radionuclides commonly employed in radiopharmaceuticals have short half-lives, most radiopharmaceuticals must be prepared on the day of use. This is accomplished most frequently with the aid of a nonradioactive reagent kit and radioactivity obtained from a radionuclide generator. The reagent kit is usually a multidose vial that contains the compound (ligand) to be labeled (ie, attachment of the radionuclide to the compound) and other components necessary to accomplish the labeling process and allow administration of the final product. The radionuclide generator most often employed is the technetium generator. The radionuclide technetium Tc-99m is produced by the decay of molybdenum Mo-99. Molybdenum-99 has a half-life of 67 hr and allows the generation of Tc-99m over a period of 1 to 2 weeks. The Tc-99m is separated from the Mo-99 by passing a sterile saline solution through a column containing the Mo-99 and the Tc-99m that has been generated. The Tc-99m eluate, in the chemical form of sodium pertechnetate, is collected in a sterile vial. Aliquots of this eluate are then used to prepare radiopharmaceuticals with the reagent kits.

Quality-control issues are important in this process. The possibility of the presence of Mo-99 in the eluate must be determined, because this radionuclide has a longer half-life, emits a more damaging form of radiation (beta), and is in the wrong chemical form. The half-life of Tc-99m is 6.0 hr, and only gamma radiation is emitted from these radioactive atoms. Gamma radiation is less likely to produce damage to cells than is beta or alpha radiation. The purity of the desired compound must be determined following preparation of the radiopharmaceutical with the sodium pertechnetate and a reagent kit. This generally is accomplished using paper or thin-layer chromatography procedures. A specified percentage of the radioactivity must be incorporated in the specified compound (ie, the radiopharmaceutical). If a significant fraction of the radioactivity remains as sodium pertechnetate, the radiopharmaceutical product will not distribute in the body as expected and might cause confusion or even an improper diagnosis.

A few radiopharmaceuticals are employed in the treatment of disease. Like diagnostic radiopharmaceuticals, these compounds are designed to localize in the diseased tissue. Instead of employing the emitted radiation to trace the distribution of the radiopharmaceutical as is done for diagnosis, however, the radiation is intended to destroy cells in the diseased area. The radiation deposits its energy in a very localized area and in a manner that leads to the enhanced probability of causing some deleterious effect to a key component of the cell such as DNA. Beta radiation is the most common type of radiation employed to treat diseases.

Perhaps the best known approach to therapy with a radiopharmaceutical involves the use of radioactive iodine, I-131, administered as sodium iodide to the patient. The I-131 is taken up by the thyroid gland and incorporated into thyroid hormones. Whereas small, diagnostic dosages of I-131 produce negligible biological damage, the beta radiation emitted by large, therapeutic dosages of I-131 destroys thyroid tissue. Depending upon the disease state, hyperthyroidism or cancer, the amount of radioactive iodide given to the patient varies considerably. The usual dosage ranges for treatment of hyperthyroidism (partial destruction) and thyroid carcinoma (total destruction) are 140 to 370 MBq (4–10 mCi) and 3700 to 5550 MBq (100 to 150 mCi), respectively. In contrast, less than 1 MBq (a few microcuries) of I-131 is given for diagnostic purposes. This is an important consideration when counseling a patient regarding the use of radioactive iodine for diagnostic procedures.

One of the more recent developments in oncologic nuclear medicine is the use of monoclonal antibodies labeled with a gamma-emitting radionuclide for diagnostic imaging and with a beta-emitting radionuclide for subsequent therapy. For example, ibritumomab, the parent murine monoclonal antibody of rituximab, selectively binds to the CD20 antigen found on the surface of B-lymphocytes and lymphatic tumor cells. When radiolabeled with gamma-emitting In-111, ibritumomab tiuxetan is used for diagnostic imaging in patients with non-Hodgkin's lymphoma; when radiolabeled with beta-emitting Y-90, ibritumomab tiuxetan is used for subsequent radioimmunotherapy of non-Hodgkin's lymphoma in these same patients.

To practice nuclear pharmacy, pharmacists must have specialized training in several areas such as nuclear physics, radiation detection instrumentation, radiochemistry, and radiation protection. An experiential component of this training in a practice setting is essential as well. The level of knowledge and experience necessary, as well as services provided, vary with the practice site. The majority of nuclear pharmacists practice in a commercial nuclear pharmacy. Most practitioners in this setting have a first professional degree, while nuclear pharmacists in an institutional site commonly have received an advanced degree (eg, an MS). The basic functions are similar; however, the pharmacist in the larger hospital may be more involved with clinical service, investigational products, and teaching. The pharmacist in a commercial nuclear pharmacy inherently spends considerable time preparing and dispensing radiopharmaceuticals, because one pharmacy generally services 10 to 15 different hospitals and clinics.

The main objectives of this chapter are to review the development of nuclear pharmacy and describe functions of a nuclear pharmacist regardless of the practice site. Regulatory restrictions and the specialized training required to practice nuclear pharmacy are addressed. The relevance of pharmaceutical care to nuclear pharmacy is considered as well as the importance of various diagnostic imaging modalities to the management of patients and to the assessment of therapeutic outcomes.

DEVELOPMENT OF NUCLEAR PHARMACY

Natural radioactivity was first observed in 1867 by Niepce de Saint-Victor, who noticed *fogging* in a silver chloride emulsion while working with uranium salts. He attributed this effect, however, to luminescence phenomena. While performing similar phosphorescence experiments in 1896, Antoine Henri Becquerel, now credited as the discoverer of radioactivity, noted that uranium emitted penetrating rays that were similar to the x-rays identified a year earlier by Wilhelm Roentgen. However, it was not until 1898, after Marie and Pierre Curie had determined that these emissions were originating from the unstable elements radium and polonium, that the phenomenon of radioactivity truly was recognized. By 1899, Ernest Rutherford had determined the existence of two distinct types of radiation, which he called alpha and beta. A year later, Paul Villard identified a third type of radiation, which was called gamma. The theory of radioactive disintegration was advanced in 1902 by Ernest Rutherford and Frederick Soddy. The discovery of artificially produced radioactive nuclides occurred on New Year's Eve, 1933, in an experiment conducted by Frederic Joliet and Irene Curie. They noticed that positrons continued to be emitted, but at an inverse exponential rate, following irradiation of aluminum foil with a polonium preparation. By the end of July 1934, Enrico Fermi had produced radioisotopes of 40 elements

by neutron bombardment. Also in 1934, Ernest O Lawrence invented the cyclotron and produced numerous radionuclides by bombarding stable atoms with artificially accelerated particles. In 1946, radionuclides produced in the Oak Ridge National Laboratory reactor were made widely available for biological and medical purposes.

Shortly after the discovery of radium, Henri Becquerel reported a skin burn received from a vial of radium that he carried in his pocket. Following additional experiments on his own skin, Pierre Curie suggested that the destructive biological effects from radium might have a possible medical use. Consequently, Paul Oudin first used an external source of radium in the treatment of uterine cervical cancer in 1904. By 1911, clinical trials using *Curie therapy* with parenteral injections of radium also were carried out in attempts to cure arthritis, lupus erythematosus, various cancers, and several other poorly defined diseases. Unfortunately, these initial attempts at internal therapeutic use of a radionuclide proved to be valueless and may have actually contributed to the induction of leukemia in some patients given very high doses. In 1938, following his brother's invention of the cyclotron, John Lawrence made the first clinical therapeutic application of an artificial radionuclide when he used P-32 to treat leukemia. By 1942, several investigators were using I-131 to treat hyperthyroidism, and successful treatment of thyroid cancer with I-131 was first reported in 1946.

The diagnostic use of radionuclides had its beginning in the development of the tracer concept, pioneered by Georg de Hevesy. In 1923, Professor de Hevesy used tracer principles for the first time by employing Pb-212 to study the absorption of lead nitrate in bean plants. In what was probably the first human application of a radionuclide in a diagnostic study, Herman Blumgart and associates, in 1927, determined the arm-to-arm circulation time in patients following an antecubital injection of Rn-222 in one arm and detecting its presence some time later in the other arm. The introduction of an improved radiation detector by H Geiger and W Müller in 1929 stimulated further *in vivo* applications using radioisotopes. Development of imaging devices during the 1950s and 1960s, including the rectilinear scanner, the scintillation camera, and the coincidence positron emission tomographic (PET) scanner, together with an explosive growth in radioisotope production and radiopharmaceutical development, propelled the clinical applications of radionuclides into the modern era of nuclear medicine.

The rapid increase in the medical use of radionuclides during these early years corresponded to the increased production and availability of radionuclides produced by cyclotrons and by nuclear reactors. Abbott Laboratories began marketing a line of radioactive pharmaceuticals in 1948. Two years later, the vice-chairman of the Joint Committee on Atomic Energy suggested that atomic energy should be a matter of concern to practicing pharmacists. In that same year, John E Christian, a professor of pharmacy at Purdue University, stated unequivocally that hospital pharmacists should be prepared to provide information and assistance in the establishment of radioisotope facilities and programs. In 1954, GB Hutchinson indicated that preparations containing radioactivity that are intended for human use are indeed pharmaceuticals and should fall under the purview of pharmacists. A report of the first Committee on Isotopes of the American Society of Hospital Pharmacists (ASHP), appointed in 1954, presented pictorially the first functional nuclear pharmacy in this country, established at the University of Chicago Clinics. In 1957, Captain William H Briner, a pharmacist at the National Institutes of Health (NIH), recognized the expanding applications of radiopharmaceuticals for the diagnosis of disease and the necessary involvement of pharmacists to ensure the formulation of radioactive chemicals into radioactive pharmaceuticals. After obtaining intensive training at the Oak Ridge National Laboratory, Captain Briner established a small unit in the NIH Pharmacy Department for the receipt, preparation, and control of radiopharmaceuticals. This was the second nuclear pharmacy established in the country and the longest still in existence (the first was closed after 1 year). For his many pioneering contributions to the field, Captain Briner often is referred to as the father of nuclear pharmacy practice.

With the advent of the Tc-99m generator in the late 1960s, a source of a versatile radionuclide became readily available to thousands of hospitals. As technetium was found to be complexed and chelated by numerous organ-specific compounds, pharmaceutical manufacturers began supplying reagent kits designed for the simplified preparation of Tc-99m-labeled radiopharmaceuticals. Technetium-99m radiopharmaceutical use spread rapidly, and pharmacists increasingly became involved in the preparation and dispensing of short-lived radiopharmaceuticals for human use. In 1969, the first postgraduate program in nuclear pharmacy was established by Walter Wolf at the University of Southern California. Other early university educational programs for nuclear pharmacy included Purdue, Michigan, Tennessee, and New Mexico. Although Purdue University did not initiate a formally designated program in nuclear pharmacy until 1972, John E Christian created the Department of Bionucleonics in the School of Pharmacy at Purdue in 1959. The focus of the department was education and research in radiotracer methodology. Several early leaders in nuclear pharmacy used their training in bionucleonics to develop radiopharmaceutical services.

The decade of the 1970s witnessed tremendous growth in nuclear medicine, new radiopharmaceuticals, and nuclear pharmacy. Institutional nuclear pharmacies were established at many academic/tertiary medical centers. In 1972, the first commercial nuclear pharmacy was created in Albuquerque, NM, by Richard Keesee, an assistant professor in the University of New Mexico College of Pharmacy. The facility was affiliated with the College of Pharmacy and located in the Bernalillo County Medical Center. Sixteen hospitals in the city of Albuquerque and surrounding cities in New Mexico were serviced by the nuclear pharmacy. The nuclear pharmacy also served as a teaching facility for the College's pharmacy students. Within a short time graduates from the program established commercial nuclear pharmacies in many major cities. Today, there are several hundred commercial nuclear pharmacies providing the major fraction of radiopharmaceuticals used in nuclear medicine procedures.

During this same decade, nuclear pharmacy matured and emerged as a true specialty in pharmacy practice. Nuclear pharmacists first met as a clearly recognized group on August 6, 1974, in Chicago at the *Nuclear Pharmacy '74* Symposium conducted under the auspices of the APhA's Academy of General Practice of Pharmacy. The Section on Nuclear Pharmacy in the APhA's Academy of General Practice of Pharmacy was established in 1975. In that same year, a Special Interest Group on Nuclear Pharmacy Practice was formed within the ASHP. Nuclear Pharmacy was recognized officially as a specialty in pharmacy practice, the first specialty so recognized, by the Board of Pharmaceutical Specialties in 1978. The first examination for board certification in nuclear pharmacy was administered on April 24, 1982, to 72 practitioners. More than 500 nuclear pharmacists have since become Board Certified Nuclear Pharmacists (BCNPs).

In the decades of the 1980s and 1990s, nuclear pharmacy saw fluctuating periods of maintenance and growth, as major changes in health care took place. Primarily related to cost considerations, there was a steady shift by hospitals from preparing radiopharmaceuticals in-house to purchasing radiopharmaceuticals as unit doses from commercial nuclear pharmacies. It is estimated that today 70–80% of all radiopharmaceutical doses are dispensed through commercial nuclear pharmacy channels. In a fashion similar to conventional retail pharmacy, commercial nuclear pharmacy has evolved from predominately independent pharmacies to major chains. Currently, there are approximately 350 commercial nuclear pharmacies in the US. Of these, approximately, 70% are

members of one of several chains, and the other 30% are independents.

Nuclear pharmacy remains a dynamic and vital field, which requires communication and networking. Dissemination of information is achieved through publication in professional newsletters, journals, and books and presentations at professional meetings. Nearly ubiquitous internet access allows rapid communication via e-mail and interactive group sites and provides unlimited opportunities for searching and retrieving specific information. "The Nuclear Pharmacy" web site, established in 1997 and continuously updated, serves as the unofficial site for the nuclear pharmacy profession.

PRACTICE OF NUCLEAR PHARMACY

The practice of nuclear pharmacy is composed of several domains related to the provision of nuclear pharmacy services. These domains, determined by formal task analyses, serve as the basic structure for the APhA's Nuclear Pharmacy Practice Guidelines (nee Standards). The Guidelines include lists of tasks and their related knowledge statements for each domain to aid in the further description and interpretation of nuclear pharmacy practice. Because of differences in practice setting, job responsibilities, and other factors, all of the Guidelines are not applicable to all nuclear pharmacists. Moreover, the Guidelines are not all-inclusive of this dynamic field. Hence, the pharmacist's professional judgment should be used when interpreting or applying the Guidelines.

The nine general domains involved in nuclear pharmacy practice are

1. Procurement
2. Compounding
3. Quality assurance
4. Dispensing
5. Distribution
6. Health and safety
7. Provision of information and consultation
8. Monitoring patient outcome
9. Research and development

Procurement of radiopharmaceuticals and other drugs, supplies, and materials necessary for nuclear pharmacy practice involves determining product specifications, initiating purchase orders, receiving shipments, maintaining inventory, and storing materials under proper conditions. Although these tasks appear similar to those involved in community and hospital pharmacy practice, special characteristics and requirements associated with radiopharmaceuticals present some unique demands. For example, radiopharmaceuticals or radioactive components, because of their short half-lives, are not available through conventional wholesalers; rather, they typically are ordered directly from the manufacturers.

Ordering of radiopharmaceuticals or radioactive components requires knowledge of calibration time, shipping/delivery schedule, and radioactive decay before receipt and use. Because of the necessity for overnight delivery, shipping charges are frequently a substantial portion of the acquisition cost for many radioactive items. Receipt of radioactive materials involves following regulatory procedures for opening packages, including performing surveys for radioactive contamination. Inventory control of radioactive materials is complicated by their distinctive, continuous radioactive decay; fortunately, repetitive manual calculations have been replaced by computer software programs developed for this purpose. Storage of radioactive materials must incorporate appropriate radiation shielding in addition to traditional requirements for light, temperature, and humidity.

Compounding of radiopharmaceuticals involves a wide variety of activities ranging from relatively simple tasks such as reconstituting reagent kits with Tc-99m sodium pertechnetate to complex tasks such as operating a cyclotron and synthesizing new radiochemical entities from raw materials. As with compounding activities performed by community and hospital pharmacists, compounding of radiopharmaceuticals requires receipt (or anticipation) of a valid prescription/drug order; appropriate components, supplies, and equipment; a suitable environment, especially for sterile dosage forms; appropriate recordkeeping, including written procedures and lot-specific information to ensure traceability; and validation or verification of the compounding procedure, storage conditions, and expiration.

Compounding of radiopharmaceuticals is complicated by the issues of radioactivity and of chemical reactions. Radioactivity during preparation and delay prior to patient administration must be addressed both in terms of radioactive decay (ie, exponential loss of radioactivity over time) and in terms of radiation protection (eg, shielding). Unlike the vast majority of traditional compounding, which involves mixing of ingredients, compounding of radiopharmaceuticals typically involves chemical reactions to *label* a molecule with a radionuclide. For most Tc-99m-labeled compounds, stannous reduction of Tc(VII) pertechnetate to a lower oxidation state is followed by chelation of technetium atoms by multidentate ligands. Chemical reactions involved for other radiopharmaceuticals include covalent bonding, transchelation, and coordination complexation.

The radionuclides used in compounding radiopharmaceuticals typically are obtained from three sources. Some radionuclides (eg, In-111, I-123) are purchased directly from the manufacturer; unfortunately, these tend to be expensive and have somewhat limited availability and shipment schedules. Some radionuclides (eg, F-18, C-11) are created on-site using a cyclotron; unfortunately, these tend to be expensive and on-site cyclotrons are available in only a limited number of facilities. Most radiopharmaceuticals use Tc-99m that is produced in, and eluted from, an on-site Mo-99/Tc-99m generator. Advantages of generator-produced Tc-99m are its relatively low cost, ready availability, and simplicity of use. However, because not all radiopharmaceuticals can be labeled with Tc-99m, other radionuclides obtained from the former two sources continue to be important.

The vast majority of radiopharmaceuticals are intended for parenteral administration; thus, aseptic technique is an important skill observed in nuclear pharmacy compounding and dispensing. Nuclear pharmacists also compound radiolabeled biologicals such as autologous blood cells, monoclonal antibodies, and peptides. Strict adherence to *universal precautions* (also referred to as standard precautions) and proper infection control handling is essential when radiolabeling patient blood cells, especially those obtained from patients harboring bloodborne pathogens (eg, hepatitis, human immunodeficiency virus, communicable microorganisms).

The term "compounding," as originally used in the Nuclear Pharmacy Practice Guidelines, referred to both preparation of radiopharmaceuticals according to manufacturer instructions and to extemporaneous compounding of products not commercially available. Section 127 of the Food and Drug Administration Modernization Act (FDAMA) of 1997[2] defined compounding in such a way that excluded mixing, reconstituting, or other such acts performed in accordance with directions contained in the approved product labeling. However, this section on pharmacy compounding expressly did not apply to radiopharmaceuticals. To proactively address issues related to radiopharmaceutical compounding, the APhA Section on Nuclear Pharmacy Practice established a Nuclear Pharmacy Compounding Practice Committee to develop a set of professional guidelines for the compounding of radiopharmaceuticals. These *Nuclear Pharmacy Compounding Guidelines* were approved and published in 2001. As described in these Guidelines, radiopharmaceutical compounding does not include mixing, recon-

[2] Section 127 of FDAMA 1997, which addressed application of federal law to the practice of pharmacy compounding, was nullified in 2002 by a US Supreme Court ruling in the case of Thompson, Secretary of Health and Human Services, et al. *v.* Western States Medical Center et al.

stitution, or other such acts performed in accordance with directions contained in the approved product labeling. Furthermore, these Guidelines advocate that radiopharmaceutical compounding does not include any deviation(s) from directions contained in approved product labeling which result in a final radiopharmaceutical product that is of the same quality and purity as that produced with adherence to the product labeling.

Compounding of PET radiopharmaceuticals requires more extensive controls and validation procedures than those for most other radiopharmaceuticals; hence, a supplemental document entitled *Nuclear Pharmacy Guidelines for the Compounding of Radiopharmaceuticals for Positron Emission Tomography* has been developed and published by the APhA. Similarly, a general chapter on *Radiopharmaceuticals for Positron Emission Tomography—Compounding* was published in the Eighth Supplement to USP 23 and has been included in subsequent revisions of the USP.

Quality assurance of radiopharmaceuticals involves performing the appropriate chemical, physical, and biological tests on radiopharmaceuticals to ensure the suitability of the products for use in humans. These activities include not only the completion of the test, but also interpretation of the results, evaluation of analytical test methods, calibration or functional checks of equipment and instruments used, and appropriate recordkeeping. Radiopharmaceuticals must meet all specifications described in their respective USP monographs, including such parameters as radionuclidic purity, radiochemical purity, chemical purity, pH, particle size, sterility, bacterial endotoxin, and specific activity. Often these standards are guaranteed by the manufacturer, but especially for compounded products and products for which preparation involves deviations from directions contained in their approved labeling, verification of purity specifications is the responsibility of the nuclear pharmacist.

Radionuclidic purity (ie, the fraction of radioactivity as the specified radionuclide) typically is determined by gamma spectroscopy or differential photon attenuation. A common example of a radionuclidic impurity is the presence of Mo-99 in a Tc-99m generator eluate. Radiochemical purity (ie, the fraction of the radionuclide in the specified chemical form) generally is determined by paper, thin layer, or column chromatography. A common example of a radiochemical impurity is Tc-99m pertechnetate in a Tc-99m-labeled product. Chemical purity (ie, specified amounts of nonradioactive chemicals) typically is determined by various chemical detection techniques such as color change when mixed with certain reagents. One example of a chemical impurity is aluminum (leached from the generator column) in a Tc-99m generator eluate. Hydrogen-ion concentration typically is determined with a pH meter or pH paper. Particle size of macroaggregated albumin products typically is determined by microscopic inspection of a sample placed on a hemocytometer slide. Sterility and bacterial endotoxin testing typically are performed using microbial growth media and Limulus Amebocyte Lysate methods, respectively. Specific activity (ie, ratio of radioactivity per mass) is calculated on the basis of radioactivity measurements and masses of components/products.

Dispensing radiopharmaceuticals occurs upon the receipt of a valid prescription or drug order from an authorized physician. In contrast to traditional pharmacy practice, radiopharmaceuticals are rarely dispensed directly to patients; rather, they are dispensed to hospitals or clinics for administration to patients by trained health professionals. Although multidose vials may be dispensed as a sort of *ward stock* system, radiopharmaceuticals generally are dispensed in *unit doses* ready for administration to the patient. In addition to radiopharmaceuticals, certain other drugs, such as those used in pharmacological intervention studies, frequently are dispensed by nuclear pharmacists.

The nuclear pharmacist is responsible for ensuring that the radiopharmaceutical dosage is not only consistent with the prescription order, but is also appropriate based on patient history and other factors such as age, weight, sex, surface area, and gamma camera sensitivity. Radioactive decay between preparation and dispensing times and between dispensing and administration times must be taken into account. Most of these calculations, historically done manually, routinely are incorporated in specialized computer software programs. Because most radiopharmaceuticals are parenteral products, the nuclear pharmacist must adhere to aseptic technique. With some radiopharmaceuticals, it is necessary for the nuclear pharmacist also to consider the total mass, the number of particles, or the amount of nonradioactive chemical that is present in the dispensed product. Radiopharmaceuticals also are subject to special labeling requirements such as inclusion of the standard radiation symbol and the words *Caution—Radioactive Material*.

Distribution of radiopharmaceuticals within an institution is subject to institutional policies and procedures, generally involving lead-lined boxes or other shielded containers labeled with identifying information. Distribution of radiopharmaceuticals from a commercial nuclear pharmacy to other institutions is subject to local, state, and federal regulations, including those promulgated by state boards of pharmacy, the Department of Transportation (DOT), and the Nuclear Regulatory Commission (NRC). These requirements generally relate to packaging, labeling, shipping papers, and other recordkeeping, as well as general issues related to shipper and carrier licensing and personnel training.

Health and safety are crucial elements of nuclear pharmacy practice. Radiation safety standards, including limits for radiation doses, levels of radiation in an area, concentrations of radioactivity in air and waste water, waste disposal, and precautionary procedures have been established and are enforced by the NRC. Although radiation protection may be the most visible and most regulated, other aspects of health and safety are also important. Hazardous chemicals, such as chromatography solvents, must be stored, handled, and disposed of using proper techniques, personal protective devices, containers, and environment. Biological specimens, such as blood samples obtained for preparation of labeled red cells or leukocytes, must be handled as potentially infectious, using *universal precautions*. Lastly, physical exertion, such as lifting heavy lead shields, must be done with appropriate care.

Provision of information and consultation is a highly important function of nuclear pharmacists. Employing oral and written communication skills, nuclear pharmacists convey their expert knowledge to physicians, technologists, other pharmacists, patients, and others. In addition to just reciting facts, the nuclear pharmacist should provide appropriate context and perspective so that the information is useful. Basic science information provided by nuclear pharmacists includes the biological effects of radiation, radiation physics, radiation protection, and radiopharmaceutical chemistry. Radiopharmaceutical product information provided by nuclear pharmacists includes radiopharmaceutical compounding and quality assurance, availability of radiopharmaceutical products, and radiopharmaceutical product defects. Radiopharmaceutical use information provided by nuclear pharmacists includes clinical applications of radiopharmaceuticals, radiopharmaceutical selection and dosing, pharmacological interventions and drug interactions associated with radiopharmaceuticals, adverse reactions to radiopharmaceuticals, and regulatory requirements. Such information may be of general applicability (eg, teaching), of organizational value (eg, policies and procedures), or of pertinence to the care of specific patients (eg, pharmaceutical care).

Monitoring patient outcome is an important component in the concept of pharmaceutical care. In a broad sense, this encompasses many different activities that, taken together, ensure optimal outcomes for individual patients. Within the scope of his or her practice, a nuclear pharmacist can assist in:

1. Ensuring that patients are appropriately referred to nuclear medicine.
2. Developing institutional standards for the rational use of radiopharmaceuticals and ancillary medications and conducting drug use evaluations for these drugs.

3. Prospectively screening patients regarding appropriate use of radiopharmaceuticals and ancillary medications.
4. Evaluating the safety and efficacy of radiopharmaceutical and ancillary medications.
5. Ensuring that patients receive proper preparation prior to receiving radiopharmaceuticals and ancillary medications.
6. Ensuring that appropriate interventions are used to enhance nuclear medicine procedures.
7. Ensuring that clinical problems associated with the use of radiopharmaceuticals or ancillary medications are prevented or recognized, investigated, and rectified.
8. Monitoring the safety and efficacy or outcomes of individual patients' drug regimens, surgical interventions, and other therapeutic measures using imaging modalities and radiometric technology.
9. Administering therapeutic or diagnostic radiopharmaceuticals and ancillary medications and performing nuclear medicine procedures.
10. Ensuring that information gained through the use of diagnostic radiopharmaceuticals is included as an integral component of a patient's therapeutic care plan.

While some of these activities (eg, conducting drug use evaluations) have an indirect impact on patient care, most have a direct impact on the care of the individual patients and, hence, their healthcare outcomes.

Research and development of new radiopharmaceuticals and clinical applications are vital for the viability and future growth of nuclear medicine and the nuclear pharmacy profession, let alone improvements in patient care. Nuclear pharmacist involvement may include participation in the development of new radiopharmaceuticals, including product design and laboratory testing. Similarly, nuclear pharmacists may participate in developing new compounding procedures or quality-control testing methods for existing radiopharmaceuticals. A frequent area of nuclear pharmacy involvement is participation in clinical trials of investigational radiopharmaceuticals and in the evaluation of new uses for existing radiopharmaceuticals. In addition, nuclear pharmacists often serve as members on institutional radiation safety and radioactive drug research committees.

REGULATIONS

Regulation of nuclear pharmacy practice has a fairly complex history due largely to the dichotomous nature of radiopharmaceuticals, which are viewed as both radioactive materials and as drug products. During the formative years of nuclear medicine, radiopharmaceuticals were controlled chiefly by the Atomic Energy Commission (AEC), because they typically contained *by-product* (ie, produced in a nuclear reactor) radionuclides. The 1954 Atomic Energy Act authorized the AEC to license the possession, use, and transfer of by-product materials, including radiopharmaceuticals. The AEC was replaced, in part, in 1975 by the NRC, which continues to have responsibility for licensing and other regulatory functions pertaining to by-product radioactive materials. Accelerator (eg, cyclotron) produced radionuclides have increasingly been used in radiopharmaceuticals. Because the NRC has authority to regulate by-product materials only, individual states are responsible for regulating accelerator-produced materials in a manner similar to their regulation of X-ray-producing machines. In addition, the NRC has entered into agreements with 34 states, referred to as *Agreement States,* whereby authority to control by-product materials has been transferred to the analogous state agencies. Hence, under the current regulatory scheme, the NRC regulates by-product materials only in non–agreement states, the non–agreement states regulate X-ray-producing machines and accelerator-produced materials only, and agreement states regulate all radioactive materials and X-ray-producing machines.

The primary responsibility of the NRC (and analogous state agencies) is to provide for the radiation safety of workers and the general public, to protect their health and minimize danger to life and property. In a series of chapters in Title 10 of the CFR, the NRC promulgates standards for radiation protection, licensing of facilities handling radioactive materials, the medical use of radioactive materials, and the packaging and transportation of radioactive materials. Each of these chapters has an impact on the practice of nuclear pharmacy. For example, 10 CFR Part 19 delineates requirements for providing instructions to workers regarding radiation safety practices, for reporting to workers their radiation exposures, and for notifying workers of their rights regarding inspections. 10 CFR 20 specifies radiation protection standards including maximum radiation dose limits to workers, the general public, and pregnant women; radiation monitoring of physical facilities and of personnel; proper use of radiation symbols, signs, and labels; receiving and opening packaging containing radioactive materials; and storage, control, and waste disposal of radioactive materials. 10 CFR 30 and 32 describe, respectively, rules involved with licensing for the handling and use of radioactive materials and for the manufacture and/or distribution of radioactive materials. Nuclear pharmacies, as commercial distributors of radioactive materials, are generally licensed pursuant to Part 32 regulations. 10 CFR 35 details requirements for the medical use of radioactive materials, including general administrative requirements for the radiation safety program; general technical requirements for maintenance and use of radiation instruments, for handling radiopharmaceutical dosages, for radiation surveys, for release of patients containing radioactive materials, and for storage and disposal of radioactive waste. 10 CFR 35 also details specific procedural requirements involved in the use of radiopharmaceuticals for uptake, dilution and excretion studies, for imaging and localization studies, and for therapy; training and experience requirements for radiation safety officer, authorized user physician, authorized medical physicist, and authorized nuclear pharmacist; and specific records and reports. 10 CFR 71 specifies standards for packaging of radioactive materials for transport.

An important philosophy mandated in these regulations is ALARA, an acronym for maintaining radiation exposures *As Low As Reasonably Achievable*. In practice, this means that management and workers must strive to keep radiation exposures well below maximum permissible limits. Typical ALARA goals are radiation exposures that are no more than 10% or 30% of the applicable limit, depending on type of worker activity. ALARA is achieved by judicious application of radiation protection principles (*viz,* time, distance, and shielding) and contamination control.

The regulation of radiopharmaceuticals as drug products has an interesting history. The enactment in 1962 of the Kefauver-Harris Amendments to the FD&C Act significantly increased federal control of the development, production, and premarket testing of drugs. These new requirements severely threatened the availability of radiopharmaceuticals, which many considered to be not *real drugs* because of their lack of pharmacological effects. This potential problem was averted, however, when the FDA promptly issued a temporary exemption for radioactive new drugs from these regulations, provided they were distributed in complete compliance with existing AEC regulations. The temporary exemption was rescinded, in part, in 1971 and subsequently totally revoked in 1975. Thereafter, radiopharmaceuticals have been regulated by the FDA in the same manner as all other drugs. This includes testing for safety and efficacy under Investigational New Drug (IND) provisions, approval for marketing drugs or biologicals through the New Drug Application (NDA) process, production under Current Good Manufacturing Practices (cGMPs), and information contained in labeling and promotional materials.

Although the legislative intent of the FD&C Act was that it would not interfere with the practices of medicine and pharmacy, the highly specialized practice of nuclear pharmacy led to confusion and uncertainty as to which compounding activities constituted manufacturing and which were included in the traditional practice of pharmacy. Hence, in 1984, the FDA published its *Nuclear Pharmacy Guideline: Criteria for Determin-*

ing When to Register as a Drug Establishment. In addition to common nuclear pharmacy preparation activities, such as those involving generator-produced Tc-99m and reagent kits, this FDA document specifically stated that a nuclear pharmacy that "operates an accelerator or nuclear reactor to provide radionuclides and radiochemicals to manufacture radioactive drugs to be dispensed under a prescription" does not have to register as a drug establishment. This statement has been especially important for the compounding of PET radiopharmaceuticals, whose short half-lives (eg, 2, 10, 20, and 110 minutes for O-15, N-13, C-11, and F-18, respectively) effectively preclude traditional bulk manufacturing and wide distribution and thus require preparation in close proximity to the location of use.

During the 1990s, as PET evolved from predominantly research applications to routine clinical use in patient care, the FDA began viewing the preparation of PET radiopharmaceuticals as being more complex, requiring special facilities and controls, compared to other radiopharmaceuticals. Hence, the FDA announced in 1995 that it intended to regulate PET radiopharmaceuticals as manufactured new drugs rather than as compounded products. The FDAMA of 1997 specifically addressed preparation of PET radiopharmaceuticals in its Section 121, authorizing FDA to develop procedures and requirements for cGMPs and for submission of new drug applications and abbreviated new drug applications specific for PET radiopharmaceuticals. At the time of this writing, FDA has developed draft proposed rules and guidance documents for PET radiopharmaceuticals, but finalization and implementation remain in process. Nonetheless, over the next few years, the preparation of PET radiopharmaceuticals is expected to transition from state-regulated professional compounding to FDA-regulated manufacturing.

With regard to non-PET radiopharmaceuticals, the FDAMA of 1997 expressly excluded radiopharmaceuticals from its Section 127 which dealt with pharmacy compounding.[2] The associated Conference Report stated that "nothing in [the radiopharmaceutical exclusion clause] is intended to change or otherwise affect the current law with respect to radiopharmaceuticals." Thus, it appears that the FDA's 1984 Nuclear Pharmacy Guideline continues to apply for the compounding of non-PET radiopharmaceuticals.

Radiopharmaceuticals, because of their radioactivity, also are classified as hazardous materials. Consequently, they are subject to regulation by a variety of other federal and state agencies. For example, the DOT regulates the transport of hazardous [radioactive] materials, the Occupational Safety and Health Administration (OSHA) regulates the handling of hazardous [radioactive] materials in the workplace, and the Environmental Protection Agency (EPA) regulates the disposal of hazardous [radioactive] waste.

Regulation of nuclear pharmacists also reflects the dichotomous nature of their practice involving radiopharmaceuticals as both radioactive materials and drug products. Nuclear pharmacy practice, being highly technical and specialized, has presented a rather unique challenge to the state boards of pharmacy. The National Association of Boards of Pharmacy (NABP) has assumed a leadership role in assisting individual state boards with guidance in this area. Since 1977, the NABP has published *Model Regulations for Nuclear Pharmacy,* a document that was developed and is maintained through timely revisions in consultation with the FDA, NRC, pharmacy professional organizations, and individual practicing nuclear pharmacists. Although variable, most state boards of pharmacy tend to follow, in large part, these NABP Model Regulations. One important part of these regulations is the recognition of a *Qualified Nuclear Pharmacist*. A recent version of the NABP Model Regulations contains the following definition:

"Qualified Nuclear Pharmacist" means a currently licensed Pharmacist in the State of practice, who is certified as a Nuclear Pharmacist by the State Board of Pharmacy or by a certification Board recognized by the State Board of Pharmacy, or who meets the following standards:

1. Minimum standards of training for "authorized user status" of radioactive material [cite State Radiation Control Agency or NRC licensure guide.].
2. Completed a minimum of 200 contact hours of instruction in nuclear pharmacy and the safe handling and the use of radioactive materials from a program approved by the State Board of Pharmacy, with emphasis in the following areas:
   a. radiation physics and instrumentation;
   b. radiation protection;
   c. mathematics of radioactivity;
   d. radiation biology; and
   e. radiopharmaceutical chemistry.
3. Attained a minimum of 500 hours of clinical nuclear pharmacy training under the supervision of a qualified nuclear pharmacist.

Nuclear pharmacists also are regulated with regard to handling of radioactive materials by the NRC and/or analogous state agencies. Initially, training and experience requirements to be named as an authorized user on a commercial nuclear pharmacy license were based on the criteria used for physicians or radiation safety officers. In 1994, the NRC revised its regulations to add a definition for *Authorized Nuclear Pharmacist* along with specific criteria for individuals to be recognized as such. The training requirements for an Authorized Nuclear Pharmacist established in 1994 were revised slightly by NRC in its 2002 revision of 10 CFR 35, and currently require an Authorized Nuclear Pharmacist to be a pharmacist who:

a. Is certified as a nuclear pharmacist by a specialty board whose certification process includes all of the requirements in paragraph b of this section and whose certification has been recognized by the Commission or an Agreement State; or

b.1. Has completed 700 hours in a structured educational program consisting of both:

Didactic training in the following areas–
- radiation physics and instrumentation;
- radiation protection;
- mathematics pertaining to the use and measurement of radioactivity;
- chemistry of byproduct material for medical use; and
- radiation biology; and

Supervised practical experience in a nuclear pharmacy involving–
- shipping, receiving, and performing related radiation surveys;
- using and performing checks for proper operation of instruments used to determine the activity of dosages, survey meters, and, if appropriate, instruments used to measure alpha- or beta-emitting radionuclides;
- calculating, assaying, and safely preparing dosages for patients or human research subjects;
- using administrative controls to avoid medical events in the administration of byproduct material;
- using procedures to prevent or minimize radioactive contamination and using proper decontamination procedures; and

b.2. Has obtained written certification, signed by a preceptor authorized nuclear pharmacist, that the individual has satisfactorily completed the requirements in paragraph b.1. of this section and has achieved a level of competency sufficient to function independently as an authorized nuclear pharmacist.

Prior to 1994, associated NRC regulations restricted radiopharmaceutical preparation and dispensing to FDA-approved products. However, along with the recognition of authorized nuclear pharmacists in its 1994 rule revisions, the NRC rescinded these restrictions to thereafter permit authorized nuclear pharmacists to prepare and dispense extemporaneously compounded radiopharmaceuticals in addition to commercially manufactured products.

Nuclear pharmacists who are involved in performing nuclear laboratory tests (eg, plasma and/or red cell volume determinations, Schilling tests for vitamin B-12 absorption) are subject to certain laboratory regulations. The Clinical Laboratory Improvement Amendments (CLIA) were passed by Congress in 1988 to establish quality standards for all laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results regardless of where the testing is performed. A laboratory is defined as any facility that performs

laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health. Implementation of the CLIA program, including inspection and certification of laboratories, is the responsibility of the Division of Laboratory Services of the Centers for Medicare and Medicaid Services (CMS).

EDUCATION AND CERTIFICATION

Nuclear pharmacists are specialists who must gain certain knowledge and skills beyond those of generalist practitioners. To aid educators and to ensure compliance with regulations regarding the training of nuclear pharmacists, documents have been prepared that describe the didactic knowledge base and the practice experience components that should be included in a nuclear pharmacy training program. The ASHP has developed standards for residency training in nuclear pharmacy. These standards include the qualifications of the training site, the nuclear pharmacy service, and the program director and preceptors, as well as the qualifications of the applicant. Standards for the residency program itself also are presented, including detailed goal statements and associated educational objectives in areas such as practice foundation skills, direct patient care, drug information and drug policy development, and practice management. The Section on Nuclear Pharmacy, APhA has prepared guidelines for the training of nuclear pharmacists. The guidelines encompass a detailed syllabus for didactic instruction in:

1. Radiation physics and instrumentation;
2. Mathematics of radioactivity use and measurement;
3. Radiation protection and regulations;
4. Radiation biology;
5. Radiopharmaceutical chemistry;
6. The clinical use of radiopharmaceuticals.

A detailed listing of experiential components also is described within the document, along with the suggested number of contact hours for each major area.

Pharmacists may receive the training necessary to enter the practice of nuclear pharmacy by several approaches. A few schools of pharmacy offer a series of undergraduate elective courses to fulfill the didactic requirement. Practice experience is attained either through a nuclear pharmacy within the school or through a summer internship program. Postgraduate education through an MS degree program or a residency in nuclear pharmacy provides another route by which a pharmacist can enter nuclear pharmacy practice. Many of the nuclear pharmacists in hospital practice have this type of educational background. A certificate program is another option by which a pharmacist can obtain the didactic training required by the NRC or State Board of Pharmacy. These are available through some schools of pharmacy and can vary in length from five consecutive weeks on site followed by experiential training to several months in which didactic and experiential training are intermixed. In some programs, the didactic coursework is available via videotapes or the internet, thus allowing the trainee the flexibility of learning at home or work and customizing his/her own schedule.

Regardless of the educational approach to training, nuclear pharmacists can demonstrate their competency by gaining certification in nuclear pharmacy. The Board of Pharmaceutical Specialties (BPS), established in 1976 by APhA, recognized nuclear pharmacy as the first specialty in pharmacy practice in 1978. Since 1982, the BPS has offered certification examinations in nuclear pharmacy, with successful applicants earning the status of Board Certified Nuclear Pharmacist (BCNP). Prerequisites for the certification examination include graduation from an accredited school of pharmacy, valid license to practice pharmacy, and at least 4000 hours of experience in nuclear pharmacy practice, of which:

- Up to 2000 hours may be obtained from nuclear pharmacy course work completed in academic settings;
- Up to 2000 hours may be obtained from nuclear pharmacy residency programs;
- Up to 2000 hours may be obtained from internships in licensed nuclear pharmacies or health-care facilities;
- Up to 4000 hours may be obtained from nuclear pharmacy practice in a licensed nuclear pharmacy or health-care facility.

Certification in nuclear pharmacy is issued for a period of 7 years. Recertification for an additional 7 years can be gained by successful completion of one of two processes, either by re-examination or by participation in a BPS-approved professional development (continuing education) program.

PHARMACEUTICAL CARE

Pharmaceutical care has been described as foundational to *generalist* practice. Moreover, pharmaceutical care typically has been defined as a practice in which the practitioner takes responsibility for a patient's *drug therapy* needs for the purpose of positive patient outcomes. Hence, on the surface, the *specialty* of nuclear pharmacy, which deals primarily with *diagnostic* radiopharmaceuticals, may appear to fall outside the precepts of pharmaceutical care. However, when viewed more broadly, many activities routinely performed by nuclear pharmacists directly or indirectly contribute to positive patient outcomes.

As noted in the introduction, nuclear medicine procedures are commonly employed to aid in the diagnosis of disease as well as to monitor therapeutic outcome. Both endeavors may be considered relevant to the concept of pharmaceutical care. Nuclear pharmacists and pharmacists in general provide pharmaceutical care through their knowledge of applications of radiopharmaceuticals in nuclear medicine. Bone imaging to stage cancer followed by monitoring of the course of therapy is an example of the importance of a nuclear medicine procedure to pharmaceutical care. Determination of the ejection fraction of the heart prior to and during the course of therapy with doxorubicin, to monitor the cardiotoxicity of the cancer chemotherapy agent, is another important application of nuclear medicine relevant to the role of a pharmacist in the care of a patient. Nuclear medicine procedures also are applied to patients with various types of cancer prior to and following surgical, radiation, and/or chemotherapy to monitor therapeutic response, detect residual or recurrent malignant disease, and to differentiate viable tumor from necrosis and scar.

The pharmacologic actions of therapeutic drugs frequently are used to increase the specificity or the sensitivity of nuclear medicine procedures as well as to reduce the time necessary to conduct certain procedures. These procedures are termed "drug intervention" or "pharmacological nuclear medicine" procedures. A few examples of therapeutic drugs used as interventions include sincalide and morphine sulfate in hepatobiliary imaging procedures, acetazolamide in cerebral blood flow imaging procedures, dipyridamole, adenosine, and dobutamine in myocardial perfusion imaging procedures, and furosemide and captopril in renal imaging procedures. Furosemide, for instance, is used to aid in the identification of a problem in the urinary tract. Following administration of a renally excreted radiopharmaceutical to the patient, a gamma camera monitors its accumulation in the renal collecting system. Once the collecting system is filled, furosemide is injected intravenously. If the problem in the collecting system is caused by a ureteral obstruction, most of the radioactive urine will remain in the collecting system. Conversely, if there is a nonobstructive condition, such as dilation of the renal pelvis due to prior urinary tract surgery or a previous obstruction, radioactive urine will flow out of the collecting system down the ureter to the bladder as a result of the diuretic action of the furosemide.

These interventional procedures, employing pharmacological drugs with radiopharmaceuticals, are useful in assessing

the need for surgery or other aggressive therapy versus a less drastic, more conservative medical treatment. The outcome of the procedures, as well as any subsequent follow-up procedures, will be very important in the management of the patient. The nuclear pharmacist can help develop protocols for drug intervention procedures. Dosing, storage, drug interactions, treatments for adverse reactions, and information on contraindications for interventional drugs are other traditional services that the nuclear pharmacist can provide. When several therapeutic drugs are available for the same interventional procedure, the nuclear pharmacist may become a member of the medical team responsible for selection of the optimal agent for the patient population or the individual patient.

While some therapeutic drugs are useful in nuclear medicine, others may adversely affect the localization and/or kinetics of the radiopharmaceutical. For example, drugs listed in Table 106-1 may decrease the thyroidal uptake of radioiodide given to a patient to determine thyroid function. If the drug reduces the amount of radioactivity taken up by the thyroid, a patient with hyperthyroidism might be underdiagnosed as having less severe disease or misdiagnosed as normal. This could lead to inadequate treatment of the patient's condition or, if the interference was recognized, delay appropriate treatment until valid testing could be repeated. The need to monitor for medications and other therapies prior to a bone imaging procedure is important also. As is noted in Table 106-2, unexpected organ uptake or a decrease in skeletal uptake of the bone-imaging radiopharmaceutical may occur from several different types of drugs or therapies administered to the patient before the nuclear medicine procedure.

The nuclear pharmacist provides pharmaceutical care by monitoring for interfering drugs and other factors prior to a nuclear medicine procedure or following the procedure if questions arise concerning unusual or unanticipated outcomes. Although nuclear pharmacists are not always present within the hospital or clinic, they may provide care by developing and sharing information with nuclear medicine personnel or hospital pharmacists involved in drug monitoring. Prescreening for potential problems can be helpful in preventing additional costs incurred by repeat procedures as well as limiting the radiation dose to the patient. Pharmaceutical care also is practiced by nuclear pharmacists when they utilize their knowledge of potential problems in the formulation, preparation, and dispensing of radiopharmaceutical products to prevent suboptimal results of nuclear medicine procedures due to product-related problems.

The basic clinical activities of a nuclear pharmacist are similar to those conducted by pharmacists in other areas of practice. The nuclear pharmacist is the product information specialist for nuclear medicine personnel and patients. In-service presentations on new products, drug information, and drugs or therapies that may compromise a nuclear medicine procedure are the responsibility of the nuclear pharmacist. Information on trade name versus generic products, chemical names, dosage forms, common dosages, and sources of products are provided by the nuclear pharmacist. Cost and availability are important considerations in nuclear medicine. This is especially true because of the short half-lives of radionuclides used in radiopharmaceuticals. Scheduling of patients and the timely availability of the radiopharmaceutical needed for the procedure are critical to conducting nuclear medicine services at an economically acceptable level. Counseling patients, ensuring discontinuation of medications or other therapies that may interfere with the biodistribution of a radiopharmaceutical, and individualized dosage calculations are examples of pharmaceutical care supplied by nuclear pharmacists.

The nuclear pharmacist must be aware of the route of elimination of a radiopharmaceutical and conditions that may adversely affect elimination. The status of kidney function (or dialysis therapy) can be of significance for radiopharmaceuticals eliminated by the kidneys. The bilirubin level may affect the elimination of radiopharmaceuticals employed in hepatobiliary procedures, such as those conducted in infants to distinguish biliary atresia from neonatal hepatitis. Radiopharmaceutical dosage calculations are important in such situations and, thus, constitute an important role for nuclear pharmacists. The potential absorbed radiation dose to the patient may be affected by the status of the route of elimination and, of course, pediatric versus adult population. Also, radiation dosimetry is of significance in radiation exposure to the fetus in the pregnant woman. A routine question for women of childbearing age is, "Are you pregnant or is there a possibility that you might be pregnant?" If the woman later found that she was pregnant or if the nuclear medicine procedure on a known pregnant woman is considered beneficial relative to the risk, the nuclear pharmacist can calcu-

Table 106-1. Drugs That May Decrease the Thyroidal Uptake of Radioiodide

Adrenocorticosteroids	Lugol's solution
Aminosalicylic acid	Meglumine diatrizoate
Androgens	Meprobamate
Anticoagulants (heparin, warfarin)	Methimazole
Antihistamines	Morphine
Antithyroid drugs	Para-aminosalicylic acid
Antitussives	Perchlorates
Benzodiazepines	Phenylbutazone
Cholecystographic agents (oral)	Phenytoin
Cimetidine	Propylthiouracil
Clioquinol	Resorcinol
Competing anions (Br^-, ClO_4^-, BF_4^-, SCN^-)	Salicylates
Corticotropin	Sodium diatrizoate
Epinephrine	Sodium nitroprusside
Estrogens	Sulfonamides
Expectorants (iodine-containing)	Sulfonylureas
Fluorides (inorganic)	Thiocyanates
Iodides (inorganic & topical)	Thiopental
Iodinated radiopaque contrast media	Thyroglobulin
Iodine tincture	Thyroid extracts
Iodine-containing collyria	Thyroxine
Iodoquinol	Tolbutamide
Liothyronine sodium	Sulfobromophthalein
Liotrix	Vitamin/mineral supplements
Lithium	

Table 106-2. Drugs and Therapies That May Affect the Disposition of Technetium-99m Phosphate and Diphosphonate Bone Agents

Unexpected organ uptake of the radiopharmaceutical due to the presence of	
Allopurinol	Methotrexate
Aluminum-containing antacids	Penicillamine
Amphotericin B	Pentamidine
Bleomycin	Radiation therapy
Calcium gluconate	Red blood cell transfusions
Cisplatin	Sodium diatrizoate
Cocaine	Sodium iothalamate
Cyclophosphamide	Stannous ions
Dextrose (intravenous)	Verapamil
Doxorubicin	Vincristine
Iron therapy	
Decreased bone uptake of the radiopharmaceutical due to the presence of	
Calcitonin	Indomethacin
Calcium	Iodinated contrast media
Corticosteroids	Parathyroid hormone
Dichloromethane	Iron therapy
Estrogens	Inorganic phosphates (enema)
Etidrenate disodium	
Ferrous salts	Steroid therapy
Glucocorticoids	Vitamin D_3

late the potential radiation dose to the fetus, knowing the specific organ distribution for the radiopharmaceutical, the dosage of radioactivity given, and the type of radiation emitted by the radionuclide, as well as other factors.

Nuclear pharmacists provide pharmaceutical care to breastfeeding women. There is concern for radiation exposure to the nursing child and increased exposure to the woman's breast from the radiopharmaceutical. Knowledge of the true risk is critical because the benefit of the procedure would be lost if the procedure was not conducted when the risk was minimal and, conversely, if the procedure was conducted when the risk was excessive in comparison to the benefit. The radiation risk to the child from ingestion of the radioactivity is influenced by many factors, such as the radiopharmaceutical, the characteristics of the radionuclide, the amount of radioactivity given to the mother, and the frequency and volume of feeding. Several guidelines, including NRC's Regulatory Guide 8.39, have been published that address the course of action to be taken, which may be interruption for a given time interval or total cessation of breastfeeding. Using patient-specific data and certain assumptions, the nuclear pharmacist can determine the appropriateness and applicability of these guidelines and formulate specific recommendations for individual patients.

Although documented adverse reactions to radiopharmaceuticals are comparatively rare, the nuclear pharmacist provides pharmaceutical care by monitoring for adverse reactions. Adverse reactions to radiopharmaceuticals, if they do occur, are usually mild and transient and require little medical treatment. The most common of these is a skin rash associated with Tc-99m diphosphonate bone agents. However, a few life-threatening reactions (eg, anaphylaxis) have been reported for some radiopharmaceuticals such as Tc-99m sulfur colloid. The nuclear pharmacist should ensure that epinephrine, pressor amines, corticosteroids, antihistamines, and advanced cardiopulmonary life-support systems are readily available in the unlikely event that a severe reaction was to occur. Also, the nuclear pharmacist can dispel unrealistic fears of allergic reactions to radiopharmaceuticals, such as a patient scheduled for a diagnostic thyroid procedure using radioactive iodine who has a history of reactions to iodinated X-ray contrast media or to seafood. In this instance, the nuclear pharmacist can reassure the patient that the radiopharmaceutical and iodinated X-ray contrast media are distinctly different in chemical structure and that the amount (mass) of radioactive iodine to be administered is only one millionth of the average daily ingestion of iodine from dietary sources.

Drug Utilization Evaluation (DUE) and Drug Utilization Review (DUR) are important functions for nuclear pharmacists, especially in a larger institutional setting. A prime example is associated with the nuclear medicine procedure employed to differentiate between an infarcted and ischemic condition in the heart. A radiopharmaceutical that localizes in myocardial muscle in proportion to coronary perfusion is injected during *stress,* commonly induced by graded exercise on a treadmill. Imaging is performed after this stress and also, separately, while the patient is in a resting state. Differentiation between an infarcted and an ischemic area can be obtained by comparison of images at rest and images at stress. If the patient has experienced a myocardial infarct, the damaged tissue will contain less radioactivity than the healthy tissue both when the heart is at rest and when it is stressed. If, however, the patient has ischemic heart disease, the affected area will appear normal at rest but will show significantly less than normal radioactivity at stress, because of stress-induced ischemia. The pharmacologically induced coronary vasodilatory effect of dipyridamole or adenosine can substitute for exercise stress in patients who are unable to exercise adequately. Patients who are elderly or obese, who have peripheral vascular disease or orthopedic problems, or who are on beta-blocker therapy are examples of candidates for pharmacological stress. In some of these patients, however, use of dipyridamole or adenosine is contraindicated due to severe bronchopulmonary disease, certain cardiac conduction disorders, or the presence of methylxanthines (eg, theophylline, caffeine). In such patients, cardiac stress can generally be achieved using dobutamine, whose pharmacologic effects include positive inotropic and chronotropic cardiac responses. The nuclear pharmacist can be extensively involved in DUE or DUR activities associated with these pharmacologic stress procedures.

With an increasing number of therapeutic radiopharmaceuticals being developed, marketed, and used, new opportunities are becoming available for nuclear pharmacists to provide pharmaceutical care to patients receiving radiopharmaceutical therapy. Expanded roles for nuclear pharmacists in these situations include activities such as calculating individual patient dosages, counseling patients regarding their therapy, and monitoring patients for adverse or toxic effects. Nuclear pharmacists can also determine patient eligibility for early release from the treatment facility, in compliance with NRC requirements,

based on patient specific measurements and calculations. Counseling of such patients regarding radiation safety precautions to be followed after release can also be provided by nuclear pharmacists.

Patient-specific pharmaceutical care presents a major challenge for nuclear pharmacists practicing in a commercial nuclear pharmacy. These pharmacists typically dispense unit dose radiopharmaceuticals to physicians in hospitals or clinics; they have little if any direct patient interaction and have only limited, if any, access to patient medical records. In most states, these nuclear pharmacists are exempted from mandatory requirements for patient counseling. Hence nearly all pharmaceutical care activities, either general or patient-specific, are undertaken indirectly through physicians and other healthcare providers. This situation could be improved by establishing convenient mechanisms for nuclear pharmacists to access patient information (eg, by electronic networking) and to communicate directly with patients (eg, video teleconferencing). Another viable approach could be to establish a close working relationship with one or more on-site hospital or clinic pharmacists. This partnering between an on-site pharmacist and a nuclear pharmacist specialist, somewhat analogous to a physician generalist consulting with a physician specialist, could be an efficient way for nuclear pharmacist specialists to provide enhanced pharmaceutical care to many more patients.

EXPANDED SERVICES

Nuclear pharmacists traditionally provide radiopharmaceuticals and professional services to nuclear medicine. However, some nuclear pharmacists have encouraged the expansion of services into other areas of medical imaging. Imaging modalities such as computerized tomography (CT), magnetic resonance imaging (MRI), ultrasound, and other radiographic procedures as well as nuclear medicine are used commonly to aid in the determination of a disease state and to monitor therapeutic outcomes. Each of these diagnostic imaging modalities often employs some form of *contrast agent* to enhance the utility of the imaging procedure. All of these contrast agents are classified as drugs. They have specified indications, contraindications, warnings, precautions, and dosages. They may cause adverse reactions ranging from minor to life-threatening effects, and may be involved in various drug interactions or otherwise interfere with subsequent procedures. Specific preparation for a patient, including pretreatment with certain drugs, prior to an imaging procedure may be necessary. Pharmacologic drug interventions may also be important in performing some of these imaging procedures. Patient counseling is another concern for those who conduct imaging procedures. Based on these drug-related issues, it is obvious that the services of a pharmacist should be provided to patients and personnel in diagnostic imaging areas. While the nuclear pharmacist may be the logical person to provide this service, the physical location and time constraints of many nuclear pharmacists do not allow the full extent of pharmaceutical care that should be provided. Nonetheless, even the nuclear pharmacist in a commercial nuclear pharmacy can serve as a valuable source of information and can partner with institutional pharmacists. Pharmacists in community and hospital settings can establish working relationships with nuclear pharmacists who can provide consultation in these areas.

Some nuclear pharmacists have also encouraged the expansion of services into therapeutic radiology or radiation oncology. For example, brachytherapy uses radioactive devices (also called sources) that are inserted into cancerous tissues to deliver localized radiation therapy. These radioactive devices are generally solids (eg, seeds or wires) but in some cases may be a liquid contained in a balloon. Nuclear pharmacists can be involved in providing device product services including ordering, storage, inventory, dosage assay, and dispensing. As applicable, nuclear pharmacists can determine patient eligibility for early release from the treatment facility, in compliance with NRC requirements, based on patient specific measurements and calculations and can provide counseling of such patients regarding radiation safety precautions to be followed after release.

SUMMARY

Nuclear pharmacy is a specialized practice of pharmacy focusing on radiopharmaceuticals. Nonetheless, the basic functions and responsibilities of the nuclear pharmacist are the same as those for others who practice pharmacy. The nuclear pharmacist is an expert in a specific class of drugs but also must remain current on all medications employed in the treatment of disease, especially those used for interventional studies, those that potentially interfere with nuclear medicine procedures, and those whose effectiveness or toxicity may be monitored by nuclear medicine studies. The knowledge and capabilities of a nuclear pharmacist build upon the basic skills and knowledge imparted to all pharmacists through the education required to enter the practice of pharmacy. The additional training needed to become a nuclear pharmacist can be attained by several routes. Although some nuclear pharmacists practice in a hospital setting, most nuclear pharmacists practice in commercial nuclear pharmacies that provide services to numerous nearby hospitals and clinics.

Pharmaceutical care activities are an important aspect of nuclear pharmacy practice. The majority of these activities are indirect, often performed in consultation with nuclear medicine staff. Direct, patient-specific pharmaceutical care is difficult for nuclear pharmacists practicing in commercial settings; in these situations, partnering between a nuclear pharmacist and an on-site pharmacist may be a viable option. Some nuclear pharmacists have also expanded their roles to provide services in other diagnostic imaging areas and in radiation oncology regarding contrast media drugs and radioactive devices for brachytherapy, respectively.

The specialty practice of nuclear pharmacy has been instrumental in leading pharmacy into the development and the recognition of specialties in pharmacy. The dedication of early pioneers and the support of professional pharmacy organizations have been of great significance in the development of nuclear pharmacy to the degree of excellence experienced today. Practitioners, educators, and other professionals are challenged by the past to build on and surpass the success of those that have gone before. As is true for all of pharmacy, the future of the profession cannot stand upon the past, but only on innovative care and services provided by those with a vision for the future.

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CHAPTER 107

Nutrition in Pharmacy Practice

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Practicing pharmacists are asked many questions about foods and nutrition, including specific questions about which products or supplements a client may be considering for purchase and what amount of a product to ingest. A review of basic nutrition and knowledge of dietary standards and guidance helps provide the pharmacist with sound information to supply the client.

NUTRITION 101

Nutrients are chemical substances found in food that are needed for life. The realization that nutrients are chemicals helps the pharmacist understand why there are interactions with drugs, which also are composed of chemicals. Putting together the chemicals from food and drugs is more potentially reactive because of the introduction into the complex system of the body.

There are over 40 different nutrients needed by the body for growth, reproduction, and maintenance of tissue and body regulations. For classification purposes nutrients are divided into six basic categories: proteins, carbohydrates, lipids, vitamins, minerals, and water. The only additional substance needed for life is oxygen. Nutrient groups providing kilocalories (kcal) and thus supplying a source of energy for the body are carbohydrates, proteins, and fat. The Dietary Reference Intakes lists a wide range of acceptable percent of total kilocalories for carbohydrate, 45–65%, for protein, 20–35%, and for fat, 10–35%. Currently in the average US diet, the percent of total kilocalories provided by carbohydrate, protein, and fat is approximately 50, 16, and 34, respectively with much individual variation due to personal diet patterns and behaviors. Another additional source of energy in the US diet is alcohol.

Each category of nutrients performs different, but interrelated, functions in the body. Carbohydrates provide kilocalories for energy and dietary fiber for bulk. Often divided into complex and simple, carbohydrates are found in many food groups, including grains, milk, fruits, and vegetables. Complex carbohydrates include starchy vegetables such as corn and potatoes, many foods prepared from grains such as breads, cereals and pastas and legumes, dried beans, and peas. Simple carbohydrates are the main sugars found in fruit, fructose, and in milk, lactose, and in foods made from sugar such as jellies and syrups. Proteins play the major role in growth, maintenance, and repair of body tissue. Protein can be used by the body to supply kilocalories when carbohydrates and fats are not supplied in adequate amounts, but this is not a desirable function of proteins. Proteins are supplied by both animal and vegetable sources. Animal sources include meats, poultry, fish, eggs, milk, and milk products such as cheese and yogurt. Vegetable sources include nuts, seeds, legumes and smaller amounts in grains and some vegetables. Lipids provide the primary source of kilocalories in the US diet. The term *lipid* is used to encompass both fats and oils, terms that simply indicate the nature of the lipid at room temperature. Fats are solids and oils are liquid at room temperature. Lipids provide essential fatty acids, are components of cell membranes, are involved in synthesis of some hormones, and surround and cushion internal organs as adipose tissue. Vitamins are organic compounds needed in small amounts to help the body function in normal growth, reproduction, and maintenance. They do not supply kilocalories but do facilitate chemical reactions that extract energy from the metabolism of carbohydrate, fat, and protein. Minerals function in a wide array of metabolic roles in the body ranging from enzyme components to electrolyte balance to providing structure for hard tissues. Vitamins and minerals are more fully discussed in Chapter 92. Water is also a nutrient and, next to oxygen, the most important substance needed for life. Approximately two-thirds of the weight of the body is water. Water is important in the proper removal of waste products from the body, is a component of body secretions, helps to regulate body temperature, and provides for lubrication of the body.

Nutrient needs are estimated by balance studies on both animals and humans that compare nutrient intake and excretion, by biochemical markers of a nutrient in the body components and excreta, and by clinical and physical evaluation of humans in both health and disease. Not all types of study are possible on humans; thus a variety of studies is used to estimate a single requirement or a range in the requirement for the nutrient. Nutrients can be consumed in quantities that are too little for good health, a range that is generally thought to be conducive to good health, and an amount, for some nutrients, that cannot only be detrimental to good health, but could be toxic to life. Current research is focused on identifying which nutrients and in what amount have a protective effect in preventing or reducing the risk of chronic diseases.

FOODS AND NUTRITION STANDARDS AND DIETARY GUIDANCE

DIETARY REFERENCE INTAKES—The Recommended Dietary Allowances (RDA) have been recognized universally as the standard for levels of nutrients recommended in the American diet. In 1997, new terminology was introduced and the

standards were expanded. Published by the Institute of Medicine, National Academy of Sciences, National Research Council, updated nutrient values will be released in the future as a series of reports over several years, versus one large report approximately every 10 years. The values will continue to serve as benchmarks for nutrient intakes for the American diet. It will be necessary for the pharmacist to understand the new terminology to best advise clients.

The term Dietary Reference Intakes (DRI) is used as a generic term to refer to four different sets of data. Estimated Average Requirements (EAR) is the intake that meets the estimated nutrient needs of half of the individuals in a specific life stage and gender group. This figure is to be used as a basis for developing an RDA for a nutrient and to be used by nutrition policymakers in the evaluation of the adequacy of nutrient intakes of the specific group and for planning how much a specific group should consume. The RDA will continue to be the intake that meets the nutrient need of almost all (97–98%) of the healthy individuals in a specific age and/or gender group. The RDA should be used in guiding individuals to achieve adequate nutrient intake aimed at decreasing the risk of chronic disease. It is based on estimating an average requirement plus an increase to account for the variation within a particular group.

Adequate Intake (AI) is used when sufficient scientific evidence is unavailable to estimate an average requirement. AIs can be used by individuals and professionals as a goal for intake when a RDA cannot be determined for the nutrient. The AI is derived through experimental or observational data that show a mean intake that appears to sustain a desired indicator of health. Tolerable Upper Intake Level (UL) is used to indicate the maximum intake by an individual that is unlikely to pose risks of adverse health effects in almost all healthy individuals in a specified group. The UL is not intended to be a recommended level of intake, and there is no established benefit for individuals to consume nutrients at levels greater than those given by the RDA or the AI.

The DRIs have been under continual revision since 1997, with electrolytes and water recommendations to be released in September 2003. Table 107-1 includes the most recent values for elements, Table 107-2 for vitamins, Table 107-3 for the macronutrients, and Table 107-4 for electrolytes and water.

DIETARY GUIDANCE—Numbers associated with the DRI standards, reported as grams, milligrams, and micrograms, are not easily interpreted to consumers unless they are related to food and a diet pattern. The practicing pharmacist needs to know acceptable guidelines that are consumer friendly to assist the client. Dietary guidance is meant to be individualized to the client, and it is the individualization that can take a simplistic educational tool and make it fit within an individual's complex need. Dietary guidance fosters time-honored concepts of good nutrition: variety, balance, and moderation. Variety refers to choosing different foods each day from within different food groups; balance refers to including foods from all food groups daily; and moderation refers to controlling serving size to allow for variety and balance within a kilocalorie allowance.

THE DIETARY GUIDELINES FOR AMERICANS AND THE FOOD GUIDE PYRAMID—The Dietary Guidelines for Americans[1] provide advice about nutrition and food choices related to disease prevention for healthy Americans age 2 years and older. The guidelines have been published every 5 years since 1980 by the US Department of Agriculture (USDA) and the US Department of Health and Human Services (DHHS). This standard is also helpful in advising clients with modified diets, as all diets, normal and modified, are based on the same general principles. The current edition of the Dietary Guidelines, released in 2000, is in Figure 107-1. There are 10 Dietary Guidelines, listed under three overall themes. It is intended that all 10 be used together to plan appropriate nutritional care for individuals and groups. The 2000 Dietary Guidelines for Americans include

Aim for Fitness . . .

- Aim for a healthy weight.
- Be physically active every day.

Build a Healthy Base . . .

- Let the Pyramid guide your food choices.
- Choose a variety of grains daily, especially whole grains.
- Choose a variety of fruits and vegetables every day.

Choose Sensibly . . .

- Choose a diet that is low in saturated fat and cholesterol and moderate in total fat.
- Choose beverages and foods to moderate your intake of sugars.
- Choose and prepare foods with less salt.
- If you drink alcoholic beverages, do so in moderation.

Words such as *variety*, *low*, and *moderate* have different meanings to different people. A review of each of the guidelines assists the practitioner in helping clients interpret this standard guidance. Specific issues of current debate are integrated within this review of the guidelines.

Aim for Fitness

AIM FOR A HEALTH WEIGHT—The 2000 edition of the Dietary Guidelines placed greater emphasis on the importance of maintenance of a healthy weight. The practicing pharmacist is asked multiple questions about weight gain and loss by consumers. These questions range from asking for interpretation of standards associated with weight to selection of products or programs to assist in weight gain or loss. Clients may be most comfortable with standard weight and height charts (Table 107-5), but a National Institutes of Health (NIH) panel suggests health care providers use the Body Mass Index (BMI) as a standard. The BMI is calculated by weight in kilograms divided by height in meters, squared. This measure minimizes the effect of height and correlates with other more precise measures of body fatness. The BMI standard is increasingly used in the professional and lay literature (Table 107-6).

Excess weight can be detrimental to good health, and the desire for weight loss is a major concern of many Americans. The current increase in the prevalence of overweight in the US is a major public health concern, particularly in children. Co-morbidities associated with excess weight include commonly known ones such as coronary heart disease (CHD), stroke, hypertension, diabetes mellitus, gout, dyslipidemias, cholecystitis, and gallstones. Less commonly known co-morbidities include obstructive sleep apnea, osteoarthritis of weight-bearing joints, reduced fertility, increased risk of accidents caused by less physical agility, and impaired obstetrical performance.

Pharmacists often are asked to help the consumer select specific food products or supplements advertised to assist with weight loss or gain, as these products are frequently available in the pharmacy setting. A well-balanced diet for weight loss should not require the purchase of any special product. In general, clients wishing to lose weight need professional advice if they wish to select any weight loss product or regimen. Table 107-7 lists NIH guidelines for choosing a weight-loss program, and Table 100-8 lists a means to analyze weight-loss approaches. The minimum number of servings of the Food Guide Pyramid provides approximately 1200 to 1400 kcal. This amount of kilocalories would be an acceptable weight-loss regimen for most adults.

BE PHYSICALLY ACTIVE EACH DAY—In the fall of 2002, the DRI report addressed activity for the first time. No doubt this was in response to the increasing public health concern regarding overweight and obesity. The recommendation is for one hour per day of total activity time, which correlates with

Table 107-1. Food and Nutrition Board, Institute of Medicine-National Academy of Sciences Dietary Reference Intakes: Elements

DIETARY REFERENCE INTAKES: ELEMENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Arsenic	No biological function in humans although animal data indicate a requirement	Infants	ND[b]	ND	Dairy products meat, poultry, fish, grains and cereal	No data on the possible adverse effects of organic arsenic compounds in food were found. Inorganic arsenic is a known toxic substance.	None
		0–6 mo	ND	ND			
		7–12 mo					
		Children					
		1–3 y	ND	ND			
		4–8 y	ND	ND			
		Males				Although the UL was not determined for arsenic, there is no justification for adding arsenic to food or supplements.	
		9–13 y	ND	ND			
		14–18 y	ND	ND			
		19–30 y	ND	ND			
		31–50 y	ND	ND			
		50–70 y	ND	ND			
		>70 y	ND	ND			
		Females					
		9–13 y	ND	ND			
		14–18 y	ND	ND			
		19–30 y	ND	ND			
		31–50 y	ND	ND			
		50–70 y	ND	ND			
		>70 y	ND	ND			
		Pregnancy					
		≤18 y	ND	ND			
		19–30 y	ND	ND			
		31–50 y	ND	ND			
		Lactation					
		≤18 y	ND	ND			
		19–30 y	ND	ND			
		31–50 y	ND	ND			
Boron	No clear biological function in humans although animal data indicate a functional role	Infants		(mg/d)	Fruit-based beverages and products, potatoes, legumes, milk, avocado, peanut butter, peanuts	Reproductive and developmental effects as observed in animal studies.	None
		0–6 mo	ND	ND			
		7–12 mo	ND	ND			
		Children					
		1–3 y	ND	3			
		4–8 y	ND	6			
		Males					
		9–13 y	ND	11			
		14–18 y	ND	17			
		19–30 y	ND	20			
		31–50 y	ND	20			
		50–70 y	ND	20			
		>70 y	ND	20			
		Females					
		9–13 y	ND	11			
		14–18 y	ND	17			
		19–30 y	ND	20			
		31–50 y	ND	20			
		50–70 y	ND	20			
		>70 y	ND	20			
		Pregnancy					
		≤18 y	ND	17			
		19–30 y	ND	20			
		31–50 y	ND	20			
		Lactation					
		≤18 y	ND	17			
		19–30 y	ND	20			
		31–50 y	ND	20			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-1. ***(continued).***

DIETARY REFERENCE INTAKES: ELEMENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Calcium	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation	Infants	(mg/d)	(mg/d)	Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli	Kidney stones, hypercalcemia, milk alkali syndrome, and renal insufficiency	Amenorrheic women (exercise- or anorexia nervosa-induced) have reduced net calcium absorption There is no consistent data to support that a high protein intake increase calcium requirement.
		0–6 mo	210*	ND[b]			
		7–12 mo	270*	ND			
		Children					
		1–3 y	500*	2,500			
		4–8 y	800*	2,500			
		Males					
		9–13 y	1,300*	2,500			
		14–18 y	1,300*	2,500			
		19–30 y	1,000*	2,500			
		31–50 y	1,000*	2,500			
		50–70 y	1,200*	2,500			
		>70 y	1,200*	2,500			
		Females					
		9–13 y	1,300*	2,500			
		14–18 y	1,300*	2,500			
		19–30 y	1,000*	2,500			
		31–50 y	1,000*	2,500			
		50–70 y	1,200*	2,500			
		>70 y	1,200*	2,500			
		Pregnancy					
		≤18 y	1,300*	2,500			
		19–30 y	1,000*	2,500			
		31–50 y	1,000*	2,500			
		Lactation					
		≤18 y	1,300*	2,500			
		19–30 y	1,000*	2,500			
		31–50 y	1,000*	2,500			
Chromium	Helps to maintain normal blood glucose levels	Infants	(μg/d)		Some cereals, meats, poultry, fish, beer	Chronic renal failure	Individuals with Wilson's disease, Indian childhood cirrhosis and idiopathic copper toxicosis may be at increased risk of adverse effects from excess copper intake.
		0–6 mo	0.2*	ND			
		7–12 mo	5.5*	ND			
		Children					
		1–3 y	11*	ND			
		4–8 y	15*	ND			
		Males					
		9–13 y	25*	ND			
		14–18 y	35*	ND			
		19–30 y	35*	ND			
		31–50 y	35*	ND			
		50–70 y	30*	ND			
		>70 y	30*	ND			
		Females					
		9–13 y	21*	ND			
		14–18 y	24*	ND			
		19–30 y	25*	ND			
		31–50 y	25*	ND			
		50–70 y	20*	ND			
		>70 y	20*	ND			
		Pregnancy					
		≤18 y	29*	ND			
		19–30 y	30*	ND			
		31–50 y	30*	ND			
		Lactation					
		≤18 y	44*	ND			
		19–30 y	45*	ND			
		31–50 y	45*	ND			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-1. *(continued).*

DIETARY REFERENCE INTAKES: ELEMENTS							
NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Copper	Components of enzymes in iron metabolism	Infants	(μg/d)	(μg/d)	Organ meats, seafood,nuts seeds, wheat bran cereals, whole grain products, cocoa products	Gastrointestinal distress, liver damage	None
		0–6 mo	200*	ND[b]			
		7–12 mo	220*	ND			
		Children					
		1–3 y	**340**	1,000			
		4–8 y	**440**	3,000			
		Males					
		9–13 y	**700**	5,000			
		14–18 y	**890**	8,000			
		19–30 y	**900**	10,000			
		31–50 y	**900**	10,000			
		50–70 y	**900**	10,000			
		>70 y	**900**	10,000			
		Females					
		9–13 y	**700**	5,000			
		14–18 y	**890**	8,000			
		19–30 y	**900**	10,000			
		31–50 y	**900**	10,000			
		50–70 y	**900**	10,000			
		>70 y	**900**	10,000			
		Pregnancy					
		≤18 y	**1000**	8,000			
		19–30 y	**1000**	10,000			
		31–50 y	**1000**	10,000			
		Lactation					
		≤18 y	**1300**	8,000			
		19–30 y	**1300**	10,000			
		31–50 y	**1300**	10,000			
Fluoride	Inhibits the initiation and progression of dental caries and stimulates new bone formation	Infants	(mg/d)	(mg/d)	Fluoridated water, teas, marine fish, fluoridated dental products	Enamel and skeletal fluorosis	None
		0–6 mo	0.01*	0.7			
		7–12 mo	0.5*	0.9			
		Children					
		1–3 y	0.7*	1.3			
		4–8 y	1*	2.2			
		Males	2*	10			
		9–13 y					
		14–18 y	3*	10			
		19–30 y	4*	10			
		31–50 y	4*	10			
		50–70 y	4*	10			
		>70 y	4*	10			
		Females					
		9–13 y	2*	10			
		14–18 y	3*	10			
		19–30 y	3*	10			
		31–50 y	3*	10			
		50–70 y	3*	10			
		>70 y	3*	10			
		Pregnancy					
		≤18 y	3*	10			
		19–30 y	3*	10			
		31–50 y	3*	10			
		Lactation					
		≤18 y	3*	10			
		19–30 y	3*	10			
		31–50 y	3*	10			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-1. ***(continued).***

DIETARY REFERENCE INTAKES: ELEMENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Iodine	Component of the thyroid hormones; and prevents goiter and cretinism	Infants	(μg/d)	(μg/d)	Marine origin, processed foods, iodized salt	Elevated thyroid stimulating hormone (TSH) concentration	Individuals with autoimmune thyroid disease, previous iodine deficiency, or nodular goiter and distinctly susceptible to the adverse effect of excess iodine intake. Therefore, individuals with these conditions may not be protected by the UL for iodine intake for the general population.
		0–6 mo	110*	ND[b]			
		7–12 mo	130*	ND			
		Children					
		1–3 y	90	200			
		1–4 y	90	300			
		Males					
		9–13 y	**120**	600			
		14–18 y	**150**	900			
		19–30 y	**150**	1,100			
		31–50 y	**150**	1,100			
		50–70 y	**150**	1,100			
		>70 y	**150**	1,100			
		Females					
		9–13 y	**120**	600			
		14–18 y	**150**	900			
		19–30 y	**150**	1,100			
		31–50 y	**150**	1,100			
		50–70 y	**150**	1,100			
		>70 y	**150**	1,100			
		Pregnancy					
		≤18 y	**220**	900			
		19–30 y	**220**	1,100			
		31–50 y	**220**	1,100			
		Lactation					
		≤18 y	**290**	900			
		19–30 y	**290**	1,100			
		31–50 y	**290**	1,100			
Iron (mg/d)	Component of hemoglobin and numerous enzymes; prevents microcytic hypochromic anemia	Infants	(mg/d)	(mg/d)	Fruits, vegetables and fortified bread and grain products such as cereal (nonheme iron sources), meat and poultry (heme iron sources)	Gastrointestinal distress	Non-heme iron absorption is lower for those consuming vegetarian diets than for those eating nonvegetarian diets. Therefore, it has been suggested that the iron requirement for those consuming a vegetarian diet is approximately 2-fold greater than for those consuming a nonvegetarian diet. Recommended intake assumes 75% of iron is from heme iron sources.
		0–6 mo	0.27*	40			
		7–12 mo	11	40			
		Children					
		1–3 y	7	40			
		4–8 y	10	40			
		Males					
		9–13 y	**8**	40			
		14–18 y	**11**	45			
		19–30 y	**8**	45			
		31–50 y	**8**	45			
		50–70 y	**8**	45			
		>70 y	**8**	45			
		Females					
		9–13 y	**8**	40			
		14–18 y	**15**	45			
		19–30 y	**18**	45			
		31–50 y	**18**	45			
		50–70 y	**8**	45			
		>70 y	**8**	45			
		Pregnancy					
		≤18 y	27	45			
		19–30 y	27	45			
		31–50 y	27	45			
		Lactation					
		≤18 y	10	45			
		19–30 y	9	45			
		31–50 y	9	45			

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[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

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Table 107-1. *(continued).*

DIETARY REFERENCE INTAKES: ELEMENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Magnesium	Cofactor for enzyme systems	Infants	(mg/d)	(mg/d)	Green leafy vegetables, unpolished grains, nuts, meat, starches, milk	There is no evidence of adverse effects from the consumption of naturally occurring magnesium in foods Adverse effects from magnesium containing supplements may include osmotic diarrhea. The UL for magnesium represents intake from a pharmacological agent only and does not include intake from food and water.	None
		0–6 mo	30*	ND[b]			
		7–12 mo	75*	ND			
		Children					
		1–3 y	**80**	85			
		4–8 y	**130**	110			
		Males					
		9–13 y	**240**	350			
		14–18 y	**410**	350			
		19–30 y	**499**	350			
		31–50 y	**420**	350			
		50–70 y	**420**	350			
		>70 y	**420**	350			
		Females					
		9–13 y	**240**	350			
		14–18 y	**380**	350			
		19–30 y	**310**	350			
		31–50 y	**320**	350			
		50–70 y	**320**	350			
		>70 y					
		Pregnancy					
		≤18 y	**400**	350			
		19–30 y	**350**	350			
		31–50 y	**360**	350			
		Lactation					
		≤18 y	**360**	350			
		19–30 y	**310**	350			
		31–50 y	**320**	350			
Manganese	Involved in the formation of bone, as well as in enzymes involved in amino acid, cholesterol, and carbohydrate metabolism	Infants	(mg/d)	(mg/d)	Nuts, legumes, tea, and whole grains	Elevated blood concentration and neurotoxocity	Because manganese in drinking water and supplements may be more bioavailable than manganese from food, caution should be taken when using manganese supplements especially among those persons already consuming large amounts of manganese from diets high in plant products. In addition, individuals with liver disease may be distinctly susceptible to the adverse effects of excess manganese intake.
		0–6 mo	0.003*	ND			
		7–12 mo	0.6*	ND			
		Children					
		1–3 y	1.2*	2			
		4–8 y	1.5*	3			
		Males					
		9–13 y	1.9*	6			
		14–18 y	2.2*	9			
		19–30 y	2.3*	11			
		31–50 y	2.3*	11			
		50–70 y	2.3*	11			
		>70 y	2.3*	11			
		Females					
		9–13 y	1.6*	6			
		14–18 y	1.6*	9			
		19–30 y	1.8*	11			
		31–50 y	1.8*	11			
		50–70 y	1.8*	11			
		>70 y	1.8*	11			
		Pregnancy					
		≤18 y	2.0*	9			
		19–30 y	2.0*	11			
		31–50 y	2.0*	11			
		Lactation					
		≤18 y	2.6*	9			
		19–30 y	2.6*	11			
		31–50 y	2.6*	11			

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Table 107-1. ***(continued).***

DIETARY REFERENCE INTAKES: ELEMENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Molybdenum	Cofactor for enzymes involved in catabolism of sulfur amino acids, purines and pyridines.	Infants	(μg/d)	(μg/d)	Legumes, grain products and nuts	Reproductive effects as observed in animal studies.	Individuals who are deficient in dietary copper intake or have some dysfunction in copper metabolism that makes them copper-deficient could be at increased risk of molybdenum toxicity.
		0–6 mo	2*	ND[b]			
		7–12 mo	3*	ND			
		Children					
		1–3 y	**17**	300			
		4–8 y	**22**	600			
		Males					
		9–13 y	**34**	1,100			
		14–18 y	**43**	1,700			
		19–30 y	**45**	2,000			
		31–50 y	**45**	2,000			
		50–70 y	**45**	2,000			
		>70 y	**45**	2,000			
		Females					
		9–13 y	**34**	1,100			
		14–18 y	**43**	1,700			
		19–30 y	**45**	2,000			
		31–50 y	**45**	2,000			
		50–70 y	**45**	2,000			
		>70 y					
		Pregnancy					
		≤ 18 y	**50**	1,700			
		19–30 y	**50**	2,000			
		31–50 y	**50**	2,000			
		Lactation					
		≤ 18 y	**50**	1,700			
		19–30 y	**50**	2,000			
		31–50 y	**50**	2,000			
Nickel	No clear biological function in humans has been identified. May serve as a cofactor of metalloenzymes in microorganisms.	Infants	(mg/d)	(mg/d)	Nuts, legumes, cereals, sweeteners, chocolate milk powder, chocolate candy	Decreased body weight gain Note: As observed in animal studies	Individual with preexisting nickel hypersensitivity (from previous dermal exposure) and kidney dysfunction are distinctly susceptible to the adverse effects of excess nickel intake
		0–6 mo	ND	ND			
		7–12 mo	ND	ND			
		Children					
		1–3 y	ND	0.2			
		4–8 y	ND	0.3			
		Males					
		9–13 y	ND	0.6			
		14–18 y	ND	1.0			
		19–30 y	ND	1.0			
		31–50 y	ND	1.0			
		50–70 y	ND	1.0			
		>70 y	ND	1.0			
		Females					
		9–13 y	ND	0.6			
		14–18 y	ND	1.0			
		19–30 y	ND	1.0			
		31–50 y	ND	1.0			
		50–70 y	ND	1.0			
		>70 y	ND	1.0			
		Pregnancy					
		≤ 18 y	ND	1.0			
		19–30 y	ND	1.0			
		31–50 y	ND	1.0			
		Lactation					
		≤ 18 y	ND	1.0			
		19–30 y	ND	1.0			
		31–50 y	ND	1.0			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-1. *(continued).*

DIETARY REFERENCE INTAKES: ELEMENTS							
NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Phosphorus	Maintenance of pH, storage and transfer of energy and nucleotide synthesis	Infants	(mg/d)	(mg/d)	Milk, yogurt, ice cream, cheese, peas, meat, eggs, some cereals and breads	Metastalic calcification, skeletal porosity, interference with calcium absorption	Athletes and others with high energy expenditure frequently consume amounts from food greater than the UL without apparent effect.
		0–6 mo	100*	ND[b]			
		7–12 mo	275*	ND			
		Children					
		1–3 y	**460**	3,000			
		4–8 y	**500**	3,000			
		Males					
		9–13 y	**1,250**	4,000			
		14–18 y	**1,250**	4,000			
		19–30 y	**700**	4,000			
		31–50 y	**700**	4,000			
		50–70 y	**700**	4,000			
		>70 y	**700**	3,000			
		Females					
		9–13 y	**1,250**	4,000			
		14–18 y	**1,250**	4,000			
		19–30 y	**700**	4,000			
		31–50 y	**700**	4,000			
		50–70 y	**700**	3,000			
		>70 y	**700**				
		Pregnancy					
		≤18 y	**1,250**	3,500			
		19–30 y	**700**	3,500			
		31–50 y	**700**	3,500			
		Lactation					
		≤18 y	**1,250**	4,000			
		19–30 y	**700**	4,000			
		31–50 y	**700**	4,000			
Selenium	Defense against oxidative stress and regulation of action, and the oxidation status of vitamin C and other molecules	Infants	(μg/d)	(μg/d)	Organ meats, seafood, plants (depending on content)	Hair and nail brittleness and loss	None
		0–6 mo	15*	45			
		7–12 mo	20*	60			
		Children					
		1–3 y	20	90			
		4–8 y	30	150			
		Males					
		9–13 y	40	280			
		14–18 y	55	400			
		19–30 y	55	400			
		31–50 y	55	400			
		50–70 y	55	400			
		>70 y	55	400			
		Females					
		9–13 y	40	280			
		14–18 y	55	400			
		19–30 y	55	400			
		31–50 y	55	400			
		50–70 y	55	400			
		>70 y	55	400			
		Pregnancy					
		≤18 y	60	400			
		19–30 y	60	400			
		31–50 y	60	400			
		Lactation					
		≤18 y	70	400			
		19–30 y	70	400			
		31–50 y	70	400			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-1. ***(continued).***

DIETARY REFERENCE INTAKES: ELEMENTS							
NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Zinc	Component of multiple enzymes and proteins; involved in the regulation of gene expression.	Infants	(mg/d)	(mg/d)	Fortified cereals, red meats, certain seafood	Reduced copper status	Zinc absorption is lower for those consuming vegetarian diets than for those eating nonvegetarian diets. Therefore, it has been suggested that the zinc requirement for those consuming a vegetarian diet is approximately 2-fold greater than for consuming a nonvegetarian diet.
		0–6 mo	2*	4			
		7–12 mo	3	5			
		Children					
		1–3 y	**3**	7			
		4–8 y	**5**	12			
		Males					
		9–13 y	**8**	23			
		14–18 y	**11**	34			
		19–30 y	**11**	40			
		31–50 y	**11**	40			
		50–70 y	**11**	40			
		>70 y	**11**	40			
		Females					
		9–13 y	**8**	23			
		14–18 y	**9**	34			
		19–30 y	**8**	40			
		31–50 y	**8**	40			
		50–70 y	**8**	40			
		>70 y	**8**	40			
		Pregnancy					
		≤18 y	**12**	34			
		19–30 y	**11**	40			
		31–50 y	**11**	40			
		Lactation					
		≤18 y	**13**	34			
		19–30 y	**12**	40			
		31–50 y	**12**	40			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type.** Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantothenic acid, biotin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference intakes for Calcium, Phosphorous, Magnesium. Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Paniothenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000);* and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

maintenance of a healthy weight. Total activity time includes cumulative activities such as an exercise plan as well activities associated with daily life such as climbing stairs. The report suggests a moderate to higher intensity exercise plan for those in a sedentary occupation.

Build a Healthy Base

LET THE PYRAMID GUIDE YOUR FOOD CHOICES— No single food supplies all the nutrients needed by the body. Therefore, it is important to eat a variety of foods, on a daily basis, to meet all the nutrient needs of the body. The Food Guide Pyramid[2], Figure 107-2, was developed by the USDA to help interpret the Dietary Guidelines. It is anticipated the Food Guide Pyramid will be revised in the near future. Multiple versions of the Food Guide Pyramid are available for many different cuisines and ethnic food patterns. Both the Dietary Guidelines for Americans and the Food Guide Pyramid support the concept that all foods can fit in a well-balanced diet and help to eliminate the negative and untrue perception that there are good foods and bad foods. There are no good foods and bad foods, but there are good diets and bad diets. The pyramid shape emphasizes that the foundation of a sound diet should be foods from the bread, cereal, rice, and pasta group. Build on this foundation by adding foods from the vegetable and fruit groups, and then from the milk and meat groups. Each group suggests a range of servings to consume each day. Fats, oils, and sweets are to be used sparingly and are represented in the top section of the pyramid. The top section is not considered a group of foods, and there are no suggested serving ranges for the fats, oils, and sweets. It should be remembered that fats and sweets can often be "hidden" in some baked foods such as muffins, etc. The complete name of the milk and meat groups identifies food alternatives within each group that provide many of the same basic nutrients as milk or meat. For example, calcium, an important nutrient supplied by the milk group can be obtained through other foods (eg, yogurt, hard cheeses such as cheddar, cottage cheese, or even cheese foods). Not all alternatives supply the same amount of calcium. It takes 2 cups of cottage cheese and 2 oz of a processed cheese food to equal the amount of calcium in only 1 cup of milk or yogurt. Calcium alternatives also are found in the vegetable group and in legumes. Basic nutrition texts and educational information about the Dietary Guidelines and the Food Guide Pyramid from the USDA and the HHS are helpful in interpreting specifics about these educational tools.

Table 107-2. Food and Nutrition Board, Institute of Medicine-National Academy of Sciences Dietary Reference Intakes: Vitamins

DIETARY REFERENCE INTAKES: VITAMINS							
NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Biotin	Coenzyme in synthesis of fat, glycogen, and amino acids	Infants	(μg/d)		Liver and smaller amounts in fruits and meals	No adverse effects of biotin in humans or animals were found. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of biotin are limited, caution may be warranted.	None
		0–6 mo	5*	ND[b]			
		7–12 mo	6*	ND			
		Children					
		1–3 y	8*	ND			
		4–8 y	12*	ND			
		Males					
		9–13 y	20*	ND			
		14–18 y	25*	ND			
		19–30 y	30*	ND			
		31–50 y	30*	ND			
		50–70 y	30*	ND			
		>70 y	30*	ND			
		Females					
		9–13 y	20*	ND			
		14–18 y	25*	ND			
		19–30 y	30*	ND			
		31–50 y	30*	ND			
		50–70 y	30*	ND			
		>70 y	30*	ND			
		Pregnancy					
		≤18 y	30*	ND			
		19–30 y	30*	ND			
		31–50 y	30*	ND			
		Lactation					
		≤18 y	35*	ND			
		19–30 y	35*	ND			
		31–50 y	35*	ND			
Choline	Precursor for acetylcholine, phospholipids and betaine	Infants	(mg/d)	(mg/d)	Milk, liver, eggs, peanuts	Fishy body odor, sweating, salivation, hypotension, hepatotoxicity	Individuals with trimethylaminuria, renal disease, liver disease, depression and Parkinson's disease, may be at risk of adverse effects with choline intakes at the UL.
		0–6 mo	**125***	ND			
		7–12 mo	**150***	ND			
		Children					
		1–3 y	200*	1000			
		4–8 y	250*	1000			
		Males					
		9–13 y	375*	2000			
		14–18 y	550*	3000			
		19–30 y	550*	3500			
		31–50 y	550*	3500			
		50–70 y	550*	3500			
		>70 y	550*	3500			
		Females					
		9–13 y	375*	2000			
		14–18 y	400*	3000			
		19–30 y	425*	3500			
		31–50 y	425*	3500			
		50–70 y	425*	3500			
		>70 y	425*	3500			
		Pregnancy					
		≤18 y	450*	3000			
		19–30 y	450*	3500			
		31–50 y	450*	3500			
		Lactation					
		≤18 y	550*	3000			
		19–30 y	550*	3500			
		31–50 y	550*	3500			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Folate Also known as: Folic acid Folacin Pteroylpoly-glutamates Note: Given as dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folate from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.	Coenzyme in the metabolism of nucleic and amino acids; prevents megaloblastic anemia	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	(μg/d) 65* 80* **150** **200** **300** **400** **400** **400** **400** **400** **300** **400** **400** **400** **400** **400** **600** **600** **600** **500** **500** **500**	(μg/d) ND[b] ND 300 400 600 800 1,000 1,000 1,000 1,000 600 800 1,000 1,000 1,000 1,000 800 1,000 1,000 800 1,000 1,000	Enriched cereal grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	Masks neurological complication in people with vitamin B_{12} deficiency. No adverse effects associated with folate from food or supplements have been reported. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of folate are limited, caution may be warranted. The UL for folate applies to synthetic forms obtained from supplements and/or fortified foods.	In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet. It is assumed that women will continue consuming. or fortified food until their 400 μg from supplements pregnancy is confirmed and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube.
Niacin Includes nicotinic acid amide, nicotinic acid (pyridine-3-carboxylic acid), and derivatives that exhibit the biological activity of nicotinamide. Note: Given as niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).	Coenzyme or cosubstrate in many biological reduction and oxidation reactions—thus required for energy metabolism	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	(mg/d) 2* 4* 6 8 **12** **16** **16** **16** **16** **16** **12** **14** **14** **14** **14** **14** 18 18 18 17 17 **17**	(mg/d) ND ND 10 15 20 30 35 35 35 35 20 30 35 35 35 35 30 35 35 30 35 35	Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	There is no evidence of the adverse effects from consumption of naturally occuring niacin in foods. Adverse effects from niacin containing supplements may include flushing and gastrointestinal distress. The UL for niacin applies to synthetic forms obtained from supplements, fortified foods, or a combination of the two.	Extra niacin may be required by persons treated with hemodialysis or peritoneal dialysis, or those with malabsorption syndrome.

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[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Pantothenic Acid	Coenzyme in fatty acid metabolism	Infants	(mg/d)	(mg/d)	Chicken, beef potatoes, oats cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, whole grains	No adverse effects associated with panthothenic acid from food or supplements have been reported. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of panthothenic acid are limited, caution may be warranted.	None
		0–6 mo	1.7*	ND[b]			
		7–12, mo	1.8*	ND			
		Children					
		1–3 y	2*	ND			
		4–8 y	3*	ND			
		Males					
		9–13 y	4*	ND			
		14–18 y	5*	ND			
		19–30 y	5*	ND			
		31–50 y	5*	ND			
		50–70 y	5*	ND			
		>70 y	5*	ND			
		Females					
		9–13 y	4*	ND			
		14–18 y	5*	ND			
		19–30 y	5*	ND			
		31–50 y	5*	ND			
		50–70 y	5*	ND			
		>70 y	5*	ND			
		Pregnancy					
		≤18 y	6*	ND			
		19–30 y	6*	ND			
		31–50 y	6*	ND			
		Lactation					
		≤18 y	7*	ND			
		19–30 y	7*	ND			
		31–50 y	7*	ND			
Riboflavin	Coenzyme in numerous redox reactions	Infants	(mg/d)	(mg/d)	Organ meats, milk, bread products and fortified cereals	No adverse effects associated with riboflavin consumption from food or supplements have been reported. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of riboflavin are limited, caution may be warranted.	None
Also known as: Vitamin B_2		0–6 mo	0.3*	ND			
		7–12 mo	0.4*	ND			
		Children					
		1–3 y	**0.5**	ND			
		4–8 y	**0.6**	ND			
		Males					
		9–13 y	**0.9**	ND			
		14–18 y	**1.3**	ND			
		19–30 y	**1.3**	ND			
		31–50 y	**1.3**	ND			
		50–70 y	**1.3**	ND			
		>70 y	**1.3**	ND			
		Females					
		9–13 y	**0.9**	ND			
		14–18 y	**1.0**	ND			
		19–30 y	**1.1**	ND			
		31–50 y	**1.1**	ND			
		50–70 y	**1.1**	ND			
		>70 y	**1.1**	ND			
		Pregnancy					
		≤18 y	**1.4**	ND			
		19–30 y	**1.4**	ND			
		31–50 y	**1.4**	ND			
		Lactation					
		≤18 y	**1.6**	ND			
		19–30 y	**1.6**	ND			
		31–50 y	**1.6**	ND			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Thiamin Also known as: Vitamin B_1 Aneurin	Coenzyme in the metabolism of carbohydrates and branched-chain amino acids	Infants	(mg/d)		Enriched, fortified, or whole-grain products; bread and bread products, mixed foods whose main ingredient is grain, and ready-to-eat cereals.	No adverse effects associated with thiamin from food or supplements have been reported. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of thiamin are limited, caution may be warranted.	Persons who may have increased needs for thiamin include those being treated with hemodialysis or paritoneal dialysis, or individuals with malabsorption syndrome.
		0–6 mo	0.2*	ND[b]			
		7–12 mo	0.3*	ND			
		Children					
		1–3 y	**0.5**	ND			
		4–8 y	**0.6**	ND			
		Males					
		9–13 y	**0.9**	ND			
		14–18 y	**1.2**	ND			
		19–30 y	**1.2**	ND			
		31–50 y	**1.2**	ND			
		50–70 y	**1.2**	ND			
		>70 y	**1.2**	ND			
		Females					
		9–13 y	0.9	ND			
		14–18 y	1.0	ND			
		19–30 y	**1.1**	ND			
		31–50 y	**1.1**	ND			
		50–70 y	**1.1**	ND			
		>70 y	**1.1**	ND			
		Pregnancy					
		≤18 y	**1.4**	ND			
		19–30 y	**1.4**	ND			
		31–50 y	**1.4**	ND			
		Lactation					
		≤18 y	**1.4**	ND			
		19–30 y	**1.4**	ND			
		31–50 y	**1.4**	ND			
Vitamin A Includes provitamin A carotenoids that are dietary precursors of retinol. Note: Given as retinol activity equivalents (RAEs), 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. To calculate RAEs from REs of provitamin A carotenoids in foods, divide the REs by 2. For pre-formed vitamin A in foods or supplements and for pro-vitamin A carotenoids in supplements, 1 RE = RAE.	Required for normal vision, gene expression, reproduction, embryonic development and immune function	Infants	(μg/d)	(μg/d)	Liver, dairy products, fish	Teratological effects, liver toxicity Note: From preformed Vitamin A only.	Individuals with high alcohol intake, pre-existing liver disease, hyperlipidemia or severe protein malnutrition may be distinctly susceptible to the adverse effects of source excess preformed vitamin A intake. β-carotene supplements are advised only to serve as a provitamin A for individuals at risk of vitamin A deficiency.
		0–6 mo	400*	600			
		7–12 mo	500*	600			
		Children					
		1–3 y	**300**	600			
		4–8 y	**400**	900			
		Males					
		9–13 y	**600**	1,700			
		14–18 y	**900**	2,800			
		19–30 y	**900**	3,000			
		31–50 y	**900**	3,000			
		50–70 y	**900**	3,000			
		>70 y	**900**	3,000			
		Females					
		9–13 y	**600**	1,700			
		14–18 y	**700**	2,800			
		19–30 y	**700**	3,000			
		31–50 y	**700**	3,000			
		50–70 y	**700**	3,000			
		>70 y	**700**	3,000			
		Pregnancy	**750**	2,800			
		≤18 y	**770**	3,000			
		19–30 y	**770**	3,000			
		31–50 y					
		Lactation					
		≤18 y	**1,200**	2,800			
		19–30 y	**1,300**	3,000			
		31–50 y	**1,300**	3,000			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin B_6	Coenzyme in the metabolism of amino acids, glycogen and sphingold bases	Infants	(mg/d)	(mg/d)	Fortified cereals, organ meats, fortified soy-based meat substitutes	No adverse effects associated with Vitamin B_6 from food have been reported. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of Vitamin B_6 are limited, caution may be warranted. Sensory neuropathy has occurred from high intakes of supplemental forms.	None
		0–6 mo	0.1*	ND[b]			
		7–12 mo	0.3*	ND			
		Children					
		1–3 y	**0.5**	30			
		4–8 y	**0.6**	40			
		Males					
		9–13 y	**1.0**	60			
		14–18 y	**1.3**	80			
		19–30 y	**1.3**	100			
		31–50 y	**1.3**	100			
		50–70 y	**1.7**	100			
		>70 y	**1.7**	100			
		Females					
		9–13 y	**1.0**	60			
		14–18 y	**1.2**	80			
		19–30 y	**1.3**	100			
		31–50 y	**1.3**	100			
		50–70 y	**1.5**	100			
		>70 y	**1.5**	100			
		Pregnancy					
		≤18 y	**1.9**	80			
		19–30 y	**1.9**	100			
		31–50 y	**1.9**	100			
		Lactation					
		≤18 y	**2.0**	80			
		19–30 y	**2.0**	100			
		31–50 y	**2.0**	100			
Vitamin B_{12} Also known as: Cobalamin	Coenzyme in nucleic acid metabolism; prevents megaloblastic anemia	Infants	(mg/d)	(mg/d)	Fortified cereals, meat, fish, poultry	No adverse effects have been associated with the consumption of the amounts of vitamin B_{12} normally found in foods or supplements. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of vitamin B_{12} are limited, caution may be warranted.	Because 10 to 30 percent of older people may malabsorb food-bound vitamin B_{12}, it is advisable for those older than 50 year to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}.
		0–6 mo	0.4*	ND			
		7–12 mo	0.5*	ND			
		Children					
		1–3 y	**0.9**	ND			
		4–8 y	**1.2**	ND			
		Males					
		9–13 y	**1.8**	ND			
		14–18 y	**2.4**	ND			
		19–30 y	**2.4**	ND			
		31–50 y	**2.4**	ND			
		50–70 y	**2.4**	ND			
		>70 y	**2.4**	ND			
		Females					
		9–13 y	**1.8**	ND			
		14–18 y	**2.4**	ND			
		19–30 y	**2.4**	ND			
		50–70 y	**2.4**	ND			
		>70 y	**2.4**	ND			
		Pregnancy					
		≤18 y	**2.6**	ND			
		19–30 y	**2.6**	ND			
		31–50 y	**2.6**	ND			
		Lactation					
		≤18 y	**2.8**	ND			
		19–30 y	**2.8**	ND			
		31–50 y	**2.8**	ND			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin C	Cofactor for reactions requiring reduced copper or iron metallo-enzyme and as a protective antioxidant	Infants	(mg/d)	(mg/d)	Citrus fruits, tomatoes, tomato juice, potatoes, brussel sprouts, cauliflower, broccoli, strawberies, cabbage, and spinach	Gastrointestinal disturbances, kidney stones, excess iron absorption	Individuals who smoke require an additional 35 mg/d of vitamin C over that needed by nonsmokers.
		0–6 mo	40*	ND[b]			
		7–12 mo	50*	ND			Nonsmokers regularly exposed to tobacco smoke are encouraged to ensure they meet the RDA for vitamin C.
Also known as: Ascorbic acid, Dehydro-ascorbic acid (DHA)		Children					
		1–3 y	**15**	400			
		4–8 y	**25**	850			
		Males					
		9–13 y	**45**	1,200			
		14–18 y	**75**	1,800			
		19–30 y	**90**	2,000			
		31–50 y	**1.3**	2,000			
		50–70 y	**1.7**	2,000			
		>70 y	**1.7**	2,000			
		Females					
		9–13 y	**45**	1,200			
		14–18 y	**65**	1,800			
		19–30 y	**75**	2,000			
		31–50 y	**7.5**	2,000			
		50–70 y	**75**	2,000			
		>70 y	**75**	2,000			
		Pregnancy					
		≤18 y	**80**	1,800			
		19–30 y	**85**	2,000			
		31–50 y	**85**	2,000			
		Lactation					
		≤ 18 y	**115**	1,800			
		19–30 y	**120**	2,000			
		31–50 y	**120**	2,000			
Vitamin D	Maintain serum calcium and phosphorus concentrations.	Infants	(μg/d)	(μg/d)	Fish liver oils, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens that have been fed vitamin D, fortified milk products and fortified cereals	Elevated plasma 25 (OH) D concentration causing hypercalcemia	Patients on glucocorticoid therapy may require additional vitamin D.
		0–6 mo	5*	25			
		7–12 mo	5*	25			
Also known as: Calciferol		Children					
		1–3 y	5*	50			
Note: 1 μg calciferol = 40 IU vitamin D		4–8 y	5*	50			
		Males					
		9–13 y	5*	50			
The DRI values are based on the absence of adequate exposure to sunlight		14–18 y	5*	50			
		19–30 y	5*	50			
		31–50 y	5*	50			
		50–70 y	10*	50			
		>70 y	15*	50			
		Females					
		9–13 y	5*	50			
		14–18 y	5*	50			
		19–30 y	5*	50			
		31–50 y	5*	50			
		50–70 y	10*	50			
		>70 y	15*	50			
		Pregnancy					
		≤18 y	5*	50			
		19–30 y	5*	50			
		31–50 y	5*	50			
		Lactation					
		≤18 y	5*	50			
		19–30 y	5*	50			
		31–50 y	5*	50			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-2. *(continued).*

DIETARY REFERENCE INTAKES: VITAMINS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI*	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin E Also known as: α-tocopherol Note: As α-tocopherol α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the 2*R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the 2*S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.	A metabolic function has not yet been identified. Vitamin E's major function appears to be as a non-specific chain-breaking antioxidant.	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	(mg/d) 4* 5* **6** **7** **11** **15** **15** **15** **15** **15** **11** **15** **15** **15** **15** **15** **15** **15** **15** **19** **19** **19**	(mg/d) ND[b] ND 200 300 600 800 1,000 1,000 1,000 1,000 600 800 1,000 1,000 1,000 1,000 800 1,000 1,000 800 1,000 1,000	Vegetable oils, unprocessed cereal grains, nuts, fruits, vegetables, meats	There is no evidence of adverse effects from the consumption of vitamin E naturally occuring in foods. Adverse effects from vitamin E containing supplements may include hemorrhagic toxicity. The UL for vitamin E applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of the two.	Patients on anticoagulant therapy should be monitored when taking vitamin E supplements.
Vitamin K	Coenzyme during the synthesis of many proteins involved in blood clotting and bone metabolism	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	(μg/d) 2.0* 2.5* 30* 55* 60* 75* 120* 120* 120* 120* 60* 75 90* 90* 90* 90* 75* 90* 90* 75* 90* 90*	 ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND ND	Green vegetables (collards, spinach, salad greens, broccoli), brussel sprouts, cabbage, plant oils and margarine	No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals. This does not mean that there is no potential for adverse effects resulting from high intakes. Because data on the adverse effects of vitamin K are limited, caution may be warranted.	Patients on anticoagulant therapy should monitor vitamin K intake.

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in **bold type**, Adequate intakes (AIs) in ordinary type followed by an asterisk (*), and Tolerable Upper Intake Levels (ULs)[a]. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for vitamin K, thiamin, riboflavin, vitamin B_{12}, pantolhenic acid, biolin, or carotenoids. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride* (1997); *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantolhenic Acid, Biotin, and Choline* (1998); *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids* (2000); and *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc* (2001). These reports may be accessed via www.nap.edu.

Table 107-3. Food and Nutrition Board, Institute of Medicine-National Academy of Sciences Dietary Reference Intakes: Macronutrients

DIETARY REFERENCE INTAKES: MACRONUTRIENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI* G/D	AMDR	SELECTED FOOD SOURCES	ADVERSE EFFECT OF EXCESSIVE CONSUMPTION
Carbohydrate—Total digestible	RDA based on its role as the primary energy source for the brain; AMDR based on its role as a source of kilocalories to maintain body weight	Infants			Starch and sugar are the major types of carbohydrates. Grains and vegetables (corn, pasta, rice, potatoes, breads) are sources of starch. Natural sugars are found in fruits and juices. Sources of added sugars are soft drinks, candy, fruit drinks, and desserts.	While no defined intake level at which potential adverse effects of total digestible carbohydrate was identified, the upper end of the adequate macronutrient distribution range (AMDR) was based on decreasing risk of chronic disease and providing adequate intake of other nutrients. It is suggested that the maximal intake of added sugars be limited to providing no more than 25 percent of energy.
		0–6 mo	60*	ND[b]		
		7–12 mo	95*	ND		
		Children				
		1–3 y	**130**	45–65		
		4–8 y	**130**	45–65		
		Males				
		9–13 y	**130**	45–65		
		14–18 y	**130**	45–65		
		19–30 y	**130**	45–65		
		31–50 y	**130**	45–65		
		50–70 y	**130**	45–65		
		>70 y				
		Females				
		9–13 y	**130**	45–65		
		14–18 y	**130**	45–65		
		19–30 y	**130**	45–65		
		31–50 y	**130**	45–65		
		50–70 y	**130**	45–65		
		>70 y	**130**	45–65		
		Pregnancy				
		≤18 y	**175**	45–65		
		19–30 y	**175**	45–65		
		31–50 y	**175**	45–65		
		Lactation				
		≤18 y	**210**	45–65		
		19–30 y	**210**	45–65		
		31–50 y	**210**	45–65		
Total Fiber	Improves laxation, reduces risk of coronary heart disease, assists in maintaining normal blooed glucose levels.	Infants			Includes dietary fiber naturally present in grains (such as found in oats, wheat, or unmilled rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health	Dietary fiber can have variable compositions and therefore it is difficult to link a specific source of fiber with a particular adverse effect, especially when phylate is also present in the natural fiber source. It is concluded that as part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy individuals. While occasional adverse gastrointestinal symptoms are observed when consuming some isolated or synthetic fibers, serious chronic adverse effects have not been observed. Due to the bulky nature of fibers, excess consumption is likely to be self-limiting. Therefore, a UL was not set for individual functional fibers.
		0–8 mo	ND			
		7–12 mo	ND			
		Children				
		1–3 y	19*			
		4–8 y	25*			
		Males				
		9–13 y	31*			
		14–18 y	38*			
		19–30 y	38*			
		31–50 y	38*			
		50–70 y	30*			
		>70 y	30*			
		Females				
		9–13 y	26*			
		14–18 y	26*			
		19–30 y	25*			
		31–50 y	25*			
		50–70 y	21*			
		>70 y	21*			
		Pregnancy				
		≤18 y	28*			
		19–30 y	28*			
		31–50 y	28*			
		Lactation				
		≤18 y	29*			
		19–30 y	29*			
		31–50 y	29*			

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in the **bold type,** Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]Acceptance Macronutrient Distribution Range (AMDR)[a] is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. If an individual consumes in excess of the AMDR, there is a potential of increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino acids (2002).* This report may be accessed via www.nap.edu.

Table 107-3. ***(continued).***

DIETARY REFERENCE INTAKES: MACRONUTRIENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI* G/D	AMDR[b]	SELECTED FOOD SOURCES	ADVERSE EFFECT OF EXCESSIVE CONSUMPTION
Total fat	Energy source and when found in foods, is a source of *n*-6 and *n*-3 polysaturated fatty acids. Its presence in the diet increases absorption of fat soluble vitamins and precursors such as vitamin A and pro-vitamin A carotenoids.	Infants			Butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, and bakery products.	While no defined intake level at which potential adverse effects of total fat was identified, the upper end of AMDR is based on decreasing risk of chronic disease and providing adequate intake of other nutrients. The lower end of the AMDR is based on concerns related to the increase in plasma triacylglycerol concentrations and decreased HDL cheolesterol concentrations seen with very low fat (and thus high carbohydrate) diets.
		0–6 mo	31*			
		7–12 mo	30*			
		Children				
		1–3 y		30–40		
		4–8 y		25–35		
		Males				
		9–13 y		25–35		
		14–18 y		25–35		
		19–30 y		20–35		
		31–50 y		20–35		
		50–70 y		20–35		
		>70 y		20–35		
		Females				
		9–13 y		25–35		
		14–18 y		25–35		
		19–30 y		20–35		
		31–50 y		20–35		
		50–70 y		20–35		
		>70 y		20–35		
		Pregnancy				
		≤18 y		20–35		
		19–30 y		20–35		
		31–50 y		20–35		
		Lactation				
		≤18 y		20–35		
		19–30 y		20–35		
		31–50 y		20–35		
n-6 polyunsaturated fatty acids (linoleic acid)	Essential component of structural membrane lipids, involved with cell signaling, and precursor of eicosanoids. Required for normal skin function.	Infants			Nuts, seeds, and vegetable oils such as soybean, safflower, and corn oil.	While no defined intake level at which potential adverse effects of *n*-6 polyunsaturated fatty acids was identified, the upper end of the AMDR is based the lack of evidence that demonstrates long-term safety and human in vitro studies which show increased free-radical formation and lipid peroxidation with higher amounts of n-6 fatty acids. Lipid peroxidation is thought to be a component of in the development of atherosclerotic plaques.
		0–6 mo	4.4*	ND[b]		
		7–12 mo	4.6*	ND		
		Children				
		1–3 y	7*	5–10		
		4–8 y	10*	5–10		
		Males				
		9–13 y	12*	5–10		
		14–18 y	16*	5–10		
		19–30 y	17*	5–10		
		31–50 y	17*	5–10		
		50–70 y	14*	5–10		
		>70 y	14*	5–10		
		Females				
		9–13 y	10*	5–10		
		14–18 y	11*	5–10		
		19–30 y	17*	5–10		
		31–50 y	17*	5–10		
		50–70 y	14*	5–10		
		>70 y	**14***	5–10		
		Pregnancy				
		≤18 y	13*	5–10		
		19–30 y	13*	5–10		
		31–50 y	13*	5–10		
		Lactation				
		≤18 y	13*	5–10		
		19–30 y	13*	5–10		
		31–50 y	13*	5–10		

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in the **bold type,** Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]Acceptance Macronutrient Distribution Range (AMDR)[a] is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. If an individual consumes in excess of the AMDR, there is a potential of increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino acids (2002).* This report may be accessed via www.nap.edu.

Table 107-3. *(continued)*.

DIETARY REFERENCE INTAKES: MACRONUTRIENTS						
NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI* G/D	AMDR[a]	SELECTED FOOD SOURCES	ADVERSE EFFECT OF EXCESSIVE CONSUMPTION
n-3 polyunsaturated fatty acids (α-linoleic acid)	Involved with neurological development and growth. Precursor of elcosanoids.	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	 0.5* 0.5* 0.7* 0.9* 1.2* 1.6* 1.6* 1.6* 1.6* 1.6* 1.0* 1.1* 1.1* 1.1* 1.1* 1.1* **1.4*** **1.4*** **1.4*** 1.3* 1.3* 1.3*	 ND[b] ND 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2 0.6–1.2	Vegetable oils such as soybean, canola, and flax seed oil, fish oils, fatty fish, with smaller amounts in meats and eggs.	While no defined intake level at which potential adverse effects of *n*-3 polyunsaturated fatty acids was identified, the upper end of AMDR is based on maintaining the appropriate balance with n-6 fatty acids and on the lack of evidence that demonstrates long-term safety, along with human in vitro studies which show increased free-radical formation and lipid peroxidation with higher amounts of polyunsaturated fatty acids. Lipid peroxidation is thought to be a component of in the development of atherosclerotic plaques.
Saturated and *trans* fatty acids, and cholesterol	No required role for these nutrients other than as energy sources was identified; the body can synthesize its needs for saturated fatty acids and cholesterol from other sources.	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50-70 y >70 y Pregnancy ≤18 y 19–30 y 31–50 y Lactation ≤18 y 19–30 y 31–50 y	ND ND		Saturated fatty acids are present in animal fats (meat fats and butter fat), and coconut and palm kernel oils. Sources of cholesterol include liver, eggs, and foods that contain eggs such as cheesecake and custard pies. Sources of *trans* fatty acids include stick margarines and foods containing hydrogenated or partially-hydrogenated vegetable shortenings.	There is an incremental increase in plasma total and low-density lipoprotein cholesterol concentrations with increased intake of saturated or *trans* fatty acids or with cholesterol at even very low levels in the diet. Therefore, the intakes of each should be minimized while consuming a nutritionally adequate diet.

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in the **bold type,** Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]Acceptance Macronutrient Distribution Range (AMDR)[a] is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. If an individual consumes in excess of the AMDR, there is a potential of increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino acids (2002).* This report may be accessed via www.nap.edu.

Table 107-3. ***(continued).***

DIETARY REFERENCE INTAKES: MACRONUTRIENTS

NUTRIENT	FUNCTION	LIFE STAGE GROUP	RDA/AI* G/D*	AMDR[a]	SELECTED FOOD SOURCES	ADVERSE EFFECT OF EXCESSIVE CONSUMPTION
Protein and amino acids	Serves as the major structural component of all cells in the body, and functions as enzymes, in membranes, as transport carriers, and as some hormones. During digestion and absorption dietary proteins are broken down to amino acids, which become the building blocks of these structural and functional compounds. Nine of the amino acids must be provided in the diet; these are termed indespensable amino acids. The body can make the other amino acids needed to synthesize specific structures from other amino acids.	Infants			Proteins from animal sources, such as meat, poultry, fish, eggs, milk, cheese, and yogurt, provide all nine indispensable amino acids in adequate amounts, and for this reason are considered "complete proteins". Proteins from plants, legumes, grains nuts, seeds, and vegetables tend to be deficient in one or more of the indispensable amino acids and are called 'incomplete proteins'. Vegan diets adequate in total protein content can be "complete" by combining sources of incomplete proteins which lack different indispensable amino acids.	While no defined intake level at which potential adverse effects of protein was identified, the upper end of AMDR based on complementing the AMDR for carbohydrate and fat for the various age groups. The lower end of the AMDR is set at approximately the RDA.
		0–6 mo	9.1*	ND[c]		
		7–12 mo	13.5	ND		
		Children				
		1–3 y	13	5–20		
		4–8 y	19	10–30		
		Males				
		9–13 y	**34**	10–30		
		14–18 y	**52**	10–30		
		19–30 y	**56**	10–35		
		31–50 y	**56**	10–35		
		50–70 y	**56**	10–35		
		>70 y	**56**	10–35		
		Females				
		9–13 y	**34**	10–30		
		14–18 y	**46**	10–30		
		19–30 y	**46**	10–35		
		31–50 y	**46**	10–35		
		50–70 y	**46**	10–35		
		> 70 y	**46**	10–35		
		Pregnancy				
		≤18 y	**71**	10.35		
		19–30 y	**71**	10.35		
		31–50 y	**71**	10.35		
		Lactation				
		≤18 y	**71**	10.35		
		19–30 y	**71**	10.35		
		31–50 y	**71**	10.35		

NOTE: The table is adapted from the DRI reports, see www.nap.edu. It represents Recommended Dietary Allowances (RDAs) in the **bold type,** Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of almost all (97 to 98 percent) individuals in a group. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a]Based on 1.5 g/kg/day for infants, 1.1 g/kg/day for 1–3, 0.95 g/kg/day for 4–13 y, 0.85 g/kg/day for 14–18 y, 0.8 g/kg/day for adults, and 1.1 g/kg/day for pregnant (using pre-pregnancy weight) and lactating women.

[b]Acceptable Macronutrient Distribution Range (AMDR)[a] is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. If an individuals consumed in excess of the AMDR, there is a potential of increasing the risk of chronic diseases and insufficient intakes of essential nutrients.

[c]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino acids (2002).* This report may be accessed via www.nap.edu.

Meat alternatives that supply the same amount of protein as a 2-oz, cooked serving of meat include 2 eggs, 1 cup dried beans or peas (cooked), 4 tablespoons peanut butter, 2 oz hard cheese, or 1/2 cup cottage cheese. Although these foods substitute for the protein in a 2-oz serving of meat, poultry, or fish, they do not substitute for all the other nutrients found in meat such as iron, zinc, and B vitamins.

Appropriate use of the Food Guide Pyramid requires knowledge of what constitutes a serving. Evidence indicates consumers are more confused about serving sizes and how they relate to the amount of food eaten. This likely is contributing to the overconsumption of food and the increased prevalence of obesity in our society. The Food Guide Pyramid gives suggested servings and defines the serving size. A "serving" is very different from a portion as a portion is an amount of food eaten in one setting, is often more than a serving, and may contribute unwanted calories. Consider today's 20 to 46 oz beverage versus a traditional serving size of 8 oz. Table 107-9 reviews what is considered a serving.

Two specific guidelines further emphasize the foods at the first and second level of the pyramid base.

CHOOSE A VARIETY OF GRAINS DAILY, ESPECIALLY WHOLE GRAINS—Foods from grains form the base of the Food Guide Pyramid, thus illustrating that this should be the foundation of a healthy diet. These three food groups provide fewer kilocalories than many foods in the top two pyramid groups, are important sources of vitamins and minerals, and are the only food sources of dietary fiber. Grains include foods such as pasta, breads, cereals, and rice. When selecting a diet high in grains, especially bread and baked products, look for those labeled *whole grain* or that list *whole-grain* flours as one of the first ingredients on the label. Also be aware that many baked items can also be high in fat and sugar.

CHOOSE A VARIETY OF FRUITS AND VEGETABLES DAILY—The Five-A-Day campaign was initiated by the National Cancer Institute in the early 1990s to call attention to ingesting a minimum of five fruits and vegetables a day.

Evidence suggests this simple recommendation could help to reduce the risk for some cancers because of the vitamin, mineral, and fiber content of fruits and vegetables. Evidence is mounting to indicate a protective role for nutrients especially associated with fruits and vegetables. This includes the antioxidant nutrients (vitamin C, vitamin E, beta carotene, and the mineral selenium) and the B vitamin folic acid. Fruits and vegetables are the primary sources of beta-carotene, as well as vitamins A and C, whereas selenium is found in meat, fish, and eggs but also in the grains of whole-wheat bread and oatmeal. Vitamin E is found in oils used in salad dressings and margarines. Antioxidants help to prevent the oxidation of

Table 107-3. ***(continued)*.**

DIETARY REFERENCE INTAKES: MACRONUTRIENTS

NUTRIENT	FUNCTION	IOM/FNB 2002 SCORING PATTERN[a]	MG/G PROTEIN	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
Indispensable amino acids:				
Histidine	The building blocks of all proteins in the body and some hormones. These nine amino acids must be provided in the diet and thus are termed indispensable amino acids. The body can make the other amino acids needed to synthesize specific structures from other amino acids and carbohydrate precursors.	Histidine	18	Since there is no evidence that amino acids found in usual or even high intakes of protein from food present any risk, attention was focused on intakes of the L-form of these and other amino acid found in dietary protein and amino acid supplements. Even from well-studied amino acids, adequate dose-response data from human or animal studies on which to base a UL were not available. While no defined intake level at which potential adverse effects of protein was identified for any amino acid, this does not mean that there is no potential for adverse effects resulting from high intakes of amino acids from dietary supplements. Since data on the adverse effects of high levels of amino acid intakes from dietary supplements are limited, caution may be warranted.
Isoleucine		Isoleucine	25	
Lysine		Lysine	55	
Leucine		Leucine	51	
Methlonine & Cysteine		Methionine & Cysteine	25	
Phenylalanine & Tyrosine		Phenylalanine & Tyrosine	47	
Threonine		Threonine	27	
Tryptophan		Tryptophan	7	
Valine		Valine	32	

NOTE: The table is adapted from the DRI reports, see www.nap.edu.
[a] Based on the amino acid requirements derived for Preschool Children (1–3 y): (EAR for amino acid + EAR for protein); for 1–3 y group where EAR for protein = 0.88 g/kg/d.
SOURCES: *Dietary Reference Intakes for Energy, Carbohydrate. Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002). This report may be accessed via www.nap.edu.

substances in the body, including free radicals. Free radicals are compounds with an unpaired electron that can be especially destructive to electron-dense areas of the cell such as the DNA and the cell membrane. Lipids are components of cell membranes. Oxidation of lipids occurs freely in the body and in foods. The antioxidant nutrients help to decrease the amount and rate of oxidation. The oxidation of lipids is implicated in the development of arterial plaque in CHD and in the DNA changes in the cell during the initiation of a cancer. Oxidation of lipids in foods causes rancidity and spoilage. Folic acid, a member of the B vitamin family, is found in some fruits and vegetables as folate. Adequate amounts of folic acid have been proved to reduce the risk of neural-tube defects, such as spina bifida, in the developing fetus. This role of folic acid is so strong that in 1992, the US Public Health Service (USPHS) issued a recommendation for all women of childbearing age to take the vitamin as a supplement. It is important to take folic acid before conception because neural-tube development occurs in the first trimester of pregnancy. This is a time when many women would not yet know they were pregnant. To further foster the consumption of folic acid in the diet, the nutrient was added to enriched bread products starting in January 1998 and is believed responsible for the reduction of related neural tube defects. Folic acid also may be related to reduction of risk of cardiovascular disease through a role in reducing homocysteine levels.

Fiber is an important component of plant carbohydrates in our diet, and the best sources are the whole grains, fruits and vegetables, and legumes. Dietary fiber is defined as plant parts that are not digested by the human digestive tract. Animal foods such as dairy foods and meats do not contain any dietary fiber. For the first time, the DRI report in September 2002 recommended to eat 14 g of dietary fiber for every 1000 calories. This represents approximately double what most Americans currently consume. Increasing dietary fiber would decrease the incidence of diverticulosis and potentially problems associated with constipation. Table 107-10 includes a representative fiber content of selected types of foods.

Not all food fiber acts the same in the body. Contributing a smaller part of the total fiber content of foods are soluble fibers that act in the small intestine. Soluble fiber is related to less absorption of dietary cholesterol and also plays a role in the control of blood glucose. Insoluble fibers act in the large intestine where they add bulk and foster regular elimination of wastes. Food sources have a mixture of soluble and insoluble. When asked about fiber supplements, the clinician should first stress food sources such as grains, fruits, vegetables, and legumes because food sources offer the added benefit of the vitamins and minerals associated with these foods. Additionally plant foods carry a variety of phytochemicals, substances in plants that increasingly are being found to offer benefits related to good health.

KEEP FOOD SAFE TO EAT—The addition of this dietary guideline in the 2000 edition illustrates the increasing concern over food borne illness and the importance of handling food safely in the home. Basic hygiene practices such as washing hands before handling food and washing surfaces in contact with food, such as cutting boards and counters, seem common sense, but lack of these practices contributes to food-borne illness. Although these practices are recommended for everyone, they are especially important for the vulnerable population groups such as pregnant women and those with a compromised immune system.

Choose Sensibly

CHOOSE A DIET THAT IS LOW IN SATURATED FAT AND CHOLESTEROL AND MODERATE IN TOTAL FAT—With all the increased emphasis on fats in the diet, it is important for the professional to understand that some dietary fat is needed for good health. Fats provide essential substances such as essential fatty acids and are sources of the fat-soluble vitamins A, E, D, and K. The Dietary Guidelines counsel Americans to choose a diet low in total fat, and particularly low in saturated fat and cholesterol. Many pharmacy clients are on medications to reduce their cholesterol or triglyceride levels. Although blood lipids and dietary lipids are not always directly associated, in general, medications intended to alter blood lipids work best if the client also is following a diet modified in fat. Dietary fat often is referred to as saturated, polyunsaturated, or monounsaturated, which refers to the degree of saturation of the fatty acid, the basic chemical unit in fat. Although the DRIs recommended a wide range for the percent of kcal from fat, the current version of the Dietary Guidelines suggests less than 30% of total kilocalories

Table 107-4. Food and Nutrition Board, Institute of Medicine-National Academy of Sciences Dietary Reference Intakes: Electrolytes and Water

DIETARY REFERENCE INTAKES: ELECTROLYTES AND WATER

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Sodium	Maintains fluid volume outside of cells and thus normal cell function.		(g/d)	(g/d)	Processed foods to which sodium chloride (salt) /benzoate/phosphate have been added; salted meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table. Salt is ~ 40% sodium by weight.	Hypertension; increased risk of cardiovascular disease and stroke.	The AI is set based on being able to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for individuals engaged in recommended levels of physical activity. Individuals engaged in activity at higher levels or in humid climates resulting in excessive sweat may need more than the AI. The UL applies to apparently healthy individuals without hypertension; it thus may be too high for individuals who already have hypertension or who are under the care of a health care professional.
		Infants					
		0–6 mo	0.12	ND[b]			
		7–12 mo	0.37	ND[b]			
		Children					
		1–3 y	1.0	1.5			
		4–8 y	1.2	1.9			
		Males					
		9–13 y	1.5	2.2			
		14–18 y	1.5	2.3			
		19–30 y	1.5	2.3			
		31–50 y	1.5	2.3			
		50–70 y	1.3	2.3			
		>70 y	1.2	2.3			
		Females					
		9–13 y	1.5	2.2			
		14–18 y	1.5	2.3			
		19–30 y	1.5	2.3			
		31–50 y	1.5	2.3			
		50–70 y	1.3	2.3			
		>70 y	1.2	2.3			
		Pregnancy					
		14–18 y	1.5	2.3			
		19–50 y	1.5	2.3			
		Lactation					
		14–18 y	1.5	2.3			
		19–50 y	1.5	2.3			
Chloride	With sodium, maintains fluid volume outside of cells and thus normal cell function.		(g/d)	(g/d)	See above; about 60% by weight of salt.	In concert with sodium, results in hypertension.	Chloride is lost usually with sodium in sweat, as well as in vomiting and diarrhea. The AI and UL are equal-molar in amount to sodium since most of sodium in diet comes as sodium chloride (salt).
		Infants					
		0–6 mo	0.18	ND[b]			
		7–12 mo	0.57	ND[b]			
		Children					
		1–3 y	1.5	2.3			
		4–8 y	1.9	2.9			
		Males					
		9–13 y	2.3	3.4			
		14–18 y	2.3	3.6			
		19–30 y	2.3	3.6			
		31–50 y	2.3	3.6			
		50–70 y	2.0	3.6			
		>70 y	1.8	3.6			
		Females					
		9–13 y	2.3	3.4			
		14–18 y	2.3	3.6			
		19–30 y	2.3	3.6			
		31–50 y	2.3	3.6			
		50–70 y	2.0	3.6			
		>70 y	1.8	3.6			
		Pregnancy					
		14–18 y	2.3	3.6			
		19–50 y	2.3	3.6			
		Lactation					
		14–18 y	2.3	3.6			
		19–50 y	2.3	3.6			

NOTE: The table is adapted from the DRI reports. See www.nap.edu. Adequate Intakes (AIs) may be used as a goal for individual intake. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake; therefore, no Recommended Dietary Allowance (RDA) was set.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCE: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* This reports may be accessed via www.nap.edu.

Table 107-4. ***(continued).***

DIETARY REFERENCE INTAKES: ELECTROLYTES AND WATER

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Potassium	Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake, and decrease markers of bone turnover and recurrence of kidney stones.		(g/d)	No UL.	Fruits and vegetables; dried peas; dairy products; meats, and nuts.	None documented from food alone; however, potassium from supplements or salt substitute can result in hyperkalemia and possibly sudden death if excess is consumed by individuals with chronic renal insufficiency (kidney disease) or diabetes.	Individuals taking drugs for cardiovascular disease such as ACE inhibitors, ARBs (Angiontensin Receptor Blockers), or potassium sparing diuretics should be careful to not consume supplements containing potassium and may need to consume less than the AI for potassium.
		Infants					
		0–6 mo	0.4				
		7–12 mo	0.7				
		Children					
		1–3 y	3.0				
		4–8 y	3.8				
		Males					
		9–13 y	4.5				
		14–18 y	4.7				
		19–30 y	4.7				
		31–50 y	4.7				
		50–70 y	4.7				
		>70 y	4.7				
		Females					
		9–13 y	4.5				
		14–18 y	4.7				
		19–30 y	4.7				
		31–50 y	4.7				
		50–70 y	4.7				
		>70 y	4.7				
		Pregnancy					
		14–18 y	4.7				
		19–50 y	4.7				
		Lactation					
		14–18 y	5.1				
		19–50 y	5.1				
Water	Maintains homeostasis in the body and allows for transport of nutrients to cells and removal and excretion of waste products of metabolism.		(L/d)	No UL.	All beverages, including water, as well as moisture in foods (high moisture foods include watermelon, meats, soups, etc.).	No UL because normally functioning kidneys can handle more than 0.7 L (24 oz) of fluid per hour; symptoms of water intoxication include hyponatremia which can result in heart failure and rhabdomyolosis (skeletal muscle tissue injury) which can lead to kidney failure.	Recommended intakes for water are based on median intakes of generally healthy individuals who are adequately hydrated; individuals can be adequately hydrated at levels below as well as above the AIs provided. The AIs provided are for total water in temperate climates. All sources can contribute to total water needs; beverages (including tea, coffee, juices, sodas, and drinking water) and moisture found in foods. Moisture in food accounts for about 20% of total water intake. Thirst and consumption of beverages at meals are adequate to maintain hydration.
		Infants					
		0–6 mo	0.7				
		7–12 mo	0.8				
		Children					
		1–3 y	1.3				
		4–8 y	1.7				
		Males					
		9–13 y	2.4				
		14–18 y	3.3				
		19–30 y	3.7				
		31–50 y	3.7				
		50–70 y	3.7				
		>70 y	3.7				
		Females					
		9–13 y	2.1				
		14–18 y	2.3				
		19–30 y	2.7				
		31–50 y	2.7				
		50–70 y	2.7				
		>70 y	2.7				
		Pregnancy					
		14–18 y	3.0				
		19–50 y	3.0				
		Lactation					
		14–18 y	3.8				
		19–50 y	3.8				

NOTE: The table is adapted from the DRI reports. See www.nap.edu. Adequate Intakes (AIs) may be used as a goal for individual intake. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake; therefore, no Recommended Dietary Allowance (RDA) was set.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCE: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* This reports may be accessed via www.nap.edu.

Table 107-4. ***(continued).***

DIETARY REFERENCE INTAKES: ELECTROLYTES AND WATER

NUTRIENT	FUNCTION	LIFE STAGE GROUP	AI	UL[a]	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Inorganic Sulfate	Required for biosynthesis of 3′-phosphoadenosine-5′-phosphate (PAPS), which provides sulfate when sulfur-containing compounds are needed such as chondroitin sulfate and cerebroside sulfate.	Infants 0–6 mo 7–12 mo Children 1–3 y 4–8 y Males 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Females 9–13 y 14–18 y 19–30 y 31–50 y 50–70 y >70 y Pregnancy 14–18 y 19–50 y Lactation 14–18 y 19–50 y	No recommended intake was set as adequate sulfate is available from dietary inorganic sulfate from water and foods, and from sources of organic sulfate, such as glutathlone and the sulfur amino acids methionine and cysteine. Metabolic breakdown of the recommended intake for protein and sulfur amino acids should provide adequate inorganic sulfate for synthesis of required sulfur-containing compounds.	No UL	Dried fruit (dates, raisins, dried apples), soy flour, fruit juices, coconut milk, red and white wine, bread, as well as meats that are high in sulfur amino acids.	Osmotic diarrhea was observed in areas where water supply had high levels; odor and off taste usually limit intake, and thus no UL was set.	

NOTE: The table is adapted from the DRI reports. See www.nap.edu. Adequate Intakes (AIs) may be used as a goal for individual intake. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake; therefore, no Recommended Dietary Allowance (RDA) was set.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCE: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* This reports may be accessed via www.nap.edu.

and a saturated fat content of less than 10% of total kilocalories. Saturated fats are found primarily in animal sources such as butter, lard and the fat associated with red meats, and in milk (other than skim) and milk products such as cheese. Poultry and fish also have some saturated fat, but, in general, less than red meats. Polyunsaturated fats primarily come from plant sources of which sunflower, corn, soybean, cottonseed, and safflower oils are primary sources; products, such as some margarines, are made from these plants oils. Monounsaturated fatty acids are of both plant and animal origin with olive oil and peanut oil the most common examples. Cholesterol is a type of fat found only in animal foods, such as butter, lard, eggs, whole and 2% milk, and milk products from these sources. Cholesterol also is produced by the body and is not a dietary essential. Lowering dietary cholesterol does not necessarily mean that the cholesterol level in the blood will correspond. Generally, approximately one third of American's blood cholesterol levels respond to a diet lower in cholesterol. Generally, less total fat, less saturated fat, and less cholesterol are associated with a reduction in the risk of cardiovascular diseases, including stroke. Following the Food Guide Pyramid is the starting place for a diet plan lower in fat. Because most saturated fat is found in animal sources and cholesterol is only found in foods of animal origin, if the diet foundation is based on grains, fruits, and vegetables, with only the suggested serving sizes from the meat and milk groups, the resulting diet is naturally low in total fat, saturated fat, and cholesterol. As apparent in Figure 107-2, the Food Guide Pyramid also helps consumers identify where fats are located in the food groupings through the use of icons to represent fats that are both naturally occurring and are added to foods.

There will always be issues regarding lipids! Current ones include *trans* fatty acids and the role of several specific fatty acids. *Trans* fatty acids refer to the orientation of the molecule when fats are hydrogenated for the purpose of providing the food industry and the consumer with fats of differing consistencies. For example, hydrogenation is used to change the physical state of oil, which is a liquid, to the physical state of a solid, as in making a solid margarine from a liquid vegetable oil. The addition of hydrogen to the molecule increases the saturation of the molecule, but also alters the structural orientation of the organic molecule from the more naturally occurring *cis* form to a *trans* form, thus a *trans* fatty acid. Estimated ranges of the

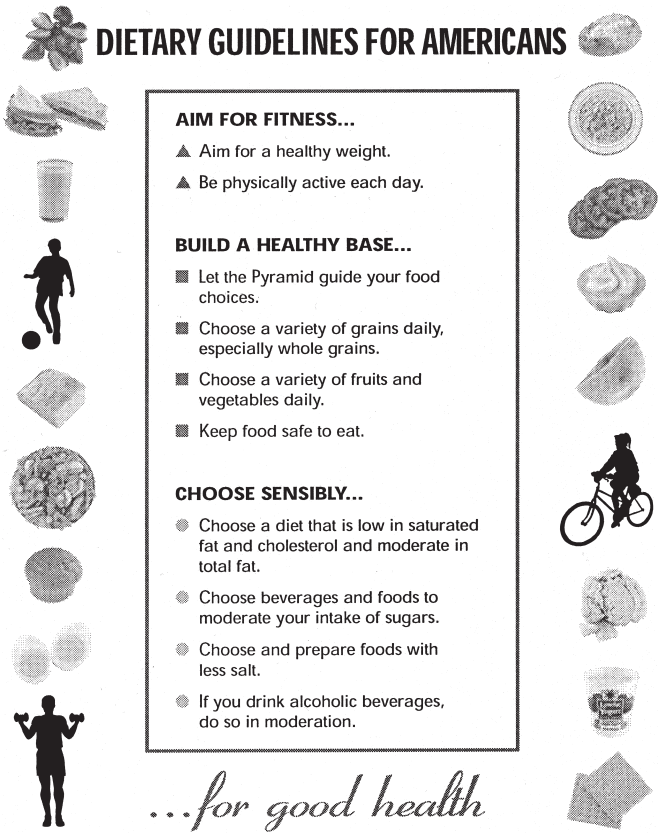


Figure 107-1. Dietary guidelines for Americans.

amount of *trans* fatty acids in the diet of Americans range from 3% to 8% of total kilocalories. There is not general agreement among scientists and health professionals on. a specific amount of *trans* fatty acids thought to be harmful, and no DRI. For 2003, the FDA is considering requiring *trans* fatty acids to be listed on food labels. The DRIs recommend intakes for 2 specific types of fatty acids, an omega-3 fatty acid, alpha-linolenic acid, and an omega-6 fatty acid, linoleic acid, both polyunsaturated fatty acids essential in the diet. Omega-3 fatty acids are commonly found in fatty fish such as salmon and tuna and in some oils such as canola or soybean oil. Through a role in reducing the tendency of blood to clot, omega-3 fatty acids may reduce the risk of CVD. These essential fatty acids also have functions related to vision, the immune system, and the hormone-like compounds they produce called eicosanoids. A general recommendation is to consume fish several times a week. Omega-6 fatty acids are found in milk and some oils such as soybean and flaxseed oils.

CHOOSE BEVERAGES AND FOODS TO MODERATE YOUR INTAKE OF SUGAR—Of all the scientific evidence associating various components of the diet with disease, there is little, if any, to support a direct role of sugar. Sugar in the diet does not cause diabetes or hyperactivity and is only indirectly associated with the promotion of dental decay. Sugars are added to the diet in popular ingredients added to food and occur naturally in some foods such as milk and fruit. The 2002 DRI report suggested added sugars not be more than 25% of total calories consumed. Consumers who eat higher amounts of

Table 107-5. Suggested Weight for Adults

	WEIGHT (LBS)[A]	
HEIGHT[B]	19–34 YEARS OLD	35 YEARS OLD AND OLDER
5′0	97–128	108–139
5′1	101–132	111–143
5′2	104–137	115–148
5′3	107–141	119–152
5′4	111–146	122–157
5′5	114–150	126–162
5′6	118–155	130–167
5′7	121–160	134–172
5′8	125–164	138–178
5′9	129–169	142–183
5′10	132–174	146–188
5′11	136–179	151–194
6′0	140–184	155–199
6′1	144–189	149–205
6′2	148–195	164–210
6′3	152–200	168–216
6′4	156–205	173–222
6′5	160–211	177–228
6′6	164–216	182–234

The higher weights in the ranges generally aplpy to men, who tend to have more muscle and bone; the lower weights more often apply to women, who have less muscle and bone.
[a] Without shoes.
[b] Without clothes.

Table 107-6. Body Weight According to Height and Body Mass Index

HEIGHT (INCHES)	BODY MASS INDEX															
BODY WEIGHT (LBS)	19	21	23	25	27	29	31	33	35	37	39	41	43	45	47	49
58	91	100	110	119	129	138	148	157	167	176	186	195	205	214	224	233
59	94	104	114	124	134	144	154	164	174	184	193	203	213	223	233	243
60	97	107	117	127	138	148	158	168	178	188	199	209	219	229	239	250
61	101	111	122	132	143	154	164	175	185	196	207	217	228	238	249	260
62	103	114	125	136	147	158	168	179	190	201	212	223	234	245	255	266
63	107	119	130	141	152	164	175	186	198	209	220	231	243	254	265	277
64	111	123	135	146	158	170	182	193	205	217	228	240	252	264	275	287
65	114	126	138	150	162	174	186	198	210	222	234	246	258	270	282	294
66	118	131	143	156	168	180	193	205	218	230	243	255	268	280	292	305
67	121	134	147	159	172	185	198	210	223	236	248	261	274	287	299	312
68	125	139	152	165	178	191	205	218	231	244	257	271	284	297	310	323
69	128	142	155	169	182	196	209	223	236	250	263	277	290	304	317	331
70	133	147	161	175	189	203	217	231	244	258	272	286	300	314	328	342
71	136	150	164	179	193	207	221	236	250	264	279	293	307	321	336	350
72	140	155	170	185	199	214	229	244	258	273	288	303	317	332	347	362
73	143	158	174	189	204	219	234	249	264	279	294	309	324	340	355	370
74	148	164	179	195	210	226	242	257	273	288	304	319	334	351	366	382
75	151	167	183	199	215	231	247	263	279	294	310	326	342	358	374	390
76	156	172	189	205	222	238	255	271	287	304	320	337	353	370	386	402

Table 107-7. NIH Guidelines for Choosing a Weight Loss Program

The diet should be safe and include all of the Recommended Dietary Allowances for vitamins, minerals, and protein.
The program should be directed toward a slow, steady weight loss unless a more rapid weight loss is medically indicated.
A doctor should evaluate health status if the client's weight loss goal is greater than 15 to 20 pounds, if the client has any health problems, or if the client takes medication on a regular basis.
The program should include plans for weight maintenance.
The program should give the prospective client a detailed list of fees and costs of additional items.

NIH = National Institutes of Health.

sugar in their diet may be lacking a good balance of vitamins and minerals but are not necessarily more likely to be overweight. The Food Guide Pyramid uses icons to represent added sugars to foods. Unlike the icons representing fats, the sugar icons only include added sugars because this is where additional kilocalories would occur in the diet, versus the naturally occurring sugars found in fruit or milk (see Fig 107-2).

CHOOSE AND PREPARE FOODS WITH LESS SALT— Sodium in the American diet comes primarily from salt or sodium chloride. Most of the salt and sodium comes from the addition of salt, or other ingredients containing salt, at the table, in cooking, and from the salt added to foods during processing. Examples of foods that receive salt during processing are salad dressings, soups, most snack foods such as chips and dips, cured meats, and most packaged foods. Sodium plays an important role in the body to help regulate body fluids and blood pressure. Most Americans consume more salt and sodium than is needed for daily balance, but most individuals simply excrete it. For this reason there is some controversy on having a general guideline for all Americans to limit the consumption of sodium.

For some Americans excess consumption of salt and sodium contributes to hypertension, kidney disease, heart disease, and a host of other problems. The taste for salt is acquired, and the general advice is to be more moderate in our consumption.

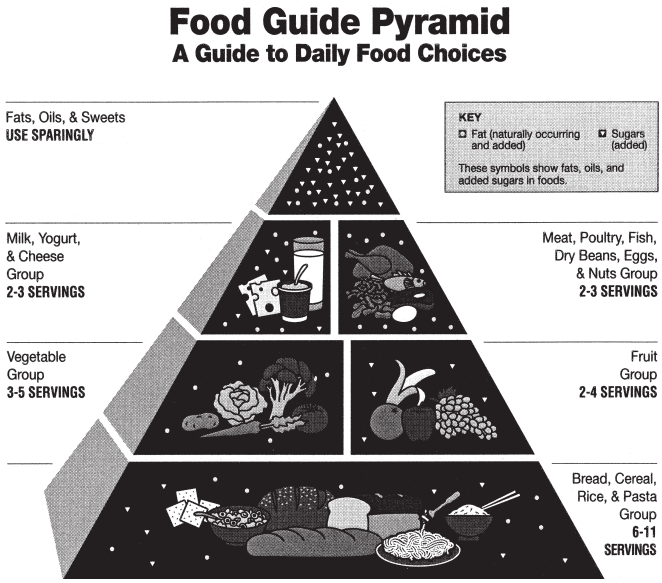


Figure 107-2. Food guide pyramid. A guide to daily food choices.

Salt-sensitive people will see a reduction in blood pressure with a reduction in sodium in the diet, but not all people are salt sensitive. A means to identify salt sensitivity is a current area of nutrition research. Many clients maintained on diuretics also follow a diet lower in sodium. The most common lower sodium diet plans are for a 2- to 3-g sodium restriction. A diet without added salt generally provides approximately 3 g of sodium, whereas a diet without added salt and the reduction of foods especially high in sodium generally provides approximately 2 g of sodium. A new DRI for sodium was released in 2004 (see Table 107-4).

IF YOU DRINK ALCOHOLIC BEVERAGES, DO SO IN MODERATION—Alcohol supplies kilocalories but no nutrients. Although some nutrients may be present in a beverage mixed with the alcohol, this is a dietary guideline because many

Table 107-8. Analysis of Weight Loss/Management Approaches

DOES THE WEIGHT LOSS MAINTENANCE APPROACH	YES	NO
1. Promise weight loss greater than 1/2 to 1 lb per week?	☐	☐
2. Claim a single or few foods are crucial to the diet?	☐	☐
3. Advocate a single source of foods, eg, a fortified beverage?	☐	☐
4. Eliminate any one or more of the food groups associated with the Food Guide Pyramid?		
Bread, cereal, rice, and pasta	☐	☐
Fruit	☐	☐
Vegetables	☐	☐
Milk, yogurt, cheese	☐	☐
Meat, poultry, fish, dry beans, eggs, and nuts	☐	☐
5. Advise less than he minimum number of servings for		
Bread, cereal, rice, and pasta (6–11)	☐	☐
Fruit (2–4)	☐	☐
Vegetables (3–5)	☐	☐
Milk, yogurt, cheese (2–3)	☐	☐
Meat and its alternatives	☐	☐
6. Suggest fewer than three meals per day?	☐	☐
7. Suggest a requirement for fewer specific foods in combination with other specific foods?	☐	☐
8. Sell a product?	☐	☐
9. Suggest the diet is all you need without reference to behavior modification?	☐	☐
10. Suggest a program without exercise?	☐	☐

If the answer to any one of these questions is "YES," you should be aware the approach does NOT conform to generally accepted standards for appropriate weight loss or weight maintenance.

Table 107-9. What Counts as a Serving?[a]

Grain Products Group (bread, cereal, rice, and pasta)
1 slice of bread
1 ounce of ready-to-eat cereal
1/2 cup of cooked cereal, rice, or pasta

Vegetable Group
1 cup of raw leafy vegetables
1/2 cup of other vegetables—cooked or chopped raw
3/4 cup of vegetable juice

Fruit Group
1 medium apple, banana, orange
1/2 cup of chopped, cooked, or canned fruit
3/4 cup of fruit juice

Milk Group (milk, yogurt, and cheese)
1 cup of milk or yogurt
11/2 ounces of natural cheese
2 ounces of processed cheese

Meat and Beans Group (meat, poultry, fish, dry beans, eggs, and nuts)
2–3 ounces of cooked lean meat, poultry, or fish
1/2 cup of cooked dry beans or 1 egg counts as 1 ounce of lean meat.
2 tbsp of peanut butter or 1/3 cup of nuts count as ounce of meat.

[a] Some foods fit into more than one group. Dry beans, peas, and lentils can be counted as servings in either the meat and beans group or vegetable group. These "crossover" foods can be counted as servings form either one or the other group, but not both. Serving sizes indicated here are those used in the Food guide Pyramid and based on both suggested and usually consumed portions necessary to achieve adequate nutrient intake. They differ from serving sizes on the Nutrition Facts Label, which reflect portions usually consumed.

Americans need guidance regarding alcoholic beverages. Moderation is defined as no more than one drink per day for women and no more than two drinks per day for men. Many clients on medications may be advised not to consume alcohol and pregnant and lactating women are advised to avoid all alcohol.

Other Dietary Guidance

Many other appropriate dietary guidance standards exist. The US Dietary Guidelines is a generic set of guidelines, whereas many standards are for specific purposes. For example, an appropriate set of guidelines is published by The American Heart Association with more focus on prevention of CVD. The American Institute for Cancer Research has a global report with a focus on a plant-based diet for prevention of cancer, and The American Cancer Society also has a set of guidelines aimed at cancer reduction risk. The American Diabetes Association releases recommendations specific to persons who have diabetes. All these guides have many components in common, namely, to follow a food pattern consistent with a variety of foods from different food groups, to maintain weight within an acceptable range, and to alter any over consumption of food components determined to be detrimental to an individual's health such as kilocalories, fat, saturated fat, cholesterol, sugar, sodium, and alcohol.

Table 107-10. Average Fiber (g) in Food Types

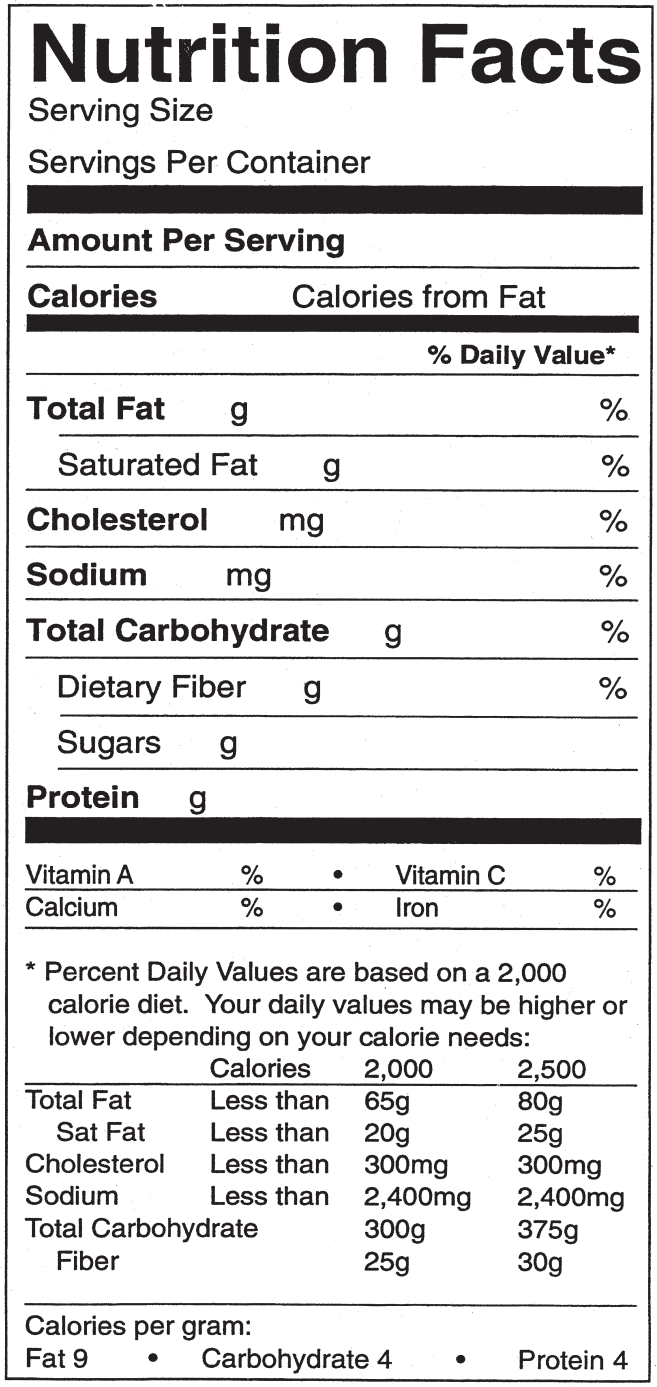
Legumes (1/2 cup)	8
Cereals, bran (1/2 cup)	8
Cereals, whole grain (1/2 cup)	3
Nuts and seeds (1 oz)	3
Starchy vegetables (1/2 cup)	3
Vegetables (1/2 cup)	2
Breads and crackers, whole grain (1 slice, 5 crackers)	2
Fruit (1 piece or 1/2 cup)	2
Meats, poultry, fish	0
Dairy products	0

FOOD AND SUPPLEMENT LABELING

LABELS—Food items and supplements are often sold in the pharmacy, making it important for the pharmacist to understand nutrition labeling regulations. A current labeling focus is to have more accurate and less misleading labeling on diet supplements. The *Nutrition Labeling and Education Act* of 1990 requires most packaged foods to list a specified set of nutrition facts on the label. Standard setting and enforcement for nutrition labeling is a responsibility of the Food and Drug Administration (FDA). Nutrition labels are helpful in complying with the Dietary Guidelines. Figure 107-3 is an example of a current food label with the minimum required facts. All the nutrition information on the label is based on the stated serving size. Larger packages, such as cereal boxes, often include additional information not required by law. At the bottom of the panel is located percent daily values based on a standard diet of 2000 kcal. Daily Values (DV) represent another standard used primarily only on nutrition labels. The DV is based on either a DRI or, in the case of dietary components without a current DRI such as fiber and cholesterol, the DV follows a generally acceptable standard such as the Dietary Guidelines. DVs give a quick analysis for those diet components of current concern. Because it takes years for labels to catch-up when standards change, the 2003 label information is not yet based on the most current DRIs.

Nutrition labeling for raw fruits, vegetables, and fish is voluntary, but the standards are consistent with those required on packaged foods in terms of the required set of information and the format in which it is presented. The FDA provides the retailer with the factual data for the voluntary listing of the 20 most commonly consumed raw fruits, vegetables, and fish, and they are posted in the store at the point of purchase. At the current time, the FDA does not plan to require labeling for fresh foods unless less than 60% of retailers do not adhere to the voluntary listing.

DESCRIPTIVE TERMINOLOGY ON LABEL—Some of the terms on labels are approved by the FDA, in conjunction with the Food Safety and Inspection Service (FSIS), to describe a food product. Other terms, such as *dietetic*, are not regulated, are discouraged by the FDA, and are not needed



Nutrition Facts

Serving Size

Servings Per Container

Amount Per Serving

Calories	Calories from Fat
	% Daily Value*
Total Fat g	%
Saturated Fat g	%
Cholesterol mg	%
Sodium mg	%
Total Carbohydrate g	%
Dietary Fiber g	%
Sugars g	
Protein g	

Vitamin A	%	• Vitamin C	%
Calcium	%	• Iron	%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Fiber		25g	30g

Calories per gram:

Fat 9 • Carbohydrate 4 • Protein 4

Figure 107-3. The representative content of a current food label with minimum required facts.

when regulated terms are used on labels. Eleven core terms form the basis of the descriptions. The eleven are *free, low, lean, extra lean, high, good source, reduced, less, light, fewer*, and *more*. Additionally synonyms are approved for the terms. Approved synonyms for *free* include *without, trivial source of, negligible source of, insignificant source of, no,* and *zero*. A food meets the definition for *low* if a large amount of the food could be eaten without exceeding the DV for the nutrient. Synonyms allowed for *low* are *contains a small amount of, low source of, little,* and *few*. A product can claim a specific food is a *good* source of a nutrient only if the food contains 10-19% of the DV for the nutrient or *high* only if the product contains 20% or more of the DV for the nutrient. Some terms cannot be used unless additional characteristics of the product also support the claim. For example products that bear claims related to *percent fat free* also must meet the definition for *low fat* and must accurately reflect the amount of fat in 100 g of the food. Table 107-11 includes the terms commonly used on products as related to specific nutrients.

ADDITIONAL LISTINGS ON LABELS—The section on a food label that lists the ingredients is not considered part of the nutrition labeling regulations, but it does conform to other regulations. Generally, ingredients are listed by their chemical to allow consumers to identify a substance they may need to avoid because of a food sensitivity or allergy. Ingredients also are listed in descending order of their amount. When looking for a whole-grain product, the words *whole grain*, should be among the first in the ingredient list.

All food labels must bear the name and address of the manufacturer and the weight. Universal bar codes allow the product to be traced to the exact place, date, and time it was manufactured. Consumers are encouraged to contact the manufacturer with any specific questions about the product. Many products also have dates on them, but, at the present time, dating is neither required or regulated.

HEALTH CLAIMS ON FOODS—Health claims are only allowed if there is sufficient scientific basis for a relation between nutrient and health or disease. All health claim wording must be pre-approved by the FDA and must state the relationship of the claim to the total daily diet. As of February 2003, health claims were allowed for the following diet and health relationships:

- Calcium and osteoporosis
- Dietary lipids (fat) and cancer
- Dietary saturated fat and cholesterol and risk of coronary heard disease
- Dietary sugar alcohol and dental caries
- Fiber-containing grain products, fruits, and vegetables and cancer
- Folic acid and neural tube defects
- Fruits and vegetables and cancer
- Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of coronary heart disease
- Sodium and hypertension
- Soluble fiber from certain foods and risk of coronary heart disease
- Soy protein and risk of coronary heart disease
- Stanols/sterols and risk of coronary heart disease

The regulation of organic foods, and rules for labeling, became effective in October 2002. Foods may now be labeled *organic* if no chemical fertilizers, sewage sludge, or synthetic pesticides are used, and if the food has not been genetically modified or irradiated.

LABELS ON DIETARY SUPPLEMENTS—The *Dietary Supplement Health and Education Act of 1994* required the FDA to develop labeling requirements specifically designed for products containing ingredients such as vitamins, minerals, herbs, or amino acids intended to supplement the diet. Information similar to the Nutrition Facts panel on foods is now required. Health claims on supplements must follow the same regulations as health claims on foods and may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases. However, unlike drugs, and even foods, dietary supplements are not currently required to follow quality control measures. Therefore, the supplement may or may not have the amount of ingredients as stated on the label, and may even contain ingredients, including contaminants, that are not listed on the label. Unlike foods, dietary supplements are also allowed to make structure and/or function claims. These claims are not pre-approved by the FDA and can be immensely confusing to the consumer.

Labeling regulations for supplements were first on a voluntary basis, with requirements becoming effective in March 1999 for all products labeled after that date. Products on the market before March 1999 that carried the voluntary labeling as suggested by the FDA can remain on the market shelf. Those prod-

Table 107-11. Meanings of Descriptive Words for Specific Nutrients

Sugar
Sugar free: less than 0.5 grams (g) per serving
No added sugar, Without added sugar, No sugar added:
- No sugars added during processing or packing, including ingredients that contain sugars (for example, fruit juices, applesauce, or dried fruit).
- Processing does not increase the sugar content above the amount naturally present in the ingredients. (A functionally insignificant increase in sugars is acceptable from processes used for purposes other than increasing sugar content.)
- The food that it resembles and for which it substitutes normally contains added sugars.
- If the food doesn't meet the requirements for a low- or reduced-calorie food, the product bears a statement that the food is not low-calorie or calorie-reduced and directs consumers' attention to the nutrition panel for further information on sugars and calorie content.

Reduced sugar: at least 25 percent less sugar per serving than reference food

Calories
Calorie free: fewer than 5 calories per serving
Low calorie: 40 calories or less per serving and if the serving is 30 g or less or 2 tablespoons or less, per 50 g of the food
Reduced or Fewer calories: at least 25 percent fewer calories per serving than reference food

Fat
Fat free: less than 0.5 g of fat per serving
Saturated fat free: less than 0.5 g per serving and the level of trans fatty acids does not exceed 1 percent of total fat
Low fat: 3 g or less per serving, and if the serving is 30 g or less or 2 tablespoons or less, per 50 g of the food
Low saturated fat: 1 g or less per serving and not more than 15 percent of calories from saturated fatty acids
Reduced or Less fat: at least 25 percent less per serving than reference food
Reduced or Less saturated fat: at least 25 percent less per serving than reference food

Cholesterol
Cholesterol free: less than 2 milligrams (mg) of cholesterol and 2 g or less of saturated fat per serving
Low cholesterol: 20 mg or less and 2 g or less of saturated fat per serving and, if the serving is 30 g or less or 2 tablespoons or less, per 50 g of the food
Reduced or Less cholesterol: at least 25 percent less and 2 g or less of saturated fat per serving than reference food

Sodium
Sodium free: less than 5 mg per serving
Low sodium: 140 mg or less per serving and, if the serving is 30 g or less or 2 tablespoons or less, per 50 g of the food
Very low sodium: 35 mg or less per serving and, if the serving is 30 g or less or 2 tablespoons or less, per 50 g of the food
Reduced or Less sodium: at least 25 percent less per serving than reference food

Fiber
High fiber: 5 or more per serving. (Foods making high-fiber claims must meet the definition for low fat, or the level of total fat must appear next to the high-fiber claim.)
Good source of fiber: 2.5 g to 4.9 per serving
More or Added fiber: at least 2.5 g more per serving than reference food

ucts with no voluntary labeling will be subject to the new rules. Words such as *high potency* will be required for the product to meet the standard of 100% or more of the DRI or the DV established for that nutrient. *High potency* also can be used with multi-ingredient products if two thirds of the nutrients that are in the product are present at levels that are more than 100% of the DRI or the DV. The term "antioxidant" may be used in conjunction with previously defined terms of *good*, *high*, or *good and high* for products for which scientific evidence shows that after absorption of a sufficient quantity, the antioxidant nutrient or nutrients inactivate free radicals or prevent radical-initiated chemical reactions in the body.

ISSUES RELATED TO SUPPLEMENTS—General agreement on taking nutritional supplements is lacking among medical and nutrition professionals. In general a wise nutritional strategy is to obtain nutrients from foods as part of a well-balanced diet, and supplements should not be taken as an excuse for not obtaining sufficient nutrients from the daily diet. However, supplementation, including the amount to be taken, is appropriate when the supplement has been shown to be safe through sound scientific discovery. Supplementation is needed when food intake may be variable, such as in childhood; when needs may be temporarily increased, such as in pregnancy and lactation; when a specific recommendation from an appropriate source has been made, such as the USPHS recommending folic acid for all women of childbearing age; or when the client has a medical condition that is altering digestion, absorption, metabolism, or excretion of nutrients, such as malabsorption syndromes, renal disease, etc. Surveys have associated supplement users with higher intake of nutrients from foods, with whites, women, older persons, those who have higher education and incomes, and more common among persons who believe diet affects disease. In general, large epidemiological studies have demonstrated supplement use has not lowered overall mortality but has sometimes been associated with a reduced risk of a specific disease.

Over-the-counter (OTC) supplements continue to offer the client a wide variety of substances, including nutrients, packaged in many different combinations. Labeling regulations on supplements help to interpret the information, but the pharmacist should not rely solely on the label in giving advice. The pharmacist can best answer specific questions about supplements and their claims if the scientific literature is thoroughly understood, including all possible advantages and disadvantages of the supplement. An important concept to remember is that nutrients do not function individually, but rather in complex interrelations. Single doses of nutrients can upset natural balances and interrelations. Because of nutrient interrelations, the best advice when a supplement is warranted or desired, is to take one that supplies an acceptable amount of all the nutrients and does not exceed the DRI standard for any one nutrient. This suggestion is consistent with recommendations of the American Medical Association, the Food and Nutrition Board of the National Academy of Sciences, the American Dietetic Association (ADA), the American Society for Clinical Nutrition, and the National Council Against Health Fraud.

FUNCTIONAL FOODS, PHARMACOTHERAPY, AND NUTRACEUTICALS—As scientific evidence has advanced the knowledge of beneficial relations among food, nutrition, health, and disease, a new arena for foods, and food technology, has emerged. Terms such as functional foods, pharmafoods, pharmaceuticals, pharmacotherapy, and nutraceuticals now exist with little current agreement on standardized definitions and many different definitions published in the literature. The terms have in common that nutrients may have a beneficial effect in the prevention and treatment of disease. The public is aware of some of the terms owing to use in the popular press. Literally hundreds of food components exist, and through bioengineering, those components proved of benefit could be increased in the food supply. For example, the antioxidant beta-carotene could be increased in a food or even added to foods that normally would not have this precursor to vitamin A. Strong research is needed to help answer which nutrients need to be increased in the diet whether in the form of foods or as a supplement and what level is needed to gain a benefit and cause no harm. As the media reports suspected benefits, pharmacists are increasingly asked for recommendations about supplements and foods. Until solid evidence is generated, including amounts to recommend, the best advice remains to eat a wide variety of foods with an emphasis on plant foods to form the foundation of the diet.

ADDITIVES IN FOOD AND SUPPLEMENTS—A food additive is any substance that becomes part of a food product. Technically speaking, supplements could be considered additives because they become part of the diet even when they are not in a food product.

Food additives can be intentionally added, such as salt or cinnamon, or unintentionally added, such as when a pesticide used to treat crops unintentionally is incorporated into the plant or when a drug given to an animal unintentionally ends up in the food product supplied by that animal. Even chemical substances that migrate from package materials can become unintentional additives. Generally, additives intentionally added to foods impart properties that yield an improved food supply.

Broad purposes of food additives include maintaining or improving nutritional value such as the addition of vitamins and minerals to a food product. The surge in the addition of calcium to juices and other foods is a good example of this function. A second broad purpose of additives is to maintain freshness in the food. The addition of antioxidants to foods processed with fat, such as potato chips, helps to prevent the fat from becoming rancid, and preservatives help to prevent spoilage as well as changes in color, texture, and flavor of food. A third broad purpose of additives is to help in the processing and preparation of foods such as when emulsifiers are added to peanut butter and mayonnaise to keep the product smooth or to salad dressings and chocolate milk to keep the product in a homogenous solution rather than allowing it to separate. A fourth broad purpose of additives is to make food more appealing. This represents the most widely used additive examples and includes coloring agents, natural and synthetic flavors, flavor enhancers, and sweeteners. The flavor of strawberries in ice cream can come from a strawberry or a chemical flavoring, and the pink color is added because consumers expect strawberry ice cream to be pink. Consumers use additives in the home preparation of food through the use of salt, pepper, sugar, and other ingredients. The most widely used food additives by the food industry are sugar, salt, and corn syrup. These three plus citric acid, baking soda, vegetable colors, mustard, and pepper account for more than 98%, by weight, of all food additives used in the US.

Food additives are regulated under the same basic law as are drugs; the *Food, Drug & Cosmetics (FD&C) Act*. Food and color additive amendments occurred in 1958 and 1960. Only two groups of additives were exempt at that time from a strict testing and approval process. Additives already in use and found to cause no harm when the amendments were added, in 1958 and 1960, were placed on a *generally recognized as safe* (GRAS) list, and a second list of prior sanctioned additives were exempt because of previously meeting the regulatory requirements. However, if questions should arise about the GRAS substances, the testing required would meet all current regulations. Colors used in drugs are the same colors approved for use in foods. All new additives must undergo years of testing, similar to the testing required for new drugs, before being approved by the FDA.

Unintentional additives are monitored through collection and analysis of foods at their point of production and through the FDA Total Diet Study. The Total Diet Study purchases all types of regular foods from the grocery four times a year and in four regions of the US. These foods are then prepared in their usual manner and tested for all substances present in the final product, including nutrients as well as additives. The incidence of unintentional additives, such as pesticides, must be less than amounts established by the FDA, FSIS, and the Environmental Protection Agency (EPA). One approved food process, the irradiation of foods, is regulated as an additive. This is to assure consumers that any changes in the food from irradiation are monitored by the same strict regulations as all other substances added to foods.

FOODS AND NUTRITION MISINFORMATION—In this chapter, several recommendations from reputable sources about eating healthfully have been discussed, but all the recommendations from reputable sources do not begin to compare in number to the abundance of misinformation that exists about foods and nutrition. Notwithstanding the immense cost of purchasing foods and supplements for which no added benefit is known, foods and nutrition misinformation may be harmful when it contributes to false hope and delay of appropriate treatment for an ailment. Misinformation may occur because of a cultural influence, misinterpretation of scientific studies, or as a result of fraudulent business practice. The dietary supplements labeling regulations should help control the latter. Pharmacists should know general ways to spot misinformation and the most common myths related to foods and nutrition. Of the top health frauds listed by the FDA, many are related to nutrition. These included instant weight-loss schemes; supplements to boost sexual ability; fraudulent arthritis products; megavitamin and mineral therapies for cancer, AIDS, and other ailments; false nutritional schemes such as bee pollen, OTC herbal remedies, wheat germ capsules, and protein supplements; chelation therapy; and specific diets and vitamin and mineral supplements to treat candidiasis. In general, suspect misinformation when the following has occurred

- *Recommendations promise a quick fix, such as loss of 5 lb a week*. Use Table 107-7 as a way to determine the merit of a diet program.
- *Dire warnings of danger are listed for a single food or product or regimen.* Hundreds of foods and approximately 90,000 meals are eaten over a normal lifetime. It would take a lot of any one food for it to severely affect health. Avoiding specific foods does not guarantee a healthy diet. A healthy diet is about what is eaten, not what is avoided.
- *A single food is recommended as superior to all other foods.* No one food, or even several foods, has all the nutrients needed for life.
- *The nation's food supply is reported as being unable to provide adequate nutrients through overprocessing, requiring the purchase of special products or supplements to overcome the deficit.* The US has the best, safest, and most regulated food supply in the world.
- *Claims that sound too good to be true such as an increase in metabolism simply by taking a supplement.* Activity is needed to get any significant increase in metabolism to burn kilocalories.
- *Recommendations based on a single study, a study with few subjects, a study that was not conducted as a double blind, a study that was not confirmed by other studies, a study that was not peer reviewed, or a study that was complex but is listing simplistic recommendations*. Professionals must learn how to interpret scientific studies.
- *A list of good or bad foods.* There are no good or bad foods, but there are good and bad diets.
- *Recommendations made to help sell a product*. A well-balanced diet does not require the purchase of a specific product.
- *Recommendations from studies that ignore differences among individuals, treating all people the same.* People come in all sizes and shapes and are individual in their diet patterns and behaviors.

Table 107-12. Usual Medical Nutrition Therapy in Selected Health Conditions

HEALTH CONDITION	USUAL NUTRITION THERAPY
Coronary Heart Disease	Achievement and maintenance of appropriate weight range. Optimization of serum lipid levels by alteration of dietary total fat, saturated fat, polyunsaturated fat, monounsaturated fat, cholesterol, and carbohydrate content of diet. May include sodium modification.
Diabetes Mellitus	Achievement and maintenance of appropriate weight range. Food intake to achieve normalized blood glucose values in conjunction with, or without, insulin therapy. Optimization of serum lipid levels via dietary lipid alterations listed under Coronary Heart Disease.
HIV/AIDS	Maintenance of appropriate weight range, including use of meals replacement supplements as necessary. May require parenteral nutrition and repletion of specific nutrients as assessed. Management of nutrition-related issues, ie, food safety, drug/nutrient/food interactions, and food regimens and general guidance to help offset related problems ie, nausea, vomiting, satiety, dysphagia. Attention to the social aspects of food as well as restorative and maintenance aspects. Clients need assistance in evaluating supplement information and nutrition products.
Hypertension	Achievement and maintenance of appropriate weight range. Attention to adequate amounts of fruits and vegetables, calcium, magnesium customary limitation of salt, sodium, and alcohol. and potassium with
Neoplastic Disease	Same as HIV/AIDS listed above.
Obesity	Achievement and maintenance of appropriate weight range. Alteration of serum parameters often associated with Obesity, ie, blood lipids.
Chronic Renal Disease	General nutrition therapies include varying levels of protein, depending on the disease stage; decreasing dietary phosphorus, potassium, sodium, and fluids and increasing calcium via the diet and/or supplements. Weight maintenance within a normal range and vitamin and mineral supplements are also concerns when individually warranted.

MEDICAL NUTRITION THERAPY—The assessment and development of nutrition care plans, along with monitoring and evaluation, for clients who have diseases that could benefit from nutrition intervention is termed Medical Nutrition Therapy (MNT). The MNT process is effective in treating disease and preventing disease complications, resulting in health benefits and cost savings for the public. Many health-care advocacy and government groups have published recommendations that include MNT. These include, but are not limited to, the National Cholesterol Education Program, the National High Blood Pressure Education Program, the American Diabetes Association, the American Cancer Society, the National Academy of Sciences Committee on Nutritional Status During Pregnancy and Lactation, and the Nutrition Screening Initiative. Many health problems that warrant MNT also include medication(s).

Foremost in any MNT is the individualization of a nutrition care plan to the client. The client should be assessed as to their nutritional status and how it may be compromised by the specific disease process. Assessment includes attention to anthropometric measures (ie, height, weight, and adipose deposits), biochemical measures (ie, all pertinent laboratory values), clinical evaluations (ie, a physical assessment of the body), and a diet evaluation to assess the usual diet and factors that affect eating behavior. After a thorough assessment, the nutrition professional can determine the best nutrition care plan for the individual, taking into account the medical and drug therapy the client will be receiving during their illness. All diet plans for MNT use the Dietary Guidelines for Americans and the DRIs as basic guidelines. An appropriate nutrition care plan first attempts to feed the client in as normal a fashion as possible, using enteral nutrition or the gut for entry of nutrients. In some cases the client may require the administration of nutrition outside the gut, parenteral nutrition, to achieve the nutrition goal. When the client is in a stage of growth, (ie, childhood), a major goal of MNT is to foster a normal growth pattern. Many chronic diseases result in anorexia, presenting feeding challenges to the client and nutrition professional.

The individualization of the nutrition care plan is important, but general aspects can be listed as customary with specific conditions (Table 107-12). When a client has multiple conditions (ie, both hypertension and diabetes mellitus), the MNT must include aspects related to the control of both disease entities.

RESOURCES—The practicing pharmacist can benefit immensely from making contact with nutritional professionals. Ultimately, it is the client who benefits from the teamwork of all health professionals. The Registered Dietitian (RD) is the nutrition counterpart to the Registered Pharmacist. The RD provides general nutrition guidance as well as MNT individualized to the client's specific needs. Through its National Center for Nutrition and Dietetics, the ADA maintains a Nutrition Hot Line for professionals and consumers at 1-800-366-1655. Callers can listen to prerecorded food and nutrition messages, locate RDs in their area for nutrition counseling, and seek answers to questions from RDs. The information is available in both English and Spanish and also via telecommunications device for the deaf. The ADA also publishes refereed position papers on issues of importance about foods and nutrition. Many of the position papers related to information in this chapter are included in the chapter bibliography. Increasingly, the worldwide web (www) is being used by consumers and professionals for information. The professional must be able to evaluate all resource information, including the www, as to its validity and usefulness. In the bibliography are several resources to provide information on evaluation of nutrition information.

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Note—FANSA is made up of The American Dietetic Association, The American Society for Clinical Nutrition, Inc., American Society for Nutrition Sciences, and Institute of Food Technologists. For information contact National Center for Nutrition and Dietetics, American Dietetic Association, 120 South Riverside Plaza, Suite 2000, Chicago, IL 60606.
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American Society for Nutritional Sciences: http://www.asns.org
Center for Nutrition Policy and Promotion http://www.usda.gov/cnpp
Dietary Reference Intakes http://www.nas.edu
Food and Drug Administration (FDA) http://www.fda.gov
Food and Nutrition Information Center (FNIC) http://www.nalusda.gov/fnic/
Food Safety and Inspection Service (FSIS) http://www.fsis.usda.gov
Healthfinder—US Government (A gateway consumer health information web site from the US Government. Find selected online publications, clearinghouses, databases, web sites, and support and self-help groups, as well as the government agencies and not-for-profit organizations that produce reliable information for the public) http://www.healthfinder.gov/
National Council Against Health Fraud http://www.ncahf.org/
National Organic Program. http://www.ams.usda.gov/nop
Tufts University Navigator (Reviews websites using set criteria and a panel of nutrition professionals) http://navigator.tufts.edu/

CHAPTER 108

Pharmacoepidemiology

Michael D Murray, PharmD, MPH

Pharmacoepidemiology, or drug epidemiology, is the study of the effects of drugs in populations of people. The discipline is an amalgam of clinical pharmacology, clinical epidemiology, medical informatics, and biostatistics. There are a number of reasons why pharmacoepidemiology has recently emerged as a discipline. Traditional clinical pharmacology directs much of its attention to the pharmacokinetics and pharmacodynamics of drugs. These studies usually involve small numbers of subjects (6–25) who are studied intensively to obtain an understanding of drug absorption, distribution, metabolism, or excretion. Studies of these parameters determine the dose and frequency of administration of new drugs in the treatment of patients and are required before drugs are marketed. However, such studies tell us little about certain experiences of drugs after they are marketed. It is in this postmarketing phase that the tools of clinical epidemiology come into play, especially in determining the frequency of adverse drug effects.

Though new drug products undergo the careful scrutiny of Phase I through III testing, some drug products are recalled soon after they are marketed. There are a litany of such experiences including phocomelia from thalidomide, Guillain-Barré syndrome from influenza vaccine, endometrial cancer from diethylstilbestrol, cardiac valve disorders from the combination use of fenfluramine and phentermine (Fen-Fen), anaphylaxis from zomepirac, hepatic failure from bromfenac, and cardiac arrest from interactions from drugs like mibefradil or terfenadine when administered with drugs that inhibit P-450 CYP 3A4 such as ketoconazole and erythromycin. A major reason for these drug product recalls is that premarketing studies treat too few patients (typically 3000–4000) to detect uncommon drug effects. An adverse effect that occurs in only 1 in 25,000 persons would go unnoticed in only 4000 treated patients in the premarketing phase. Yet once the drugs are marketed, they often reach millions of patients and rare events can become manifest. Hence, premarketing studies have insufficient statistical power to detect rare adverse effects.

The effect of sample size on the statistical power of a study is shown in Figure 108-1. In general terms, the *power* of a test is the ability of a statistical test used in a study to detect a relationship between an exposure (drug) and an event or outcome. The highest value the power can have is one, and the lowest is zero. The figure shows the power curve for a clinical trial in which the outcome of interest occurs in 4 of every 1000 patients in one treatment group and in 1 in every 1000 patients in another treatment group. For clinical trials, it is generally desirable to keep the power of a study above 0.80. From the figure it can be seen that fewer than 4000 patients in each group would yield insufficient power to detect a difference between groups when alpha is 0.05 and a two-tailed test is performed. Another way to interpret the curve is to consider that an adverse effect occurred in 0.4% of patients receiving a drug, and the same adverse effect occurred in 0.1% of patients receiving placebo; more than 8000 patients would need to be recruited into the study to detect such an effect. The cost of such a study would be prohibitive.

Another important reason that important adverse events are not identified in the premarketing drug experience is that although subjects in premarketing studies have the disease that the drug is targeted to treat, they are otherwise healthy people. Typically, premarketing studies exclude patients who have complicating factors such as renal or hepatic insufficiency, diabetes mellitus, or heart failure. But once the drugs are marketed, they often reach patients with a multitude of comorbidities and complicating conditions. In this real world setting of care, treated patients are sicker, and adverse drug reactions are more common.

Because adverse effects of drug products are more commonly observed after marketing, the Food and Drug Administration (FDA) created the MedWatch Medical Products Reporting Program, which is the largest drug and device surveillance program in the US (see below). A similar program is operated by the World Health Organization (WHO). Such drug surveillance programs are important ways for drug regulatory agencies to keep their fingers on the pulse of the adverse drug experiences of countries.

Now that the interface between pharmacoepidemiology and clinical pharmacology and clinical epidemiology is clearer, the question remains as to how medical informatics and biostatistics enter into the mix. Health systems such as managed-care organizations, hospitals, clinics, and medical centers generate a large volume of data on patients. Increasingly, such data are being captured and stored in huge databases. Data found in these warehouses often come from many sources including the pharmacy, laboratory, radiology, and patient-care clinics and wards. To conduct studies of outcomes of patients who have been prescribed drugs requires merging these large files from disparate sources. Such integrated databases are becoming larger and richer. When such data are available through time and are linked using a unique patient identifier, a variety of studies of the effects of drugs in large populations of patients (ie, pharmacoepidemiologic studies) are possible.[1] The analysis of such large data sets requires the tools of biostatistics. The types of statistical procedures used in the analysis of data for pharmacoepidemiologic studies can range from simple counts of events to sophisticated mathematical models. Some of the procedures that apply to pharmacoepidemiology are described in this chapter.

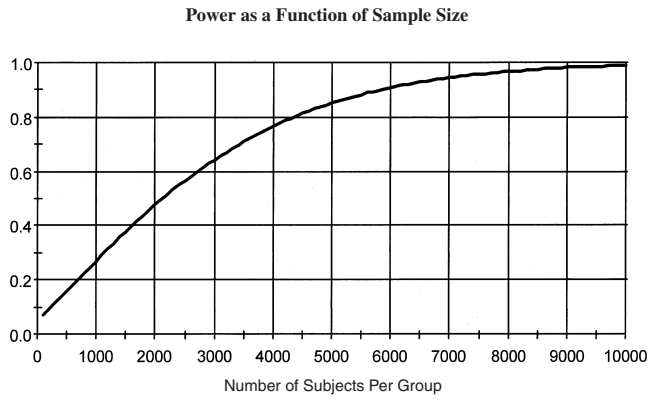

Figure 108-1. Power as a function of sample size in two treatment groups. The study was designed to detect an event that occurs in 4 out of 1000 patients in one group and 1 patient in 1000 in the other group.

TYPES OF STUDIES

Table 108-1 lists the various types of studies that are used in pharmacoepidemiology. There are two fundamental types of pharmacoepidemiologic studies—experimental and nonexperimental. These are distinguished by the method in which subjects are assigned to treatments. Nonexperimental studies can be further categorized as descriptive and analytic studies.

In experimental studies, the investigator assigns treatments to subjects, or patients may be randomly assigned to treatment in some forms of experimental or analytic studies. Patients enrolled in *randomized clinical trials* have their treatment assigned at random. It is the most common experimental method for testing drug effects and is considered the best available evidence in clinical research. Important characteristics of the randomized clinical trial are described below.

Field trials are another form of experimental study, used to study dietary factors and vaccines. In field trials the investigator makes the treatment available and then determines how well it works with careful follow up. Examples of field trials include studies of ascorbic acid in preventing the common cold, studies of poliomyelitis vaccines, and the Multiple Risk Factor Intervention Trial (MRFIT). MRFIT studied the effect of preventives such as diet and drugs on the incidence of myocardial infarction in 12,866 high-risk persons. It has been estimated that the MRFIT study would cost more than $500 million to conduct in 1997 dollars. Community intervention trials are similar to field trials, but the treatment intervention is directed at a town or community such as fluoridation of drinking water to prevent dental caries.

In nonexperimental studies, patients are not assigned to treatments by the investigator. Most of these studies enroll patients who are receiving care, including medications, from conventional settings of care such as clinics and hospitals. Nonexperimental studies are usually descriptive. Descriptive studies are conducted to describe or summarize data. For example, an investigator may wish to know the types of drugs prescribed at an outpatient pharmacy by drug class. These data would help the investigator determine what types of drugs could be studied more rigorously using the prescription data from this setting. Clearly, if there were only five prescriptions for a particular drug, then the investigator might only be able to conclude that the drug is not used very often. Descriptive data are helpful in *hypothesis-generation* and determining whether there are

Table 108-1. Types, Characteristics, and Examples of Pharmacoepidemiology Studies

STUDY TYPE	DESCRIPTION	NUMBER OF PATIENTS (PER TREATMENT GROUP)	RELATIVE COST	EXAMPLE
Experimental studies				
Randomized clinical trials	Study patients with specific disease	50 to 5000	$$ to $$$$	Efficacy of alteplase and reteplase in preventing death after a myocardial infarction
Field trials	Study subjects to prevent disease	>5000	$$$$	Vaccination to prevent polio
Community intervention trials	Study communities to prevent disease	>5000	$$$	Fluoridation of water to prevent dental cavities
Nonexperimental studies				
Prospective cohort	Observe groups of patients treated with the same drug	>5000	$$$$	Nurses Health Study Cohort
Retrospective cohort	Extract data from an existing repository to look at outcomes of exposed groups	>5000	$	Risk of renal insufficiency from NSAIDs
Case-control	Determine the association between a drug and rare event	20 to 1000	$$ to $$$	Risk of Alzheimer's disease and vitamin use
Cross-sectional	Determine the prevalence of drug use in a patient population at a given time	50 to 1 million	$	Profile of calcium-channel antagonists in a managed-care organization
Ecological	Determine the association between drug use of a population or group and an event	5 to 100 groups	$	Deaths from asthma and the quantities of metered-dose inhalers dispensed
Case series	Reveal the common experiences of a number of patients following drug exposure	3 to 30	$	Valvular heart disease associated with fenfluramine-phentermine (Fen-Phen)
Case report	Reveal the experience of a single patient following drug exposure	1	$	Toxic epidermal necrolysis from phenytoin

sufficient numbers of patients, prescriptions, events, etc, to conduct a more rigorous study. Such studies might include profiles of drug use, drug surveillance, patient types, or disease types.

Analytical nonexperimental studies are often used to *test hypotheses.* For example, one might find from a descriptive study that patients prescribed one type of nonsteroidal anti-inflammatory drug (NSAID) have a greater prevalence of gastropathy than those receiving other NSAIDs. One might then ask whether this is because this NSAID is truly more gastrotoxic or whether sicker patients who are prone to develop gastropathy are also more likely to be prescribed this drug. To tease-out the answer to this question would require a study that gives rates of gastropathy that control for illnesses that increase the likelihood of gastropathy and use of other drugs and foods that might also increase the risk of gastropathy among these patients.

DRUG SURVEILLANCE—The FDA's MedWatch is a drug surveillance program that looks for signals of adverse drug effects among all marketed drugs and then provides careful follow up when necessary. A benefit of surveillance programs is that there is early recognition of important problems. For example, who would have anticipated the recent problem involving the anorectic drugs Fen-Phen that resulted in heart valve abnormalities in those who took this weight-reducing combination? Other events that were identified by such post-marketing surveillance (PMS) programs that led to drug withdrawals include the sometimes fatal arrhythmias from CYP 3A4 drug interactions involving mibefradil (Posicor), terfenadine (Seldane), astemizole (Hismanal), and cisapride (Propulsid). Hence, the benefit of PMS is in monitoring for signals in the population of patients being treated day-to-day with drugs.

MedWatch and similar sentinel programs are important tools for the detection of rare effects, but they have several important limitations. Foremost among the limitations is that these programs depend on voluntary reporting. Because the signal comes from submissions to the FDA, predominantly by pharmacists, it is important for pharmacists to complete MedWatch forms when major new and unusual problems are identified in the care of patients. Reports of known adverse effects of marketed drugs are not required. A MedWatch form can be found in Figure 108-2. Reports may also be submitted online at https://www.accessdata.fda.gov/scripts/medwatch/. The big problem is that such forms are often not completed for heretofore unknown drug misadventures, and thus the signal is not generated or is generated later, only after many patients may have suffered. Pharmacist participation in drug surveillance programs is a central way to contribute to pharmacoepidemiology. See also Chapter 115.

DRUG USE—In pharmacoepidemiology, one needs to know two numbers to calculate the rates of events of interest. First, one needs to know the numerator (eg, numbers of adverse events). When reporting of such events is consistent and complete, one can then estimate this numerator using drug surveillance programs such as MedWatch. Again, it is important to realize that the estimate of events is only as good as the reporting of events. However, surveillance programs cannot provide an accurate estimate of the denominator, namely, the number of patients exposed to the drug product. These denominator data can be accessed by drug use.

Drug use data are improving, largely because of increasing use of computer information systems in health care. Computerization of pharmacy is ubiquitous owing largely to the need to process and store prescriptions. The increase in pharmacy benefit management companies has further consolidated prescription data. Moreover, there are corporations that can provide national estimates of drug use. One such corporation, IMS America, has prescription data for the US and many of the Western European countries. These data can be used to provide estimates of drug use and as such provide an estimate of the denominator when calculating the rates of events.

On a smaller scale, pharmacists employed by hospitals and managed-care organizations are familiar with the drug use review programs that have roots in pharmacoepidemiologic method and are required by the Joint Commission on the Accreditation of Healthcare Organizations. Such programs are described in Chapter 127. In the 1970s, these programs involved the intensive collection of the indications, processes, and outcomes of drug use at hospitals. However, in 1989, the use of clinical indicators was encouraged to monitor the delivery of patient care. Clinical indicators are measurements made to monitor and assess the quality and appropriateness of drug use. The notion is to measure, interpret, and improve care over time. Instead of comprehensive collection of data, the indicators are aimed at providing screens or flags to identify problem areas that then would become targets for more-detailed study of a particular drug or class of drugs. The overall focus of these programs is to provide appropriate, safe, effective, and efficient use of medications.[2] However, although such programs aimed at measuring clinical indicators are too small in scope to measure rare events, they are very effective in studying indications for drug use and monitoring processes.

There are several key points to address concerning institutional programs to improve drug use. First, these are very important studies to improve the use of drugs at a particular institution. When such programs are formally conducted within the framework of continuous quality improvement, the benefits to the institution and its patients are endless. However, these programs involving drug use measurement and quality indicators are not usually conducted as formal research studies that address explicit study questions or test hypotheses. It would be a mistake to assume otherwise. This is a common error made when collecting data for such programs. The biggest problem is that such programs monitor too few patients to conclude that a particular outcome of interest does or does not occur. For example, suppose that an investigator is interested in the incidence of vomiting in patients prescribed a new antibiotic. If 10 consecutive patients are monitored and no vomiting occurs, perhaps there were too few patients monitored to observe this adverse effect, the dose administered was too low to elicit the effect, or vomiting was not among the parameters being monitored during the period of patient observation. Thus, surveillance, drug use, and continuous quality improvement programs may not be designed appropriately or have sufficient numbers of patients to address a specific research question. Instead, other epidemiologic approaches must be employed.

THE RANDOMIZED CONTROLLED TRIAL—The gold standard in determining the beneficial and adverse effects of drugs is the prospective, blinded, randomized clinical trial. It is helpful to understand the merits and drawbacks of the randomized clinical trial for better understanding of the advantages and disadvantages of the various types of epidemiologic studies. When patients are randomly assigned to treatments, many biases are controlled that would otherwise preclude valid results. Ideally, neither the patient nor the physician is able to distinguish between the drug products being tested because they are "blinded." Persons performing assessments or measurements of interest should also be blinded to treatment. Typically, randomized clinical trials are conducted when comparing the efficacy of two drugs or of one drug against a placebo. Rarely, is a randomized clinical trial conducted to determine whether drugs differ in their propensity to cause adverse drug reactions.

One may wonder, why not just use randomized clinical trials for all studies of drugs? There are four primary reasons.

Randomized clinical trials often are prohibitively expensive (ie, costing millions of dollars). Unless the issue is of the utmost importance, federal monies are not made available to conduct the study. If it is a new drug product, the innovator drug company must be certain that after doing the study, it can recoup its investment.

Randomized clinical trials are often unethical for studies of the adverse effects of drugs. How many patients would enroll for a study with the sole purpose of determining the incidence of gastrointestinal (GI) perforation from a new drug?

Large numbers of patients are needed to conduct studies of rare events. Even after the moral and ethical issues for a study

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 8/31/00
See OMB statement on reverse

FDA Use Only

Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
____ lbs
or
____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address

phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

Figure 108-2. MedWatch program report form (FDA Form 3500, Expires 3/31/2005).

are resolved, if it is a rare event, then the numbers of patients needed to determine the true incidence of the effect or address a specific study question would be enormous.

Randomized clinical trials take a long time to conduct. If a question must be addressed in a timely fashion, such as for regulatory action, clearly a randomized clinical trial conducted over 3 years could not provide an answer to a question soon enough.

Primarily, for these reasons, pharmacoepidemiologic methods have been the preferred method of inquiry, especially for determining the adverse effects of drugs.

Because many relevant and important drug-related questions cannot be addressed with randomized clinical trials, the nonexperimental methods of pharmacoepidemiology are especially important. For such clinically important and relevant questions, nonexperimental methods of pharmacoepidemiology must be used. Among such methods are the cohort and case-control studies as shown in Figure 108-3. These and other common pharmacoepidemiologic methods are described below.

THE COHORT STUDY—Cohorts are groups. Cohort studies are, therefore, studies of groups of patients having some common drug exposure of interest. For example, one may wish to learn about the benefits and risks of the NSAIDs on the population of patients likely to be prescribed them. The cohort or group would be defined on the basis of patients' exposure to NSAIDs. There are two types of cohort studies: prospective and retrospective.

PROSPECTIVE COHORT—In terms of scientific evidence and control over the factors of interest, the prospective cohort study is often the preferred type of cohort study. As implied in its name, the prospective study looks forward in time (Fig 108-3). Doing so allows the investigator maximum control over the study definition and its conduct.

The event of interest or dependent variable (eg, development of aplastic anemia) can be specifically defined, and its occurrence carefully monitored.

The potential confounding factors and variables that must be controlled in the analysis can also be defined and measured.

Despite these advantages, prospective cohort studies can be very expensive to conduct and in similar fashion to the randomized clinical trial can cost millions of dollars to assemble and follow the cohort over time. An example of a prospective cohort study is the Nurse's Health Study, which began in 1976.

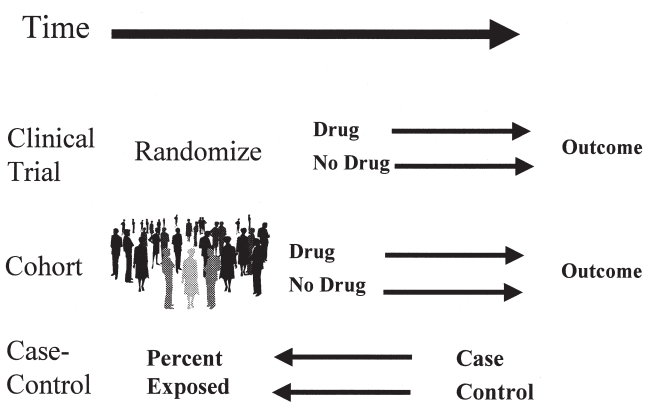

Figure 108-3. Orientation of studies relative to time. In the clinical trial, patients are randomly assigned to treatment groups and monitored prospectively for the outcome of interest. In the cohort study, treatment groups are assembled on the basis of their treatments or other distinguishing characteristics and followed until the occurrences of the outcome. With the prospective cohort study the outcome of interest occurs after the study onset and with the retrospective study the outcome has already occurred when the study starts. In the case-control study, the prevalence of past treatments is compared in a group of patients with the outcome of interest (cases) and a control group of patients who did not experience the outcome at the time data were collected.

The cohort comprises 121,700 female nurses who completed life-style and medical histories. This cohort study has proved valuable in determining various aspects of female health, especially as it relates to cardiovascular disease.[3,4]

RETROSPECTIVE COHORT—As its name implies, the retrospective cohort study looks back on existing data. These data usually come from large, computer databases. However, data can also come from paper charts or medical records. In these studies, cohorts are assembled in the same way as in prospective cohort studies, namely, on the basis of exposure to certain drugs of interest. The major advantage of retrospective cohort studies is lower costs. These are much less expensive to conduct than either clinical trials or prospective studies. The major disadvantage is that there are many forms of bias (see below) that are found in retrospective studies.

Conceptually, retrospective cohort studies are conducted the same way as prospective cohort studies.

The cohort is defined by determining the index date when the drug of interest was first prescribed. Although the index date will differ for each patient, it acts as the anchor for two key viewpoints: (1) for looking forward in time for the occurrence of the outcomes of interest (eg, myocardial infarction or renal insufficiency) and (2) for looking backward in time for the baseline factors that must be controlled in the analysis.

Data on the outcomes and baseline factors are extracted from the database or charts for all patients in the cohort. Fundamentally, the extraction process is similar whether performed by computer or by hand.

Regardless of whether cohort studies are prospective or retrospective, there are a number of critical characteristics to such studies. Drug exposure should be verified to prevent misclassification of cohort membership. A common problem in pharmacoepidemiologic studies is that patients could get a medication from a pharmacy that is not among those from which data are derived, physicians may provide the drug as a sample from their office, or the drug may be available as an OTC drug and as such can be directly available to the patient. If a drug is available from multiple sources, then the investigator should demonstrate that all sources were included in the cohort formed for study.

THE CASE-CONTROL STUDY—Methodologically, case-control studies are the diametric opposite of cohort studies (Fig 108-3). Generally, case-control studies are conducted when the outcome of interest is rare. Instead of beginning with a group of patients using the same drug (with a common exposure) and following them until they have a specific event, as with the cohort study, in the case-control study one first identifies a group of patients with a common event or disease. These are the *cases*. For example, if an investigatory wished to determine whether a certain drug caused aplastic anemia (a rare event), first, patients with aplastic anemia would be identified. The *controls* would be people who are representative of the underlying population from which the cases came but who did not have the outcome of interest. In the aplastic anemia example, the investigator would search for patients who came from the same setting of care as the cases or from the same community. Sometimes controls are matched to cases on certain background factors that predict or confound the outcome, such as age, gender, or smoking status.

The idea of the case-control study is to compare the prevalence of exposure between the cases and controls. This is the difficult aspect of such studies and is often a contentious issue that results in plenty of debate. A single report of a case-control study in a journal can result in using twice as much journal space publishing the letters to the editor than used for the original report. The main reason for this is that there are many ways in which bias can enter into the design, conduct, and interpretation of these studies. When obtaining data directly from patients pertaining to the exposure, there may be a major difference between patients' memories of their drug use in the case and those of control groups. This recall bias is described below.

THE CASE REPORT—The case report is the presentation of the experience of a single patient. It is usually presented in a way that supports a hypothesis or an answer to a question of interest. Case reports are often referred to as *hypothesis-generating* because these bring forth evidence that supports a hypothesis or conclusion. For example, the presentation of the medications for a patient that were administered until the development of aplastic anemia might suggest that one or more of these drugs could have caused the aplastic anemia. However, it could not be concluded that another patient who took one or more of the same drugs would be at equal risk, because of the many other factors that also cause aplastic anemia, such as viral infections or exposure to insecticides, which may not be part of a patient's medical record or their recollection and would, therefore, not be reported.

When the common experiences of more than one patient are presented, this is referred to as a *case series*. Obviously, the greater the number of common experiences, the stronger the evidence to support a conclusion. For example, if five patients developed aplastic anemia after exposure to the same medication, this would raise suspicion beyond that for only one such patient. A good example of the impact of the case series is the 24 patient reports describing valvular heart abnormalities from concurrent fenfluramine and phentermine use.[5] These data were compelling enough for the withdrawal of fenfluramine from the market.

THE CROSS-SECTIONAL STUDY—This is a study conducted to obtain the prevalence of an outcome in a given set of patients such as those being treated with a drug at a single time point. Cross-sectional studies are often referred to as *snapshot* studies. Because data are collected all at once, the temporal relationship between the use of the drug and the outcome of interest cannot be determined in cross-sectional studies. This is a problem if the investigator is trying to make cause-and-effect inferences.

THE ECOLOGICAL STUDY—There are times when data are not available at the patient level, but there is interest in getting a preliminary understanding of the relationship between the use of a drug and an outcome. This may entice an investigator to use aggregate data to compare the gross amount of drug used and the rate of occurrence of an event for a community, state, or country. In other words, the unit of analysis in ecological studies is a population instead of a patient. An example of such an approach is the comparison of the numbers of prescriptions of β-adrenergic agonist inhalers dispensed in a country and the numbers of deaths from asthma. Such a relationship would be confounded by the increasing use of medications with increasing severity of illness (ie, sicker patients use more β-adrenergic agonist inhalers and are more likely to die of their disease, regardless). Another problem is that the investigator might not even know whether the patients who died were even prescribed the medication, a dilemma known as the *ecological fallacy*. Hence, it can be observed that although ecological studies are easy to conduct, there may be major problems when using the data to make cause-and-effect inferences.

MEASUREMENTS

As with any scientific discipline, valid measurements are critical for accurate interpretation of the results of pharmacoepidemiologic studies. There are several fundamental metrics helpful to understand. For descriptive studies these include frequencies, distributions, prevalence, and incidence rates. For analytical studies these include the rate difference, rate ratio, relative risk, and odds ratio. A description of these measurements and how they are calculated are found in Table 108-2.

FREQUENCIES—In epidemiology, the prevalence and incidence of events are the most commonly used metrics; they are also the most commonly confused. The primary issue that distinguishes *prevalence* from *incidence* is the types of patients counted per unit time. As can be seen in Figure 108-4, the prevalence of an event is equal to the number of patients with the outcome of interest at a single point (cross-section) in time. Prevalence is often reported as a proportion or percentage (eg, the prevalence of asthma was 12%). If the measurement is made on all patients at a single moment in time (a snapshot), then it is referred to as a *point prevalence*. For example, consider the vertical dashed line in Figure 108-4. At that point in time, the prevalence of drug use is 4/1000 patients or 0.4%. If the measurement is made on all patients during a specific time interval, for example one year, then this is called a *period prevalence*. As shown in Figure 108-4, the period prevalence is 0.7%, 0.7%, 0.7%, and 0.8% for 1996, 1997, 1998, and 1999, respectively.

However, if an investigator begins with a group of patients naïve to an outcome and go forward in time and count all patients who contracted the disease or had the event, this is called the *incidence*. Incidence is measured as counts of patients with the outcome per unit time (12 per 100,000 person-years). The incidence of drug use in Figure 108-4 is 8/996 persons over the 4 years or 2/1000 person-years. The reason that 996 persons is used instead of 1000 persons is that one must remove from the denominator the patients who already have had the event of interest.

Accurate numerators and denominators are needed to calculate accurate prevalence and incidence rates. Though simple to say, depending on the data available for analysis, they may be impossible to compute accurately. Sometimes both the numerator and denominator are poorly ascertained. This is often

Table 108-2. Types of Measurements in Pharmacoepidemiology Studies

MEASURE	DEFINITION	COMMENTS
Prevalence	Frequency of cases at a given time or period	Often confused with incidence; reported as a percentage
Point prevalence	Frequency of cases at an instant	Used in cross-sectional studies
Period prevalence	Frequency of cases within a period such as 1 yr	Often confused with point prevalence
Incidence	Frequency of new cases in a population over a period	Mostly reported as a rate, such as 10/100,000 person-years
Relative risk or risk ratio	Incidence in the exposed group divided by the incidence in the unexposed	Addresses the number of times greater risk in exposed than in the unexposed; a relative risk of 1 means that the risk is equal with and without exposure
Odds ratio	An odds is the probability of an outcome happening divided by the probability of the event not happening; an odds ratio is the odds of the event in those exposed divided by the odds in the unexposed	Provides an estimate of the relative risk for rare outcomes; an odds ratio of 1 means that there is no association between exposure and outcome
Attributable risk or risk difference	Incidence in the exposed group minus incidence in the unexposed	Addresses the incidence of a disease attributed to an exposure

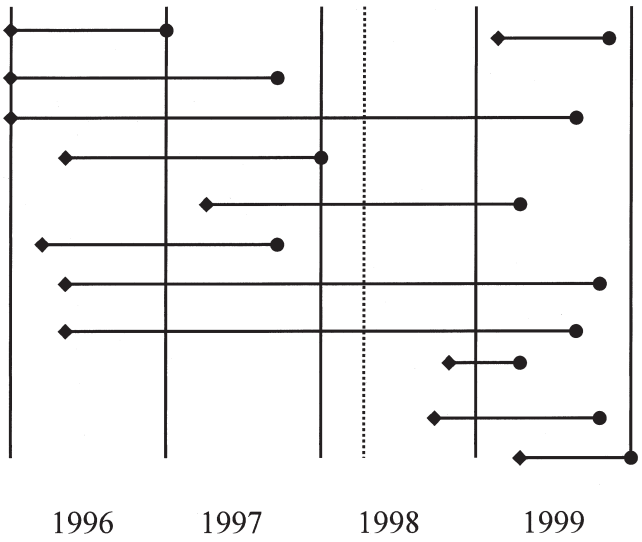

Figure 108-4. Distribution of the experiences of 12 patients prescribed a medication over a 4-year period, to illustrate the difference between prevalence and incidence. *Diamonds* indicate the date of the first prescription; *circles* indicate the stop date.

observed in sentinel surveillance programs such as MedWatch in which the numerator contains only those patients who had the outcome of interest *and* were reported. The denominator can only be estimated on the basis of national drug-use data, which must often be found in the literature or purchased from a vendor. Often the numerator is carefully calculated, but the denominator is unknown. For example, one may know when a certain event such as hospitalization for a specific reason occurs in patients prescribed a specific drug or drug class, but the investigator may not be able to estimate accurately the number of patients in the underlying population. This occurs in open health-care systems in which patients are free to switch health-care plans. Lack of an accurate denominator can limit the usefulness of large databases such as those found in managed-care organizations. Investigators have often resorted to using the client enrollment file for denominator data. However, fluctuations in the numbers of clients can make enrollment data misleading, even over short intervals such as one year.

PREDICTION—Occasionally, an investigator wants to know whether a certain drug predicts a future benefit or adverse effect. For such studies, one needs to know whether the benefit or risk occurred for all patients and also the status of factors of interest before the patients were first prescribed the drug. An example of such a study would be determining the risk of renal impairment from a drug. It would be important to know patients' renal function before the drug of interest was administered. These data would allow one to adjust the predictive model on the basis of baseline renal function for these patients. If the investigatory was comparing two drugs, it would be important to have such data to know that renal function was similar in the two groups at baseline or whether this was taken into account.

BIAS

Bias is deviation from the truth. It affects all forms of experimentation and is described in Chapter 12. However, a number of biases that are unique to pharmacoepidemiology differ conceptually from those in laboratory studies and merit special attention. Generally, these can be classified as selection bias, measurement bias, and confounding bias. Because clinical studies cannot be controlled as carefully as laboratory studies, many forms of bias must be considered as possible explanations for the results of pharmacoepidemiologic studies. Indeed, Sackett has catalogued 35 biases that can occur in analytic studies.[6]

SELECTION BIAS—Selection bias is a major problem of all nonrandomized clinical studies. It becomes manifest when groups for comparison are not balanced in terms of important background characteristics. When lopsided groups are compared, the investigator has difficulty interpreting the result because it is not known whether results are because of a drug exposure or because imbalances in one or more background characteristics have affected the results.

Pharmacoepidemiologists who conduct research using existing medical records need to realize that physicians' prescribing habits create biased groups. A common example of selection bias involves the prescribing patterns of physicians after the marketing of new drug products. As one might imagine, there is avid interest in learning as much as possible about the "real-world" experiences of recently marketed drugs. Soon after marketing, new drugs become the focus of inquiry. However, a big problem immediately becomes apparent when investigators compare the background characteristics of patients prescribed the newer and older drugs. What usually occurs is that patients prescribed the new drug are those who were not responding to the older therapies, and they are often sicker patients. This makes any comparison of recent and existing drugs inherently difficult.

Another example from the Regenstrief research center further illustrates selection bias. It is known that NSAIDs worsen renal function of patients with renal insufficiency. There were several reports that the NSAID sulindac was a renal-sparing NSAID, meaning that it did not worsen renal insufficiency in patients at risk of this effect as the other NSAIDs did. After reading these reports, some physicians began prescribing sulindac to their patients with preexisting renal insufficiency. When patients' baseline renal function was compared before they were prescribed NSAIDs, it was found that the patients who were prescribed sulindac had worse baseline renal function (ie, higher serum creatinine values) than patients prescribed other NSAIDs. Hence, physicians' preference for prescribing sulindac for patients with renal insufficiency created a bias in interpreting the true effect of the various NSAIDs. The end result was a bias that may have made sulindac look worse than the other NSAIDs.

There are ways to deal with selection bias for studies of existing data. Most notable among them are matching, mathematical modeling, and use of propensity scores. In matching, a control subject is matched with each case subject on important background characteristics. Using the previous example, an investigator could match patients with preexisting renal insufficiency who were prescribed sulindac with patients with preexisting renal insufficiency who were prescribed ibuprofen and look at the changes in serum creatinine afterward. Likewise, one would match those with normal prior renal function prescribed sulindac with those with normal prior renal function before they were prescribed ibuprofen.

With analysis of covariance, an investigator would put into a mathematical model a parameter that controls for differences in important background characteristics. Again, from the previous example, one would put patients' baseline serum creatinine or creatinine clearance into the model to adjust for baseline differences among the various NSAIDs being compared. Doing so would provide the estimated effect of the NSAID controlling for patients' prior renal function. The general idea is to balance comparison groups so a fair comparison is made.

Finally, propensity scores adjust for the probability that a patient will be prescribed one drug over another. To do so, a single score is calculated using logistic regression that includes all of the background characteristics that are important to a physician who was trying to decide between drugs. This score could then be used as a covariate in a mathematical model that looked at the outcome of interest. In calculating the propensity score in the example above, an investigator would want to include not only patients' baseline renal function, but perhaps

age, gender, race, indication for the NSAID (eg, rheumatoid arthritis, osteoarthritis), and other factors that would predict which NSAID physicians prescribe. Hence, though selection bias is a problem in such studies, there are ways to deal with this form of bias.

An example of how propensity score methods are used to adjust for important background characteristics is demonstrated in Figure 108-5, Panels a and b. This study used propensity scores to adjust for age and other relevant variables to determine the effects of various NSAIDs on renal function.[7] It is clear from Figure panel a, that there is an important imbalance of the mean age of patients prescribed ibuprofen and sulindac. Because renal function declines with increasing age and sulindac is more commonly prescribed for older adults than ibuprofen, such a comparison is confounded. A more appropriate comparison is shown in Figure panel b, where age subgroups of patients prescribed ibuprofen and sulindac have been matched using propensity scores. Doing so permits comparison of ibuprofen and sulindac by age-matched subgroups, which is a much more intuitive and fair comparison.

Selection bias creeps into other areas of measurement in epidemiology. It has recently become popular to use *benchmarking* to compare the experiences of one hospital with those of another. If various aspects of the underlying characteristics of hospitals being compared are not controlled, then such a comparison will be faulty. A wild extrapolation of this would be to compare the rates of death in a hospice where terminally ill patients are cared for in their final days with those of patients from an acute-care hospital. Obviously, such a comparison is fraught with error. It can also enter into the process of selecting the papers for inclusion in meta-analysis (see Chapter 12).

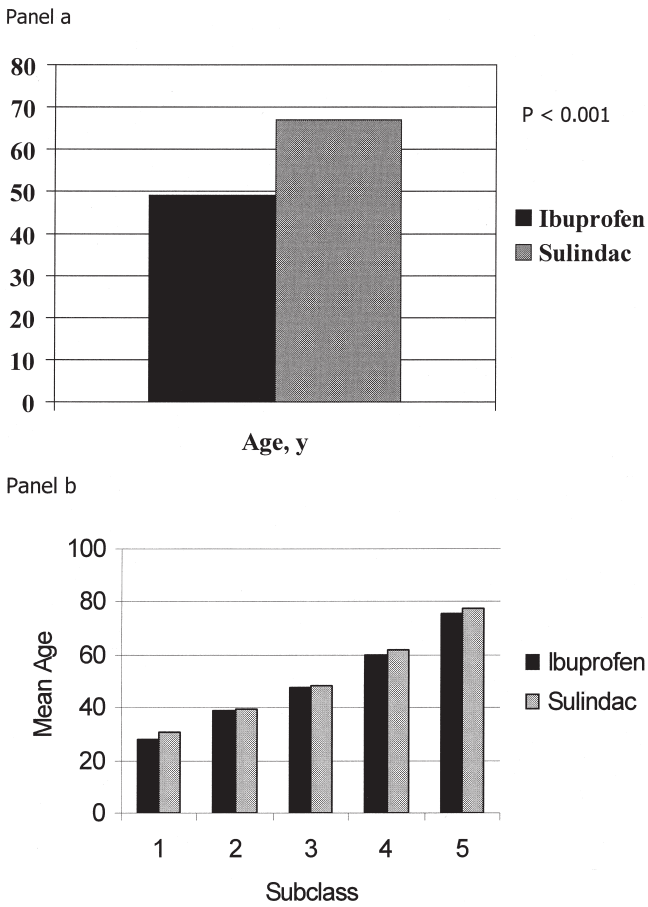

Figure 108-5A. An example of how propensity score methods are used to adjust for important background characteristics. **B.** Age subgroups of patients prescribed ibuprofen and sulindac have been matched using propensity scores.

MEASUREMENT BIAS—Measurement bias results when comparison groups are measured differently. Misclassification of the event of interest can obviously be a problem. This requires careful definition of the characteristics of a case. If the case definition is based on a diagnosis or diagnostic code (ICD-9 code), some cases may be missed or be inappropriately included. For example, using only the diagnosis of *congestive heart failure* may be too broad if the disease of interest is left ventricular systolic dysfunction. Using *congestive heart failure* only would also include patients with diastolic dysfunction, which is treated entirely differently from systolic dysfunction. A related issue is the date of onset of a disease or disorder. Which is the date of onset of diabetes for a patient—the data of the diagnosis or the date of the first fasting or random blood glucose that was over the upper critical value of normal? These issues require careful consideration in the planning stages of the study.

A common problem is that patient follow up may be inadequate and incomplete. When patients are lost to follow up, it may appear in the analysis as though they did not have the interest. This commonly occurs when patients have access to multiple-care settings. An admission to a hospital that does not contribute data to the analytic database would go unnoticed. This could be a major problem if hospital admission is the primary dependent variable for the study. Patients unable to obtain a needed (perceived or real) drug will seek care elsewhere. If this drug is a study drug of interest, then patients may be differentially lost, which can result in an important bias.

Unmeasured or missing data on key confounders and effect modifiers can destroy the validity of cohort studies. It is not feasible for large population cohort studies such as the Framingham Study or Nurses Health Study to measure everything. The data collected depend upon the types of studies anticipated. If data are not collected pertaining to a key confounder, then the results of a study in which that variable is important may not be valid.

Finally, a pharmacoepidemiologic study that has excellent *internal* validity may have limited *external* validity. Internal validity deals with how well the results of the study represent the truth for the patients who were studied. External validity addresses the question of whether the results of the study extrapolate to other settings. Persons willing to participate in clinical studies may differ from other persons in meaningful ways. A study of drug-related hospital admission in one setting of care may differ from the findings in another because of the system for remuneration at each setting instead of drug factors *per se*.

There are methods for reducing measurement biases. Most important is making certain that groups being compared derive from the same underlying population and that the instruments of measurement are the same. As mentioned previously, a major problem with the use of observational data to make inferences about drugs is that physicians may preferentially prescribe some drugs more than others for sicker patients and, subsequently, conduct laboratory tests more frequently on the sicker patients. When cohorts are assembled on the basis of use of a certain drug and the outcome of interest is a laboratory measurement, patients prescribed the drug for sicker patients will likely appear to be doing worse. This is because the drug was prescribed for the sicker patients, and those patients were more likely to have received the laboratory test. The healthier patients could have been prescribed another drug, but never been tested.

RECALL BIAS—Recall bias occurs in case-control studies and can profoundly distort the results. It occurs because of differential recall of medications between cases and controls. Recall bias occurs because cases have better recollection of the drugs that they have been prescribed than the controls, and as such the prevalence of exposure to drugs of interest will be inflated excessively in the cases compared with the controls. This

falsely increases the association between the drug and the outcome of interest. For example, if an investigator was interested in knowing the drugs associated with developing cancer, the recall of drug histories might be more complete in the patients with cancer (cases) than in the controls. If one used the medical records instead of patient recall, it might be found that physicians of patients with cancer kept more-complete drug histories than the physicians caring for control patients. Because case-control studies depend on past exposures and the recording of exposures can be lopsided between cases and controls, an investigator might find that many drugs are associated with cancer owing to these measurement errors.

Another example that makes it easy to understand this bias is to think about the last time you were nauseated and then vomited (the outcome). In this circumstance, you might be inclined to think carefully about all of the foods and drinks consumed over the last day or so, in an attempt to pinpoint the causative food and avoid it in the future. However, few people reflect on the food eaten from day to day, and often fail to remember a diet as readily when we are not ill. This is recall bias. It occurs when women who have malformed infants are compared with those with normal births; the mothers of malformed infants reflect carefully on all of the medications that were taken during pregnancy, and the mothers of normal infants pay less attention to medications used.

CONFOUNDING—Confounding is a form of bias that confuses the results of pharmacoepidemiologic studies. A confounder is a factor that is associated with the outcome of interest and that if not considered will change the results so dramatically that it could result in erroneous study conclusions. A commonly used example is that of the investigation of the relationship between alcohol use and cancer. The data support such a relationship. However, it must be realized that smoking is known to cause cancer and people who drink alcohol also are more likely to smoke. Therefore, the relationship between alcohol consumption and cancer is confounded by smoking.

There are three requisites of confounding:

- The confounder is a risk factor for the outcome of interest.
- The confounder is associated with the drug being studied.
- The confounder is not a temporary step between the drug exposure and the outcome of interest.

In the preceding example, it can be observed that

1. Smoking is a risk factor for cancer.
2. Smoking and alcohol consumption are correlated.
3. Smoking is not an intermediate step in the causal pathway between alcohol use and cancer.

Taken together, the confounder is a factor that creates a bias or lopsided study result because it is not accounted for or ascertained in the investigation. The degree of confounding is important; the confounding bias could be so small that it does not affect the study conclusions, or it could be so large that results are entirely wrong and misleading.

There are three ways to control confounding:

1. Before the study is conducted, certain types of patients could be excluded from participation. In the example above, smokers could be *excluded* to estimate the effect of alcohol on the development of cancer.
2. If the study is executed and the data on the appropriate factors were obtained, patients could be *stratified* or *grouped* according to the factor of interest. For example, the effects of alcohol on cancer could be determined in both smokers and nonsmokers.
3. If there are multiple confounders this can be accomplished by mathematical modeling. Here, the investigator would estimate the risk of cancer by retaining extra variables in the mathematical model to distinguish smokers and nonsmokers as well as other potential confounders.

The best way to deal with confounding is to avoid it, and the only way to avoid it is with randomization. Patients randomly assigned to treatments are usually balanced on factors that result in bias, including confounders. This is the key reason why randomized clinical trials are preferable for determining differences between treatments. However, randomization to exposure or treatment is not performed in nonexperimental studies.

NEWS BREAKS AND FANATICISM

Besides participating in the conduct of research, another way pharmacists participate in pharmacoepidemiology is in patient education when news (good or bad) about a drug is released by the media about pharmacoepidemiologic studies. Keeping pace with the latest news stories requires some vigilance. Almost weekly, the public hears a news report about a drug product that leads to a barrage of telephone calls to pharmacists and physicians. Often these are pharmacoepidemiologic studies. From these news reports, patients hear that the drug they are taking is associated with an adverse outcome. This strikes fear into the hearts of these patients, who promptly call their pharmacists and physicians. Alert pharmacists will be able to anticipate the rash of calls and prepare themselves to spend time alleviating patients' fears until they can arrange to visit their physicians. Unless the risk is severe (eg, arrhythmia or death) or the patient has not tolerated the drug, then the patient should continue to take the medication. An exception would be in those instances in which the drug's benefits are not well documented and there are no withdrawal symptoms, in which case the drug could be discontinued. Patients could put themselves at great risk when breaking news results in their prompt discontinuation of medications that are life-sustaining (eg, antiarrhythmics) or produce adverse withdrawal phenomena (eg, β-adrenergic antagonists or clonidine).

The author and his colleagues have examined the effects of a prepublication presentation about the hazards of *immediate-release* forms of calcium channel antagonists on prescribing of a variety of cardiovascular medications using prescriptions stored in a national database.[8] The presentation—held at a large meeting of cardiologists—received a considerable amount of coverage in the media prompting many calls by patients to pharmacies and physicians to change their medications. The results of this study indicated that many patients' prescriptions for *sustained-release* forms of calcium channel antagonists were discontinued as well as immediate-release forms. Further, less effective medications such as alpha-adrenergic antagonists were instead prescribed. This experience highlights the profound and sometimes aberrant effect of media to presentations at professional conferences before a publication undergoes peer-review.

THE FUTURE

As health care becomes more automated with computer systems, the availability of large volumes of data will increase. Because the profession of pharmacy is one of the most highly computerized areas of health care, pharmacists should have access to these data. Prescription data alone are valuable for longitudinally tracking prescribing patterns and for providing a supportive framework for drug-use review and evaluation of the management of chronic diseases. However, a critical component of such research is the integration of prescription data with data on health-care use and outcomes. Once the infrastructure for merging these data is established and data capture and extraction routines have been validated, numerous possibilities begin to emerge.

Such integrated health-care systems enable pharmacists to conduct pharmacoepidemiology, pharmacoeconomic, outcomes, and health services research. The key is ready access to valid data in a timely fashion. This requires a solid foundation of support constituted by automated information experts, programmers, administrators, clinicians, and researchers. Many health-care systems have all of these individuals in place, but they have not yet directed their attention to the value of

conducting pharmacoepidemiologic research. The primary reason for that is that most information systems have been created for billing purposes, with little attention to the use of their data for research. However, this position is slowly changing.

Pharmacists frequently are called upon to help health-care administrators understand the use of drugs in their care setting. Increasingly, administrators are requesting information on the value of pharmaceuticals being prescribed that in turn is requiring pharmacists and researchers to request prescription data that are integrated with resource-utilization data and cost or charge data. As ordinarily occurs with any new process, the first attempts to extract integrated data from huge databases are slow. However, with repeated applications of integrated data, new efficiencies occur, which make future data extractions and studies easier to conduct.

SUMMARY

Pharmacoepidemiology is a valuable contribution to the pharmaceutical sciences. It runs a spectrum from case reports that are sentinels of problems to labor-intensive and expensive randomized clinical trials considered the gold-standard of therapy. Pharmacists use the methods of pharmacoepidemiology when conducting drug-use reviews and evaluations. Pharmacoepidemiologic studies reveal little more than fodder for debate when studies are done without considering the numbers of biases that can occur. More frequently, however, pharmacoepidemiology provides the best available evidence supporting or refuting a hypothesis otherwise lacking data so that health policy can be written. The increasing use of automated databases provides pharmacists with access to large volumes of data that can be used to address many important issues. Access to these data coupled with an understanding of the principles of pharmacoepidemiologic research will permit pharmacists to contribute to society's growing need for timely answers to important questions in drug therapy.

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Associations

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CHAPTER 109

Surgical Supplies

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A professional service rendered by many pharmacists consists of supplying surgical instruments, sutures, surgical dressings, and other equipment employed by the surgical personnel during and after a surgical operation. Some pharmacists who have obtained the necessary background of information carry a complete line of such supplies and even are able to provide operating tables and other heavy equipment.

There are comparatively few such completely equipped pharmacies; the major outlet is through surgical supply houses. Every pharmacist, however, should be familiar with two of the products mentioned above, namely, *Surgical Dressings* and *Sutures,* which are discussed in detail below. The selection of the correct type of surgical dressing or suture is a critical factor in safeguarding the welfare of the patient undergoing surgery. Many items in these categories are handled routinely by pharmacists, and all of these items come within the purview of their professional responsibility.

SURGICAL DRESSINGS

DEFINITION—*Surgical dressing* is a term applied to a wide range of materials used for dressing wounds or injured or diseased tissues. Dressings may serve to

Provide an environment for moist wound healing. Desiccation of a wound is a major factor in retarding wound healing and increasing scarring. Dressings that prevent desiccation provide an optimal environment for autolysis cell migration, granulation, and reepithelialization.
Prevent maceration by permitting evaporation or absorption. In highly exudative wounds, excessive moisture and autolytic enzymes will damage repairing tissue and will provide a perfect culture medium for microbes.
Promote hemostasis.
Protect the wound from further damage (mechanical damage, microbial invasion, dehydration, maceration, chemical damage, alteration in pH).
Reduce heat loss.
Control microbial growth (by incorporation of antimicrobial drugs).
Promote autolysis.
Promote healing.
Provide compression, promoting hemostasis, and reducing edema.
Provide support.
Reduce pain, increase patient comfort, and improve functional use of wound site.
Reduce odor.
Improve the appearance of the wound site.
Reduce overall costs associated with wound treatment.

SELECTION OF A WOUND DRESSING—Dressing selection should be made on the basis of the degree of exudation, presence or likelihood of infection, presence of necrotic tissue, and anatomical site. The correct selection of a wound dressing depends not only on the type of wound but also on the stage of repair. The use of a wound dressing cannot be considered in isolation, but rather in the context of an integrated wound-care program.

CLASSIFICATION—Functionally, the simplest method of classification uses the terms *primary* and *secondary* dressing. A primary dressing directly contacts the wound. It may provide absorptive capacity and may prevent desiccation, infection, and adhesion of the secondary dressing to the wound. A secondary dressing is placed over a primary dressing, providing further protection, absorptive capacity, compression, or occlusion. Although some dressings are solely primary or secondary in nature, others have the characteristics of both. The following classification is used here:

TYPES OF WOUND DRESSINGS

Primary/secondary wound dressings
Secondary dressings
  Absorbents
  Bandages
  Adhesive tapes
Protectives

Within this classification, dressings are considered on the basis of composition.

SPECIFICATIONS—Surgical dressings and sutures are required to meet specific requirements of the USP for many characteristics. For these specific requirements and the performance of several of the official tests, eg, *Absorbency test* and *Fiber length* of cotton, *Diameter* of sutures, and *Tensile strength* of sutures, textile fabrics, and films refer to the detailed instructions provided in the USP.

PRIMARY WOUND DRESSINGS

Plain Gauze has been used as a primary dressing but will stick to all but clean, incised wounds. Although this property has been used to debride exudative, infected, and necrotic wounds, this practice may be painful and is often counterproductive, causing the removal of granhhulation tissue and new epithelium.

Impregnated Gauze is used to reduce its adherence to wounds. Cotton, rayon, or cellulose acetate gauze has been

impregnated with a variety of substances such as petroleum or paraffin (Aquaphor, *Beiersdorf,* Vaseline *(Sherwood),* KY jelly *(Johnson & Johnson),* petrolatum emulsion (Adaptic, *Johnson & Johnson*), zinc saline (NutraDress, *Derma Sciences*), or sodium chloride (mesalt, *SCA Molnlycke*). Coatings may wear off, allowing epithelial ingrowth and necessitating a dressing change. A secondary dressing should be used with these dressings to prevent desiccation, provide absorbency, and prevent the entrance of pathogens. When used with an appropriate secondary dressing, these dressings may be used in heavily exuding wounds.

Film Dressings (transparent film, occlusive or semiocclusive) are films of polyurethane with acrylic or polyether adhesives that provide a semipermeable membrane to water vapor and oxygen yet are waterproof. In lightly exuding wounds they permit enough evaporation to promote moist wound healing and prevent maceration. Film dressings exclude bacteria from wounds and permit bathing and observation of the wound. Film dressings will adhere well to intact skin and have a low adherence for wound tissue. They should not be used in infected or heavily exuding wounds.

Film dressings may wrinkle, forming channels for microbial entrance. Difficulty in handling film dressings has been overcome by special design of various application systems. In addition to their use as wound dressings, adhesive films have been used to protect areas vulnerable to pressure, friction, or shear ulceration or for infusion or cannulation sites. Examples of transparent film dressings are Bioclusive (R) Transparent Dressing *(Johnson & Johnson),* Opsite *(Smith & Nephew),* Tegaderm *(3M),* and Dermasite *(Derma Sciences)*.

PRIMARY/SECONDARY WOUND DRESSINGS

Composite Dressings have primary and secondary components that prevent adherence to the wound, with some degree of absorbency. The degree of occlusion provided by these dressings varies. Release *(Johnson & Johnson),* Telfa *(Kendall),* and Melolin *(Smith and Nephew)* consist of lightly absorbent rayon or cotton pads sandwiched between porous polyethylene films. Nu-Derm *(Johnson & Johnson)* and Lyofoam A *(Seton Healthcare Group)* consist of polyurethane foams with a film backing.

Hydrogels are complex lattices in which the dispersion medium is trapped rather like water in a molecular sponge. The *hydrogel* is typically a cross-linked polymer such as polyvinylpyrrolidone, cross-linked polyethylene oxide gel, or polyacrylamide. Hydrogels are nonadherent dressings that through semipermeable film allow a high rate of evaporation (and cooling) without compromising wound hydration. This makes them useful in burn treatment. Hydrogels are also very useful in hairy areas where entrapment of hair into the dressing would not be traumatic. Examples of hydrogels are Geliperm *(Geistlich),* Vigilon *(Bard),* Flexderm *(Dow Hickam),* and Nu-Gel *(Johnson & Johnson)*. The latter is held together with a fusible fiber scrim.

Hydrocolloid Dressings combine the benefits of occlusion and absorbency. Hydrocolloids are dispersions of particles around which water molecules and solvated ions form a shell-like structure. Fluid absorption occurs principally by particle swelling and enlargement of this structure. The *hydrocolloid* mass of these dressings consists of gum-like materials, such as guar or karaya, sodium carboxymethylcellulose, and pectin, bound by an adhesive such as polyisobutylene.

Hydrocolloid dressings display wet tack (adhesion to a wet surface) because of particle swelling. This property facilitates atraumatic removal. The dry tack of hydrocolloid dressings is due to an adhesive such as polyisobutylene, which is inactivated by moisture. The dry tack retained by the dressing around the wound preserves the edge seal. Exudate absorption by most hydrocolloid dressings results in the formation of a yellow/brown gelatinous mass that remains on the wound after dressing removal. This may be irrigated from the wound and should not be confused with pus.

Because hydrocolloids absorb water slowly, they are of little use on acutely exuding wounds. They are, however, very useful for moderately to highly exudative chronic wounds. Examples of hydrocolloid dressings include Duoderm *(ConvaTec),* Comfeel Plus *(Coloplast),* and RepliCare *(Smith & Nephew)*.

CALCIUM ALGINATE DRESSINGS—Alginic acid is a naturally occurring polysaccharide derived from brown seaweeds. As the calcium salt, these fibrous nonwoven dressings are highly absorbent and are used on moderately to highly exuding wounds. They may be held in place with gauze tape or a film dressing. They also may be used to pack wounds. Examples of calcium alginate dressings are Sorbsan *(Dow Hickam),* Algosteril *(Johnson & Johnson),* and Kaltostat *(Calgon Vestal).*

SECONDARY WOUND DRESSINGS

Absorbents

SURGICAL COTTON—Cotton is the basic surgical absorbent. It is official Purified Cotton USP.

Domestic cotton grown in the Southern US is suitable for surgical purposes. The domestic cotton plant reaches a height of 2 to 4 ft. Growing from the seeds is a pod or boll that bursts open upon ripening, exposing a mass of white cotton fibers. Each of these fibers is a minute, hair-like tube, the outer wall being pure cellulose, the opening filled with plant fluids. When the boll bursts open, the fiber collapses into a flat ribbon-like form, twisted and doubled upon itself more than 100 times from end to end.

The raw cotton fiber, mechanically cleaned of dirt and carded into layers but not otherwise treated, has a limited use for paddings and coverings of unbroken surfaces. This form is supplied under the name *nonabsorbent cotton*. It also is used frequently as cotton plugs in the bacteriological laboratory because of its nonabsorbency.

Absorbent Cotton is prepared from the raw fiber by a series of processes that remove the natural waxes and all impurities and foreign substances and render the fibers absorbent. It is a practically pure, white cellulose fiber.

Besides the familiar roll form, Purified Cotton may be obtained in various prepared forms such as cotton balls or cotton-tipped applicators.

Absorbent balls made of a uniform surgical viscose-rayon fiber also are available. These absorb fluids faster and retain their shape better than cotton balls.

Nonabsorbent Bleached Cotton, prepared by a modified bleaching process that retains the water-repellent natural oils and waxes, also is available. This cotton is identified easily by its silky feel. Because it is repellent to water, it does not become matted or inelastic. Consequently, it is well-adapted to packing, padding, and cushioning of dressings over traumatized areas and as nonabsorbent backing on sanitary napkins, combines, and drainage dressings.

Rayon, or regenerated cellulose, is made from wood or cotton linters. After dissolving it in a mixture of alkali and carbon disulfide, cellulose thread is reprecipitated in an acid-coagulating bath by passage through fine holes in a metal plate. Because plant lignins have been removed, as well as the more circular cross section, rayon fibers are softer and more lustrous than cotton.

SURGICAL GAUZES—The function of surgical gauze is to provide an absorbent material of sufficient tensile strength for surgical dressings. It is known as *Absorbent Gauze USP*.

In the process of making surgical gauze, the raw cotton fiber is cleaned mechanically and then spun or twisted into a thread, and the thread in turn is woven into an open-mesh cloth that is gray and nonabsorbent. It is bleached white and rendered absorbent by much the same processes as those used in the preparation of surgical cotton.

The gauze thus treated is dried by passing a continuous length through a tentering machine. Tenterhooks straighten, stretch, and hold it taut as it is dried. When it leaves this apparatus, the dried gauze is cut into lengths, folded, rolled, and packaged.

Gauze is classified according to its mesh, or number of threads per inch. Some types of surgical dressing require a close-meshed gauze for extra strength and greater protection, while other uses such as primary wound dressings, absorbent secondary dressings, and larger dressings to absorb purulent matter or other drainage require softer, more absorbent gauzes with a more open structure.

Various forms of pads, compresses, and dressings are made from surgical gauze, alone or in conjunction with absorbent cotton, tissue paper, and other materials.

Filmated Gauze is a folded absorbent gauze with a thin, even film of cotton or rayon distributed over each layer. This filmation fluffs up and gives ample dressing volume, yet costs less than gauze alone of equivalent volume. It possesses quick absorption and unusual softness.

Nonwoven Surgical Sponges—Nonwoven fabrics have been developed that are suitable alternatives to woven cotton gauze for use in wound cleaning, wound dressing, and tissue-handling. These nonwoven fabrics depend on dense entanglement of their synthetic fibers (Dacron, rayon, etc) to provide the fabric with an acceptable tensile strength approaching that of woven cotton gauze. They typically offer greater absorbent capacity than cotton gauze sponges of comparable bulk, while generating less lint. Specialty versions of the nonwoven sponges are available prefenestrated for IV tubing or drain-dressing procedures. One manufacturer *(Johnson & Johnson)* provides both a nonwoven sponge for wound dressing (Sof-Wick: very soft texture, very absorbent or Topper: highly absorbent, fewer dressing changes) and a nonwoven general-purpose cleansing/prep sponge (NuGauze: gauze-like texture, more absorbent than gauze). Additionally, a new universal sponge which combines the best attributes of woven and nonwoven gauze, has been created from a new fabric technology. Mirasorb (*Johnson & Johnson*) is made from a cotton blend, is more absorbent and resilient than woven gauze, provides less adherence to healthy tissue, and reduces wound damage and tissue trauma upon removal.

Selvage-Edge Gauze Strips in widths of 1/4 to 2 inches are designed specially and woven for use both as packing strips in surgery of the nose and sinuses, nasal hemostasis, etc, and as drainage wicks in the treatment of boils, abscesses, fistulas, and other draining wounds. The ravelproof, selvage edges on both sides eliminate all loose threads. These gauzes are available unmedicated or medicated with 5% iodoform. These strips are obtainable in sterile form packed in sealed glass jars. Nu Gauze Packing Strips are packaged in polystyrene containers.

Gauze Pads or Sponges are folded squares of surgical gauze. These are so folded that no cut gauze edges or loose threads are exposed. This prevents loose fibers from entering the wound. The pads are folded such that each size may be unfolded to larger sizes without exposing cut edges or loose threads. Sterilized packages of these frequently used all-gauze sponges are available in tamper-proof packages. Such sterile units particularly are well-suited to the numerous tray sets prepared in hospitals.

X-ray Detectable Gauze Pads are similar to all-gauze pads but contain inserts treated with barium sulfate. They are nontoxic, soft, and nonabrasive. They remain permanently detectable because they neither deteriorate in the body nor are affected by either sterilization or time. Examples of X-ray detectable sponges include Vistec and Kerlix (unique, crinkle-weave, soft, and absorbent), both manufactured by Kendall. Ray-Tec X-Ray Detectable Sponges *(Johnson & Johnson)* contain a nonabrasive vinyl plastic monofilament that gives a characteristic pattern in the X-ray.

Composite absorbent dressings have been developed for specific purposes. They usually consist of layers of absorbent gauze or nonwoven fabric with fillers of cotton, rayon, nonwoven fabric, or tissue paper in suitable arrangements. Composite sponges have gauze or nonwoven fabric surfaces with fillers of cotton, rayon, nonwoven fabric, or absorbent tissue.

Dressing Combines are designed to provide warmth and protection and to absorb large quantities of fluid that may drain from an incision or wound. Each combine consists of a nonwoven fabric cover enclosing fiber with or without absorbent tissue. They also may incorporate a nonabsorbent layer of cotton, tissue, or plastic film to prevent fluid from coming through to soil liners and bedding, though some combined dressings are entirely absorbent.

Laparotomy Sponges, also known as *Abdominal Packs, Tape Pads* or *Packs, Walling-Off Mops, Stitched Pads, Quilted Pads, Gauze Mops,* etc, are used to form a nonabrasive wall that will prevent abdominal or other organs from entering into the field of operation and to help maintain body temperature during exposure. They are made of four layers of 28-×-24 mesh gauze. The edges are folded in and hemmed. The entire pack is cross-stitched, and a looped tape 1/2-inch wide and 20-inches long is attached to one corner. A desirable feature of one type is an X-ray-detectable insert so firmly incorporated into the gauze that it cannot become detached. Treated with barium sulfate, the monofilament is nontoxic and, were it to be left inadvertently *in situ,* would cause no more foreign-body reaction than an ordinary dressing.

Sanitary Napkins intended for special hospital use, otherwise known as *V-Pads, Obstetrical (OB) Pads, Perineal Pads, Maternity Pads,* etc, are used in obstetrical, gynecological, or maternity cases. Napkins that have repellent tissue on the side and back surfaces of the napkin usually are preferred because of their greater fluid-holding capacity. Sanitary napkins generally come with two sizes of filler, 3 × 9-inch or 3 × 11-inch. The napkin cover generally is made from a nonwoven fabric or a nonwoven fabric supported with an open-mesh scrim. Packaged, sterilized napkins are available and used generally to reduce cross-contamination possibilities.

Disposable Cleaners made from various types of nonwoven fabrics are available. They generally offer advantages over paper in wet strength and abrasion resistance, plus having better cleaning ability. Their advantages over cloth are reduced laundry expense and cross-contamination possibilities.

Eye Pads are scientifically shaped to fit comfortably and cover the eye completely, thus protecting the eyebrow when taped. These pads are made using nonwoven fabric. Two sides are enclosed to prevent the cotton from escaping and the pad from distorting. When desired, the pad may be folded and used as a pressure dressing. Eye pads especially are useful in the outpatient clinic of the hospital, the industrial medical department, and the physician's office. They are sealed in individual sterile envelopes.

Nursing Pads are designed in a contour shape to fit comfortably under the nursing brassiere or breast binder.

Disposable Underpads are used for incontinent, maternity, and other patients with severe drainage. Such pads cost less than the average hospital-made product and provide a neat, clean, easy-to-handle pad that is changed quickly and easily disposed. Disposable briefs are available *(Johnson & Johnson, Kendall)*.

Cotton-Tipped Applicators are used to apply medications or cleanse an area. Machine-made cotton-tipped applicators are uniform in size, resulting in no waste of cotton or medications. The cotton is attached firmly to the stick and may be sterilized readily without affecting the anchorage of the cotton. They are available in 3- or 6-inch lengths.

Bandages

The function of bandages is to hold dressings in place by providing pressure or support. They may be inelastic, be elastic, or become rigid after shaping for immobilization.

Common Gauze Roller Bandage is listed in the USP as a form in which *Absorbent Gauze* may be provided. It is prepared from *Type I Absorbent Gauze* in various widths and lengths. Each bandage is in one continuous piece, tightly rolled and substantially free from loose threads and ravelings.

Muslin Bandage Rolls are made of heavier unbleached material (56 × 60 mesh). They are supplied in the same widths as the regular gauze bandage. Muslin bandages are very strong and are used wherever gauze bandages do not provide sufficient strength or support. They frequently are used to hold splints or bulky compression dressings in place.

Elastic Bandages are made in several types:

1. **Woven Elastic Bandage** is made of heavy elastic webbing containing rubber threads. Good support and pressure are provided by this type of rubber elastic bandage.
2. **Crepe Bandage** is elastic but contains no rubber. Its elasticity is due to a special weave that allows it to stretch to practically twice its length, even after repeated launderings. This elasticity makes it especially serviceable in bandaging varicose veins, sprains, etc, because it conforms closely to the skin or joint surfaces, lies flat and secure, yet allows limited motion and stretches in case of swelling so that circulation is not impaired.
3. **Conforming Bandage** is made from two plies of specially processed, high-quality, 14 × 8-inch cotton gauze folded to the center. This type is much easier to use and apply than ordinary roller bandage, since it tends to cling to itself during application, thus preventing slipping. It readily conforms to all body contours without the necessity of *reversing* or twisting. A further advantage is the fact that there can be no rough or frayed edge. Kling Conforming Gauze Bandage and Sof-King Conforming Bandage *(Johnson & Johnson)* are available in a variety of sizes up to 6 inches wide. This gauze is used widely to hold dressings or splints firmly in place and occasionally as a primary dressing when sticking to the wound is not a problem. A mercerized cotton Conforming Gauze Bandage clings to itself and thus remains in place better than gauze made of other materials. Sof-King is a one-ply rayon and polyester blend bandage that provides greater bulk for cushioning and greater absorbency.
4. **High-Bulk Bandage** is made of multiple layers (typically six) of crimped cotton gauze. The high bulk of this bandage type is designed to provide padding protection in wound dressing applications. It also provides the absorbent capacity of a cotton dressing component. One version (Sof-Band High Bulk, *Johnson & Johnson*) is made of mercerized cotton to help the bandage cling to itself, which facilitates application and improves dressing stability.
5. **Compression Bandage** is composed of cotton knitted or woven with either viscose, polyurethane, nylon, or elastane threads. The bandage is comformable and easy to apply. Its use is primarily to maintain controlled levels of pressure when compression therapy is required. As with all compression bandages, these products should be utilized with caution on patients with marked peripheral ischemia or impaired arterial blood supply. Examples of compression bandge include Tensopress *(Smith and Nephew),* Yeinopress *(Moliner),* and Setopress *(Seton Healthcare)*.

Triangular Bandages usually are made by cutting a square of bleached muslin diagonally from corner to corner, forming two right triangles of equal size and shape. The length of the base is approximately 54 inches. These bandages were brought into prominence by Esmarch and still bear his name. They are used in first-aid work for head dressings, binders, and arm slings and as temporary splints for broken bones.

Orthopedic Bandages are used to provide immobilization and support in the treatment of broken bones and in certain conditions of bones and joints. Plaster of Paris–impregnated gauze has been the standard material for this purpose. More recently introduced are synthetic cast materials made of polyester cotton or fiberglass. Various types of plastic sheets also are offered that can be shaped easily and hardened to a rigid form by cooling or chemical reaction. These are useful chiefly for splints and corrective braces.

Individually packaged plaster of Paris bandages and splints are available in a wide variety of sizes. The Specialist brand *(Johnson & Johnson)* is made from specially treated plaster, uniformly spread and firmly bonded to the fabric. This results in a high strength-to-weight ratio in casts made from such bandages. Synthetic casts are applied like plaster of Paris. The Delta-Lite Synthetic Casting System *(Johnson & Johnson)* offers both polyester, cotton fabric impregnated with a polyurethane resin, and fiberglass casting materials. Scotchcast Softcast *(3M)* consists of a knitted fiberglass substrate impregnated with a polyurethane resin containing a surface-modifying agent (reduce tack, facilitate application). The casts are water-resistant, light weight, and durable.

Orthoflex Elastic Plaster Bandages *(Johnson & Johnson)* are plaster of Paris bandages containing elastic threads in the fabric and are intended for specialized prosthetic uses.

Stockinette Bandages are made of stockinette material knitted or woven in tubular form without seams. Surgical stockinette is unbleached. Because it is soft and will stretch readily to conform comfortably to the arm, leg, or body, it is used to cover the skin prior to the application of a plaster of Paris or synthetic cast.

Cast Paddings are soft, absorbent, protective paddings, applied like a bandage to the areas affected, before application of a cast. They are composed of various fiber constructions that conform and cling, absorb moisture, and allow the skin to breathe.

Adhesive Tapes

Surgical adhesive tapes are made in many different forms, varying both in the type of backing and in the formulation of the adhesive mass according to specific needs and requirements. The tapes available today may be divided into two broad categories: those with a rubber-based adhesive and those with an acrylate adhesive. Both types have a variety of uses. When strength of backing, superior adhesion, and economy are required (eg, athletic strapping), rubber adhesives commonly are used. Acrylate adhesives on a variety of backing materials are used widely in surgical dressing applications, when reduced skin trauma is required, as in operative and postoperative procedures; they are supplied in various strength and adhesion levels.

ACRYLATE ADHESIVES—Acrylate adhesives on a nonwoven or fabric backing have been accepted widely for use as surgical tapes, owing largely to what may be termed their hypoallergenic nature. Because acrylate adhesives are basically a unipolymeric system, they eliminate the use of a large number of components in rubber-based adhesives. In poly(alkyl-acrylate) adhesives, the desired balance between adhesion, cohesion, and flow properties is determined by the choice of monomers and the control of the polymerization reactions. Once the polymer is made, no other formulating or compounding is needed. In addition, the acrylics have an excellent shelf-life because they are not affected readily by heat, light, or air, factors that tend to degrade rubber-based adhesives.

Acrylate adhesives combine the proper balance of tack and long-term adhesion. Their molecular structure permits the passage of water vapor so they are nonocclusive and thus when coated on a porous backing material do not cause overhydration in the stratum corneum. Traumatic response to surgical tapes is minimized substantially when tapes are constructed to allow normal skin moisture to pass through adhesive and backing material. With this construction, the moisture content and strength of the horny cell layers remain relatively normal. When a porous tape is removed, the planes of separation develop near the surface of the stratum corneum, in the region of the naturally desquamating cells. This allows repeated use of tape over the same site with minimal damage to the skin.

Hypoallergenic Surgical Tapes with acrylate adhesive are available with a variety of porous backing materials. Rayon taffeta cloth backing provides a high-strength tape well-suited for affixing heavy dressings. Lighter dressing applications can be accomplished with lower-strength, economical, paper-backed surgical tapes. A knitted backing tape (Dermiform, *Johnson & Johnson*) provides some of the economies of paper

surgical tape with the strength and conformability of a cloth backing. Other tapes feature elastic cloth or foam backing materials for special taping needs.

RUBBER-BASED ADHESIVES—A second group of surgical adhesive tapes is the cloth-backed and plastic-backed rubber adhesives. These are used principally where heavy support and a high level of adhesion are required. Modern rubber-based adhesive tape masses consist of varying mixtures of several classes of substances and are composed of an elastomer (para or pale crepe rubber in the case of natural rubber tapes, and synthetic elastomers made from polymers of isobutylene, alkylacrylate, or similar materials), one of several types of rosin or modified rosin, antioxidants, plasticizers and fillers, and coloring agents to give the tape the desired tint or whiteness.

ADHESIVE TAPE REACTIONS—While skin reactions formerly were accepted by the medical profession as almost predictable sequelae to the use of adhesive tape, with better understanding of the mechanisms of such reactions and progress in research and technology, the long-sought-for objective of hyporeactivity has, in large degree, been attained.

Because adhesive tape masses historically have consisted of heterogeneous and complex mixtures of organic compounds, it is not surprising that many workers have ascribed adhesive tape reaction to allergy. More-recent work, however, has shown that a true allergic response to the modern adhesive tape mass or its components is a factor in only a small proportion of clinical reactions and that most observed reactions are ascribed properly to other factors, mainly mechanical irritation and, to a lesser degree, chemical irritation. There apparently is no significant difference in reaction between patients with or without a history of allergy, but true specific dermatitis may occur more readily in persons who have manifested some other form of contact dermatitis.

Adverse manifestations produced by adhesive tape are characterized by erythema, edema, papules, vesicles, and in severe cases, desquamation. Itching may be intense, or it may be absent. The reaction may be demonstrated readily by patch-testing, and usually manifests itself early—within 24 to 48 hr. Characteristically, the reaction becomes more severe the longer the tape is left in place and continues to increase in intensity for some time after the tape is removed. This type of reaction is long-lasting and requires days for its complete subsidence.

Two distinct types of irritation can result from the mechanical dynamics of removing tape from the skin. One response—induced vasodilation—is a relatively nontraumatic, transitory effect in which no actual damage to the skin occurs. A second type—skin stripping—is a traumatic response in which skin is removed with the tape and actual damage to the epidermal layers results. Such mechanical skin removal is possibly the dominant cause of clinical reactions seen with the use of adhesive tape.

Chemical irritation from adhesive tape results when irritating components in the mass or backing of the tape permeate the underlying tissues of the skin. The tape construction can influence the reactivity of such ingredients substantially. For example, many compounds that normally do not penetrate intact stratum corneum can penetrate overhydrated corneum.

When portions of the stratum corneum are removed, the barrier capacity of the skin is damaged substantially. In this situation, any irritating components of the tape have ready access to underlying tissues. These substances then can cause a degree of irritation that is far greater than would be observed on intact skin.

PROTECTIVES

Until recently, protectives included only the various impermeable materials intended to be used adjunctively with other dressing components to prevent the loss of moisture or heat from a wound site or to protect clothing or bed liners from wound exudate. Film dressings are excellent devices to protect against infection and dislodgement of vascular cannulae and drainage sites. In addition, they may be used to protect vulnerable areas against pressure sores.

Protectives also are employed to cover wet dressings and hot or cold compresses. In common use as protectives are plastic sheeting and waxed or plastic-coated paper. These prevent the escape of moisture or heat from the dressing or the compress and protect clothing or bed linens. Rubber sheeting is a rubber-coated cloth, waterproof and flexible, in various lengths and widths for use as a covering for bedding. A so-called *nursery sheeting* is supplied, coated only on one side.

PRODUCTS FOR ADHESION PREVENTION—Adhesions are abnormal connections between organs or tissues that form after trauma, including surgery. They consist of organized fibrin and fibrovascular scar tissue and complicate all areas of surgery. In gynecological surgery, adhesions may result in infertility and pelvic pain; in intestinal surgery they may result in intestinal obstruction; in cardiac surgery they may render a second sternotomy hazardous, and in tendon surgery they will prevent mobility.

Although careful tissue handling and good hemostasis may reduce adhesion formation, there are few proven entities designed for the prevention of adhesions. Gynecare Interceed Absorbable Adhesion Barrier *(Ethicon)* is a knitted fabric of oxidized regenerated cellulose that is placed at a site where adhesions are suspected to occur. It swells and gels to form a barrier between two adjacent surfaces, allowing remesothelialization to take place. The fabric then degrades grossly by about 14 days and microscopically by about 28 days. Interceed Barrier is indicated for reducing the incidence of adhesions in pelvic gynecological surgery. Other mechanical barriers used for the prevention of adhesions include Seprafilm *(Genzyme)* and Gore-Tex Surgical Membrane *(Gore)*. Newer products available for the prevention of postoperative adhesions that are not site-specific for application include Gynecare Intergel Adhesion Prevention Solution, a ferric hyaluronate gel *(Lifecore Biomedical)* and Sepracoat, a dilute hyaluronic acid solution *(Genzyme)*.

OPERATING ROOM SUPPLIES

Hemostatic Products accelerate hemostasis by providing a thrombogenic surface that promotes platelet aggregation and fibrin polymerization. These topical hemostatic agents include collagen, gelatin, cellulose, and thrombin. These include collagen sponges and powders (Instat, *Johnson & Johnson;* Helistat, *Integra Life Sciences;* Actiofoam, *Bard;* Avitene, *Davol;* Helitene, *Integra Life Sciences*), gelatin sponges (Surgifoam, *Johnson & Johnson;* Gelfoam, *Upjohn*), and Oxidized Regenerated Cellulose USP (Surgicel, *Johnson & Johnson*). Both oxidized cellulose and oxidized regenerated cellulose are agents whose actions depend on the formation of a coagulum consisting of salts of polyanhydroglucuronic acid and hemoglobin. When applied to a bleeding surface, they swell to form a brown gelatinous mass that is absorbed gradually by the tissues, usually within 7 to 14 days. They are employed in surgery for the control of moderate bleeding when suturing or ligation is impractical or ineffective.

Thrombin (USP) solutions of bovine origin (Thrombinar, *Jones Medical*) promote hemostasis by catalyzing the conversion of fibrinogen to fibrin. They may be used in conjunction with fibrinogen concentrates prepared from autologous cryoprecipitate or from pooled donor blood.

Tissue sealants are absorbable and are used for a variety of indications including sealing of arterial punctures, sealing of air leaks during pulmonary surgery, and supporting wound healing. The area of tissue sealants is expanding rapidly, with new products reaching the market for numerous indications. Angio-seal *(Kendall),* an absorbable material, is used as a

sealant for arterial punctures. AdvaSeal *(Focal),* a synthetic absorbable sealant, is used to seal air leaks during pulmonary surgery. Tissell *(Immuno AE),* a two-component fibrin sealant, is used to promote wound healing as well as achieve hemostasis and tissue adhesion. BioGlue, (*Cryolife*) is a bovine albumin-based glue used to seal aortic aneurysms and anastomotic sites.

Tissue glues are used for topical skin adhesives and replace the need for sutures, staples, or adhesive strips for certain types of lacerations requiring closely approximated wound edges. Dermabond *(Closure Medical),* an octyl cyanoacrylate, is used as a topical skin adhesive that sloughs from the wound as reepithelialization of the skin occurs, providing sufficient time for wound healing. Indermil (Tyco Healthcare), a butyl cyanoacrylate, is another topical skin adhesive.

Disposable Sterile OR and OB Packs are prepared, packaged, and sterilized assemblies of diapering and gown units, designed to fulfill the operating and delivery room needs. They eliminate the problems of laundering, storage, assembly, and sterilization of muslin drapes and gowns. They introduce many special materials with particular properties of porosity; repellency to water, alcohol, blood and other fluids; abrasion resistance; and other desirable attributes.

Double packages of contamination-resistant paper have been developed to permit opening and use without compromising sterility. Retention of sterile characteristics until used, eliminates the need for resterilization.

Face masks for use in the operating room and where contamination must be controlled generally are made of plied, fine-mesh gauze, shaped to cover the nose, mouth, and chin. They are laundered and autoclaved. Disposable face masks with special filtration material giving high retention of particulate matter and designed for more effective fitting are available from several manufacturers. Surgine Face Mask *(Johnson & Johnson)* claims a 94% filtration efficiency with high user comfort.

SURGICAL DRESSINGS

ADHESIVE BANDAGE

Adhesive Absorbent Compress; Adhesive Absorbent Gauze

A compress of four layers of Type I absorbent gauze, or other suitable material, affixed to a film or fabric coated with a pressure-sensitive adhesive substance. It is sterile. The compress may contain a suitable antimicrobial agent and may contain one or more suitable colors. The adhesive surface is protected by a suitable removable covering.

Description—The compress is substantially free from loose threads or ravelings; the adhesive strip may be perforated, and the back may be coated with a water-repellent film.

GAUZE BANDAGE

Type I absorbent gauze; contains no dye or other additives.

Description—One continuous piece, tightly rolled, in various widths and lengths and substantially free from loose threads and ravelings.

OXIDIZED CELLULOSE

Absorbable Cellulose; Absorbable Cotton; Cellulosic Acid; Hemo-Pak *(Johnson & Johnson);* Oxycel *(Deseret Medical)*

Sterile gauze or cotton that has been oxidized chemically to make it both hemostatic and absorbable; contains 16% to 24% carboxyl (COOH) groups.

Description—In the form of gauze or lint. Is slightly off-white in color, is acid to the taste, and has a slight charred odor.

Solubility—Insoluble in water or acids; soluble in dilute alkalies.

Comments—The value of oxidized cellulose in various surgical procedures is based upon its properties of absorbability when buried in tissues and its remarkable hemostatic effect. Absorption occurs between the second and seventh day following implantation of the dry material, depending on the adequacy of the blood supplied to the area and the degree of chemical degradation of the implanted material. Complete absorption of large amounts of blood-soaked gauze may take 6 weeks or longer, and serious surgical complications and cyst formation have been reported as the result of failure to absorb. Hemostasis depends upon the marked affinity of *cellulosic acid* for hemoglobin. When exposed to blood, either *in vitro* or in surgical conditions, the oxidized gauze or cotton turns very dark brown or black and forms a soft gelatinous mass that readily molds itself to the contours of irregular surfaces and controls surgical hemorrhage by providing an artificially induced clot. Pressure should be exerted on the gauze or cotton for about 2 min to facilitate the sealing off of small, bleeding vessels.

Two factors require emphasis: (1) cellulosic acid does not enter the physiological clotting mechanism *per se* but forms what might be termed an *artificial clot* as described and, therefore, is effective in controlling the bleeding hemophiliac and (2) the hemostatic action of cellulosic acid is not enhanced by the addition of other hemostatic agents, such as thrombin (which in any case would be destroyed by the pH of the gauze unless some means of neutralization were practicable). The hemostatic effect of either one alone is greater than the combination.

It is useful as a temporary packing for the control of capillary, venous, or small arterial hemorrhage, but since it inhibits epithelialization, it should be used only for the immediate control of *hemorrhage* and not as a surface dressing. A purer and more uniform product prepared from oxidized regenerated cellulose has been developed and is available as Surgicel Absorbable Hemostat. This offers many advantages over the older, less-uniform oxidized cellulose derived from cotton and, because of its chemical uniformity, ensures dependable performance and overcomes many of the difficulties encountered with the older type of cotton product. The knitted fabric strips do not fragment, may be sutured in place easily if necessary, and provide prompt and complete absorption with minimum tissue reaction.

OXIDIZED REGENERATED CELLULOSE

Surgicel; Surgicel Nu-Knit; Surgicel Fibrillar *(Johnson & Johnson)*

Contains 18–24% carboxyl groups (COOH), calculated on the dried basis. It is sterile.

Preparation—Cellulose is dissolved and regenerated by a process similar to the manufacture of rayon, which is then oxidized.

Description—Creamy white gauze, lint, or woven material.

Solubility—Insoluble in water; soluble in alkali hydroxides.

Comments—Absorbable hemostatic.

PURIFIED COTTON

Gossypium Purificatum; Absorbent Cotton

The hair of the seed of cultivated varieties of *Gossypium hirsutum* Linné or other species of *Gossypium* (Fam *Malvaceae*), freed from adhering impurities, deprived of fatty matter, bleached, and sterilized in its final container.

Description—White, soft, fine, filament-like hairs appearing under the microscope as hollow, flattened and twisted bands, striate and slightly thickened at the edges; practically odorless and practically tasteless.

Solubility—Insoluble in ordinary solvents; soluble in ammoniated cupric oxide TS.

DEXTRANOMER

Debrisan (Johnson & Johnson)

Dextranomer is a three-dimensional cross-linked dextran polymer prepared by interaction of dextran with epichlorohydrin.

Description—White, spherical beads, 0.1 to 0.3 mm in diameter; hydrophilic. Also available dispersed in polyethylene glycol, as a paste.

Solubility—Insoluble in water or alcohol. Each gram absorbs about 4 mL of aqueous fluid, the beads swelling and forming a gel.

Comments—Topically to cleanse secreting lesions such as venous stasis ulcers, decubitus ulcers, infected traumatic and surgical wounds, and infected burns. It absorbs the exudates, including the components that tend to impede tissue repair, and thereby retards eschar formation and keeps lesions soft and pliable.

ABSORBABLE DUSTING POWDER

Starch-derivative Dusting Powder

An absorbable powder prepared by processing cornstarch and intended for use as a lubricant for surgical gloves; contains not more than 2% magnesium oxide.

Description—White, odorless powder; pH (1 in 10 suspension) between 10 and 10.8.

ABSORBENT GAUZE

Carbasus Absorbens; Gauze

Cotton, or a mixture of cotton and not more than 53.0%, by weight, of purified rayon, in the form of a plain woven cloth. If rendered sterile, it is packaged to protect it from contamination.

Description—White cotton cloth of various thread counts and weights; may be supplied in various lengths and widths and in the form of rolls or folds.

PURIFIED RAYON

A fibrous form of bleached, regenerated cellulose. It may contain not more than 1.25% titanium dioxide.

Preparation—By the viscose rayon process.

Description—White, lustrous or dull, fine, soft, filamentous fibers, appearing under the microscope as round, oval, or slightly flattened translucent rods, straight or crimped, striate and with serrate cross-sectional edges; practically odorless and practically tasteless.

Solubility—Very soluble in ammoniated cupric oxide TS or dilute H_2SO_4 (3 in 5); insoluble in ordinary solvents.

Comments—Hemostatic.

ADHESIVE TAPE

Sterile Adhesive Tape

Fabric and/or film evenly coated on one side with a pressure-sensitive, adhesive mixture. If rendered sterile, it is protected from contamination by appropriate packaging.

SUTURES AND SUTURE MATERIALS

A surgical suture is a strand or fiber used to hold wound edges in apposition during healing, and the process of applying such a strand is called *suturing*. When such material, without a needle, is used to stop bleeding by tying off severed blood vessels, the strand is called a *ligature,* and the process is known as *ligating*. Suture materials, however, have uses beyond those involved in the repair of wounds in that they often are used in reconstructive procedures.

Surgical sutures were first listed in the second supplement of USP XI in a monograph on catgut sutures, which then were designated officially as *Surgical Gut*. USP XII carried a similar monograph on surgical silk. USP XVI contained, in addition to surgical gut, a generalized monograph designed to cover all sutures in addition to catgut, and this is also true of USP XX. USP 23 additionally describes synthetic absorbable sutures.

At one time or another, nearly every form of fibrous material or wire that offered any promise at all has been used as a suture, and indeed many materials that by present standards offer no promise at all have been evaluated.

Cotton and linen were among the earliest suture materials, but the use of animal intestines and sinews also claims great antiquity. As in many other fields of science, there have been fads, and numerous materials have enjoyed varying favor through the centuries. Frequently, the acceptance of a given suture material depended on its successful use by an eminent surgeon whose authority encouraged emulation, and in many cases, there appeared to be legitimate scientific justification for such use.

Possibly the most important factor in the acceptance of suture materials has been their characteristics in the presence of infection. As knowledge of bacteriology increased and methods of sterilization improved, the earlier disadvantages of certain sutures have been overcome, so that currently a wide variety of surgical suture materials may be sterilized conveniently and effectively.

Among the widely accepted methods for the sterilization of sutures are autoclave sterilization with free access of water vapor, applicable only for those sutures that are not harmed by this process; dry heat at 310°F; ethylene oxide; and irradiation sterilization using either beta or gamma rays.

Irradiation sterilization has many advantages over the older methods insofar as commercial production is concerned. The sutures are sterilized in their final sealed packages, eliminating any danger of recontamination. The radiation dose is greater than necessary to kill even the most resistant spore-forming organisms. One great advantage of this method lies in the relative lack of deteriorating effect upon many sutures. Irradiation-sterilized surgical gut is stronger, more pliable, and easier to handle than dry-heat-sterilized surgical gut sutures.

Suture materials may be divided into two principal classes: absorbable and nonabsorbable. In the first class are found those materials that are capable of being broken down or digested by the body. Catgut, the classic absorbable suture derived from collagen-rich animal tissue, is proteinaceous in nature, and it appears that certain proteolytic enzymes in tissues are responsible for the digestion of catgut and its disappearance from the wound area. New forms of absorbable sutures based upon synthetic polyesters such as polyglycolic acid, copolymers of lactide and glycolide, polydioxanone, copolymers of glycolide and caprolactone, and a blend of glycolide, trimethylene carbonate, and dioxanone have been introduced as alternative absorbable materials.

Nonabsorbable sutures are manufactured from various materials such as polyester, nylon, or polypropylene. These materials incite a minimal foreign-body reaction at the site of placement, which resolves over time. Nonabsorbable sutures are used frequently for cardiovascular, ophthalmic, and neurological procedures.

ABSORBABLE SUTURES

SURGICAL GUT—Catgut is still used in surgical procedures, but its use, especially in the US, has declined because of the availability of new, synthetic, absorbable suture materials. Its basic constituent is collagen derived from the serosal or submucosal layer of the small intestine of healthy ruminants (cows, sheep, goats). The intestines from the freshly killed animals are cleaned of their contents and split longitudinally into ribbons. Mechanical processes remove the innermost mucosa and the outer muscularis layers, essentially leaving only the submucosal or serosal collagenous layers. This appears as a thin, strong network consisting chiefly of collagen, whose orientation and strength are increased markedly by subsequent processing. From one to five or six such ribbons are stretched, spun, or twisted under tension and dried under tension to form a uniform strand. These strands are polished to a uniform diameter and cut into appropriate lengths for packaging and sterilization.

In another method, collagen sutures are produced from collagen derived from beef tendon. The tendons are suitably treated and dispersed. The dispersed collagen is extruded, precipitated, and reconstituted as fine strands that are then twisted, stretched, tanned, and otherwise treated to give absorbable sutures with the desired characteristics.

Diameter and strength requirements for absorbable surgical suture (surgical gut) are specified in the USP, in which will be found descriptions of the suture as well as the apparatus and methods for measuring diameter, tensile strength, and sterility and other tests.

Plain and Chromicized Surgical Gut—Two varieties of catgut, distinguished by their resistance to absorptive action by tissue enzymes, are described in the USP as *Type A,* plain or untreated, and *Type C,* medium treatment. The availability of both types reflects the surgeon's requirements for catgut that will retain its tensile strength for varying periods of time or that will show an increased resistance to the proteolytic substances found in certain body tissues. This is accomplished by the incorporation of chromium salts or other chemicals to prolong its survival in tissues. Such products formerly were designated as 10-, 20-, or 40-day catgut, on the assumption that

these sutures would remain for such periods in normal tissue. The variations in catgut as a natural product, as well as the variations in patients and in sites of implantations, make such designations qualitative, so they were replaced by the more general statement of type. While many tests for the expected duration of resistance have been proposed, none is accepted fully as comparable to digestion in animal tissues, and none has been included in the USP.

Approximately half the surgical gut used in the US has been either chromicized or otherwise treated. Raw catgut is analogous to rawhide, while chromicized catgut is comparable to chrome-tanned leather. The tanning process is applied either to the ribbons before they have been twisted into the strand form or to the finished twisted strand. Treatment in the ribbon form is reported to result in a more uniform deposition of chromium salts throughout the entire cross-section of the suture, while string chromicization sometimes causes the deposition of relatively heavier concentrations of the tanning agent near the periphery of the strand, with less penetration to its center. Deficient tanning of catgut may result in its premature absorption with possible wound disruption, although such incidents now are recognized often as the effects of nutritional or other inadequacies, with resultant weakness of the tissues themselves. Excessive chrome concentration in surgical gut may produce sutures that digest slowly. Since they survive in normal tissues for a long time, they occasionally may extrude through the skin some months following surgery. The mechanism of such extrusion by highly tanned catgut or by nonabsorbable sutures is not clear, although it probably reflects the natural tendency of the body to eliminate or reject foreign material.

Tissue Reaction—Following any surgical incision, there is an outpouring of blood and lymph into and through the wound. These fluids coagulate or clot, forming a network upon which new cells may build. The capillaries in the area dilate, and the blood supply in the vicinity of the wound is increased. Leukocytes in the area also increase in number.

The absorption of surgical gut takes place along with the tissue repair processes. The leukocytes, which appear early in any wound, produce proteolytic enzymes that, among other functions, carry out the digestion of absorbable catgut sutures. After this process is well along, fibroblasts appear and begin to lay down the collagen fibers essential for the increasing strength and healing of the wound. In the first phase of wound healing, the number and character of the debriding cells, together with such secondary effects as swelling, pain, and redness, constitute *tissue reaction*. Chromic catgut elicits a less intense tissue reaction of a leukocytic or exudative type than does the plain variety.

Plain gut is digested by enzymes at a faster rate than chromic gut. The surgeon chooses either plain or chromic gut, depending on the type of tissue involved, the condition of the patient, and the estimated healing time of the wound. Small sizes of surgical gut cause less tissue reaction and irritation than large sizes. There is less digestive work for the enzymes to do. For this reason surgeons try never to use a suture that is stronger than the tissue in which it is to be used. The larger sutures merely add to tissue irritation without supplying any needed strength to the wound.

Sterilization and Packaging—Disappointing experiences with many attempts to sterilize gut by chemical means have created widespread distrust of the effectiveness of most chemicals. The exception has been the use of ethylene oxide, which has provided an effective means for sterilizing sutures. The more common methods are dry-heat sterilization (after first dehydrating the catgut) and irradiation sterilization in the final sealed packet.

At one time most surgical gut was produced and labeled as *boilable*. It was packaged in glass tubes with the strands immersed in a water-free, high-boiling tubing fluid—usually xylene. The exteriors of the tubes could be sterilized at the hospital by autoclaving—hence, the term *boilable*.

The disadvantage of boilable catgut has been that the drying necessary to permit high-temperature sterilization produces a stiff strand, which is still stiff as removed from the tube, and which requires soaking for several minutes in sterile water before surgeons find it pliable enough to use. This process no longer is used (with isolated exceptions).

The present method of packaging provides sutures ready for use as removed from the packet. The catgut, designated *nonboilable,* is contained in either a foil or plastic packet, immersed in a pliabilizing fluid that generally consists of an alcohol or mixtures of an alcohol with a small percentage of water. The water has a pliabilizing effect but would ruin the gut if the latter was subjected to high temperatures—therefore, the designation *nonboilable*.

Irradiation and ethylene oxide sterilization techniques, as described in the USP, largely have replaced the older accepted method of dry-heat sterilization. These methods have permitted the development of more-convenient packaging innovations that were not practical with the older methods.

For even greater convenience, all foil or plastic packets are now overwrapped in a secondary package. Both the contents and the outside of the inner packet are rendered sterile. By peeling open the overwrap package, the inner packet can be delivered ready for use in a sterile condition on the operating table.

Sterility Testing—Freedom from contamination is the most important property of any suture. Every lot of sutures furnished by reputable manufacturers is subjected to a series of physical and chemical tests, in accordance with prescribed USP sterility test procedures as well as validated sterilization processes. No lot of sutures is released until all of these tests have been passed successfully; hence, the surgeon has developed a justified confidence in the adequacy and sterility of these products. Because of the extraordinary reliability of radiation sterilization, acceptance of product sterility based on validated measurement and control of the radiation process is becoming more widespread.

Operating Room Procedures—Before a scheduled operation, the nurse usually selects the necessary types of sutures designated by the operating surgeon. The required number of overwrapped packages is opened by peeling apart the outer package and flipping or otherwise removing in an aseptic manner the inner sterile packets and placing them on the Mayo stand. The packets are opened by tearing, if foil, and by cutting with sterile scissors, if plastic. Straightening the nonboilable suture is accomplished by a gentle pull. They commonly are used as removed from the packet. Abuse of catgut sutures may lead to their failure in tissues, with possible serious consequences to the patient.

SYNTHETIC ABSORBABLE SUTURES—The combination of high tensile strength and absorbability that makes catgut so useful as a suture has been incorporated into synthetic fibers. Polymers derived from condensing the cyclic derivative of glycolic acid (glycolide), mixtures of glycolide and lactide (derived by cyclicizing lactic acid), dioxanone, glycolide with trimethylene carbonate, mixtures of glycolide and caprolactone and blends of glycolide, trimethylene carbonate, and dioxanone have been shown to possess properties that make them suitable for many surgical procedures. Dexon II *(Davis & Geck),* a polyglycolic acid homopolymer, and Vicryl *(Ethicon)* and Polysorb *(US Surgical),* glycolide and lactide copolymers, are melt-extruded into multifilament yarns that then are braided into various sizes of sutures. Such braids have high tensile strength and, unlike catgut, must be packaged without fluid and sterilized with ethylene oxide to avoid degradation. PANACRYL suture (*Ethicon*) is another glycolide and lactide copolymer that has long-term strength retention found useful for various orthopedic procedures. Polymers such as dioxanone *(PDS II, Ethicon),* glycolide and caprolactone *(Monocryl, Ethicon),* glycolide with trimethylene carbonate *(Maxon, Davis & Geck),* and blends of glycolide, trimethylene carbonate, and dioxanone *(Biosyn, US Surgical)* are provided as pliable monofilaments. Synthetic absorbable sutures do not undergo

the enzymically mediated absorption process that is well-known for catgut. Rather, the suture is broken down completely by simple bulk hydrolysis as it resides in the tissue, and the tissue reaction is minimal. A new device that represents the first generation of "active" sutures is VICRYL Plus Antibacterial suture (*Ethicon*). This suture has an antibacterial coating containing triclosan that inhibits the colonization of the suture by bacteria known to be associated with surgical site infections.

CARGILE MEMBRANE—This is a thin sheet of pliable tissue obtained from the appendix *(blind gut)* of the steer or ox. It is designed primarily to cover surfaces from which the peritoneum has been removed, especially where a sterile membrane would lessen the formation of adhesions. The membrane is available in sterile sheets of approximately 4 × 6 inches and sometimes is used as a packing or protective sheath. At present, the use of such material is limited.

FASCIA LATA—This is obtained from ox fascia and is designed for use as a heavy suture or repair in hernia or similar cases. It usually is attached firmly to a strong structure by means of a nonabsorbable suture. It is supplied in the form of sterile strips approximately 1/2 inches wide and 8 inches long and also in sheets about 3 × 5 inches.

It should be emphasized, in connection with the above, that catgut strands and ribbons are the only ones that are completely and readily absorbable. The other materials may be absorbed very slowly or may be incorporated in the tissues by invasion of fibroblasts.

NONABSORBABLE SUTURES

The second principal class of suture consists of natural and synthetic nonabsorbable suture materials that are relatively resistant to attack by normal tissue fluids. Several of these materials remain, apparently unchanged, for many years in tissue and usually will be found encapsulated in a thin sheath of fibrous connective tissue. When nonabsorbable sutures are used for skin closure, they usually are removed after the incision or wound has healed to the point where suture support is no longer necessary.

Silk is an important nonabsorbable surgical suture. Selected grades of degummed commercial silk fibers are used and consist chiefly of the protein fibroin as extruded by the silkworm. Many such fibers are twisted into a single strand of various diameters, as specified in the USP, and sold in the natural color or after dyeing. By far the most popular construction is braided silk, in which several twisted yarns are braided into a compact structure favored for its firmness and strength. Most braided silk is dyed and also given a treatment to render it noncapillary. In use as a skin suture this minimizes the rise of tissue fluids to the surface and thus the counterpassage inward of organisms from the surface. Further objectives of such treatments are to impart a degree of stiffness to improve the handling and tying properties, to minimize attachment of tissue cells that would cause pain on removal of the suture and to lubricate the implantation and removal of the silk. When silk or any other suture is dyed, the USP requires that it be done with a color additive approved by the FDA.

Specifications—The USP describes in the monograph for Nonabsorbable Surgical Suture (which now includes cotton, linen, metallic wire, nylon, rayon, Dacron, and silk) the respective sizes, diameters, and tensile strengths.

Uses—Silk sutures are handled easily and tolerated well by body tissue, although they may cause significant tissue reaction. In the presence of infection, however, the interstices of silk strands protect organisms from antimicrobial agents and from the body's defense mechanisms, so that chronic sinuses may form that do not heal until the silk is removed or is sloughed by the tissues. Silk, as well as any other nonabsorbable suture, occasionally migrates from the site of implantation and comes to the surface to be extruded months after the operation. In certain sites, the suture knots or ends may serve as centers for the formation of concretions or for other irritating action. Silk usually becomes encapsulated and remains in the tissues for extended periods of time as the protein slowly degrades.

DERMAL SILK—These sutures consist of natural twisted silk encased in an insoluble coating of tanned gelatin or other protein. This coating must withstand autoclaving without stripping, and its purpose is to prevent the ingrowth of tissue cells, which would interfere with its removal after use as a skin or dermal suture.

COTTON AND LINEN—Sutures derived from cellulose are among the oldest known but currently are used to a limited extent. These are twisted from fiber staple, have moderately high tensile strength, and are stable to heat sterilization. Cotton sutures prepared by suture manufacturers are uniform and have reproducible strength and largely have replaced the household sewing cotton used by many surgeons years ago. These are desirable because of their handling properties but are not used widely in critical areas where strength must be maintained for long periods of time because they slowly degrade.

Synthetic Nonabsorbable Sutures

Nylon, the first modern synthetic fiber, came into use as a suture partly as a result of World War II shortages of high-grade silk and partly because of its own merits. It is a synthetic polyamide obtained from the condensation of adipic acid and hexamethylenediamine or from the condensation-polymerization of caprolactam. It is available in the form of monofilaments (Ethilon, *Ethicon;* Dermalon, *Davis & Geck*) in the useful range of sizes, as well as in the form of multifilament fibers (Nurolon, *Ethicon;* Surgilon, *Davis & Geck;* Nylon, *Deknatel;* Bralon, *US Surgical*) braided into strands of comparable diameter. It is strong and water-resistant and has come into some use for all suturing or ligating. Monofilament nylon is used as a skin or stay suture or for plastic surgery. Braided nylon more often is buried in tissues and is subject to the same limitations as braided silk in the presence of infection.

POLYESTER FIBER—Of the numerous multifilament synthetic fibers introduced after the success of nylon, only polyester has been accepted as a suitable braided nonabsorbable suture, while polypropylene has enjoyed increasing popularity as a nonabsorbable monofilament suture. Polyester suture is prepared by melt-extruding polyethylene terephthalate into fine filaments that then are braided into various sizes. In general, the tensile strength of polyester braided sutures is superior to that of braided silk and nylon and twisted cotton. Examples of braided polyester sutures include Ethibond Excel *(Ethicon),* Surgidac *(US Surgical),* TiCron *(Davis & Geck),* Tevedek II, and Polydek, both manufactured by *Deknatel*. Novafil *(Davis & Geck),* a copolymer of polybutylene terephthalate and polytetramethylene ether glycol, is available as a monofilament polyester suture.

The polyester sutures, in contrast with most other materials except polypropylene and stainless steel, do not lose strength significantly when in contact with water or body fluids. For this reason, they have become a suture of choice when there is a critical need for permanent reinforcement as, for example, in the installation of artificial heart valves. They have the advantage of excellent knot-holding characteristics and are available in the natural color or dyed to enhance visibility in the surgical field.

Recent developments have seen the commercialization of braided polyester fiber sutures coated or impregnated with nontoxic lubricants such as polytetrafluoroethylene or silicone resins. Polybutilate, a lubricant especially designed for polyester suture use, has been derived from a condensation polymer of butanediol and adipic acid. These sutures exhibit the advantage of a smoother surface, which gives the suture improved handling properties and permits an easier and more gentle passage through tissue.

POLYOLEFIN FIBERS—Of increasing interest in the nonabsorbable suture field is the development of fibers based on polyolefins. Although polyethylene sutures have been

available, the use of polypropylene monofilament (Prolene, *Ethicon;* Surgipro, *US Surgical;* Surgilene, *Davis & Geck;* Deklene II, Deknatel) has increased greatly during recent years. Polypropylene sutures, compared to monofilament nylon, tie more secure knots and have a very low order of tissue reactivity. Because of the smoothness of polypropylene sutures, they slip through tissue easily and, because there is no tissue ingrowth, they may be removed easily when necessary. They have found wide application in cardiovascular and other surgical specialties. Another member of this family of sutures is Pronova suture (*Ethicon*) which is based on a blend of polyvinylidene fluoride and a copolymer of polyvinylidene fluoride and hexafluoropropylene. This monofilament suture is noted for its resistance to damage in the surgical field and may be useful in robotic surgery.

Polytetrafluoroethylene (PTFE) suture (Gore-Tex, *Gore*) has been recommended for use with vascular grafts derived from the same material, as well as in other surgical procedures.

Metallic Sutures

For some years increased attention has been paid to the use of various metal wire sutures and other metallic devices to assist surgical repair.

SILVER—Among the older materials that still are used to some extent are silver wire, foil, and other forms. Relatively little work has been reported recently on these items. Silver is available readily and is alleged to have some antiseptic action but in some tissues is definitely irritating. Irritation has been shown by a great many metals and alloys and now is regarded as a controlling consideration in the choice of substances for implantation in tissues.

STAINLESS STEEL—This ferrous alloy, which so long has been employed usefully in industrial and other applications in which resistance to chemical attack is essential, has been used widely in the form of wire sutures, fixation plates, screws, and other items. Stainless steel is a rather general term covering a wide variety of materials, and many of the early alloys were attacked by body fluids. The proper selection of stainless-steel compositions seems to provide a material essentially inert in tissues and free from the earlier disadvantages. Stainless-steel sutures are available as both twisted and monofilament strands and represent the strongest available material. However, they are relatively difficult to use and are employed most commonly in areas where great strength is required, such as in the repair of the sternum after chest surgery.

Surgical Meshes

Surgical meshes are used as reinforcement material to aid in tissue repair and encourage ingrowth of fibrous connective tissue. Meshes are used for umbilical, abdominal, and inguinal hernia repair procedures. Meshes can be knitted or woven of absorbable or nonabsorbable suture materials. Some examples of the variety of meshes available for surgical use include absorbable woven or knitted Vicryl flat mesh *(Ethicon)* and knitted Dexon flat mesh *(Davis & Geck);* nonabsorbable knitted polypropylene flat mesh (Prolene, and Prolene Soft Mesh, lighter-weight and more flexible, *Ethicon;* Marlex, *Bard;* Trelex, *Meadox;* Surgipro, *US Surgical;* Artrium, *Artrium*), nonabsorbable PTFE mesh manufactured by *Gore* (Mycromesh, Dual Mesh, Soft Tissue Patch), and nonabsorbable knitted polyester mesh (Mersilene, *Ethicon)*. Many of these mesh products are available in preshaped forms designed for ease of use for the specific surgical repair procedure (Prolene Hernia System, and Prolene 3D Patch, *Ethicon;* Prefix Plug, *Bard*). Other mesh devices are composites of absorbable and non-absorbable components that have the advantage of good intra-operative handling with a light-weight and flexible substrate that provides permanent wound support (Vypro I and Vypro II, *Ethicon*).

Surgical Needles

Suture materials may be threaded on eyed needles for suturing. While formerly only eyed needles were available, there is an overwhelming trend to the use of eyeless needles, one or two being attached to each individual strand. One such needle is manufactured with an open channel into which the suture can be placed, and the channel is then swaged around the strand. Another type, known as *seamless,* has a very delicate hole drilled in the shank. To prevent pullout, the shank is pressed firmly about the suture. These sutures offer great advantage in minimizing trauma. With an eyed needle an opening in tissue must be made large enough to accommodate the needle and two thicknesses of suture, but with the eyeless needle, the opening need only accommodate the needle, slightly larger than the single suture that follows. This is greatly esteemed in fine surgery such as plastic and ophthalmic work. A wide variety of eyeless needles on different sutures are now available to meet most of the demands of the surgeon. By a recent innovation, it has been possible to control the release of a suture from an eyeless needle by a gentle tug so that the surgeon need not take the time to cut the needle from the suture when it is no longer required.

VITALLIUM—This metal, which is an alloy of cobalt, chromium, and molybdenum, has been applied to many surgical problems in various forms since 1937, although not in the form of sutures or ligatures. The alloy has shown some variability in strength and stiffness and is incapable of much modification at the time of operation, but generally shows negligible tissue reactions. In addition to some use for dentures, surgical forms of vitallium include fracture plates, screws, bolts, nails and appliances, orbital implants, nasal skeletal supports, tendon rods, tubes for blood vessel anastomosis or bile duct repair, and skull plates.

Other Suturing Techniques

Although sutures and ligatures have remained the most effective and popular devices for closing wounds and hemostasis, other techniques are being used with increasing frequency. Surgical stapling devices are available that automatically approximate tissue with rows of steel staples. Such devices exist for closing skin and anastomosing blood vessels as well as for reconstructing other organs such as stomach and intestines. Some surgical staplers are designed to cut tissue before or after the staples are applied.

During the last several years, V-shaped steel, tantalum, or titanium clips have been used to clamp small blood vessels, and this alternative to ligation is becoming increasingly popular as the application instruments become more convenient and easier to use. Stainless-steel clips or staples have been used frequently to coapt skin incisions. More recently, strips of fabric or plastic material coated with a suitable adhesive have been used for the same application.

New approaches to ligating clips are represented by absorbable materials, polydioxanone and lactomer. Ligating clips made from these substances absorb after their function is completed and do not remain in the patient permanently as do metallic clips. Thus, interference with diagnostic imaging techniques such as X-ray and CAT scans is avoided.

With the advent of minimally invasive surgical procedures, the industry faces significant challenges. Several new needles and other devices have been introduced to the market, facilitating the ease with which the surgeon can approximate and suture tissue through a trocar port.

SUTURE MONOGRAPH

ABSORBABLE SURGICAL SUTURE

Surgical Catgut; Catgut Suture; Surgical Gut; Sterilized Surgical Catgut BP; Sterilized Surgical Ligature

A sterile strand prepared from collagen derived from healthy mammals or from a synthetic polymer. Its length is not less than 95.0% of that stated on the label. Its diameter and tensile strength correspond to the size designation indicated on the label, within the limits prescribed herein. It is capable of being absorbed by living mammalian tissue but may be treated to modify its resistance to absorption. It may be modified with respect to body or texture. It may be impregnated or coated with a suitable antimicrobial agent. It may be colored by a color additive approved by the FDA.

Description—Flexible strand varying in treatment, color, size, packaging, and resistance to absorption, according to the intended purpose. The collagen suture is either *Type A* Suture or *Type C* Suture. Both types consist of processed strands of collagen, but *Type C* Suture is processed by physical or chemical means to provide greater resistance to absorption in living mammalian tissue.

NONABSORBABLE SURGICAL SUTURE

Surgical Sutures; Surgical Silk; Sterile Surgical Silk

A strand of material that is suitably resistant to the action of living mammalian tissue. Its length is not less than 95.0% of that stated on the label. Its diameter and tensile strength correspond to the size designation indicated on the label, within the limits prescribed herein. It may be nonsterile or sterile. It may be impregnated or coated with a suitable antimicrobial agent.

It may be modified with respect to body or texture, or to reduce capillarity, and may be suitably bleached. It may be colored by a color additive approved by the FDA.

Description—Flexible, monofilament or multifilament, continuous strand, placed in an envelope, tube, or other suitable container or wound on a reel or spool. If it is a multifilament strand, the individual filaments may be combined by spinning, twisting, braiding, or any combination thereof. Nonabsorbable Surgical Suture is classed and typed as follows: *Class I* Suture is composed of silk or synthetic fibers of monofilament, twisted or braided construction. *Class II* Suture is composed of cotton or linen fibers or coated natural or synthetic fibers in which the coating forms a casing of significant thickness but does not contribute appreciably to strength. *Class III* Suture is composed of monofilament or multifilament metal wire.

CHAPTER 110

Health Accessories

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For too long, many pharmacists treated Home Medical Equipment (HME) as merely a convenience for their prescription patients. Physicians and other health professionals may have been convinced that the pharmacist had neither the necessary expertise nor equipment and sent their patients elsewhere for such services. In recent years, however, few aspects of professional practice have changed as much or grown as rapidly as the pharmacy's HME departments. The specially trained pharmacist is becoming recognized more widely as an expert in this area by other health professionals and can provide a professional and profitable adjunct to the pharmacy's other services.

A comprehensive HME department may include a wide variety of surgical dressings and supplies; and convalescent aids including wheelchairs, walkers, hospital beds, hydraulic patient lifters, urology and incontinence supplies, ostomy appliances, elastic supports, mastectomy breast forms, and orthopedic braces. In addition, many pharmacies specialize in home health-care equipment such as traction devices, blood-glucose monitors, blood-pressure-monitoring devices, suction machines, oxygen and respiratory-therapy equipment, nerve and muscle stimulators, phototherapy lights, apnea monitors, and rehabilitation equipment. Some pharmacies may even specialize in providing intravenous medications and supplies for enteral or parenteral nutrition.

Even more important than merely providing large varieties of health accessories is the pharmacist's growing involvement in selecting and fitting them and in instructing the patient in their proper use and maintenance. It is essential that pharmacists are not only knowledgeable and skilled, but recognize their own limitations. Professionals must prepare themselves for services that are not usually subsumed under the "practice pharmacy" definitions. HME products and services, in many cases, require specialized training if the patient is to be properly served. It is not a weakness to admit to patients, physician or others of one's need to refer to a more qualified source.

To provide these services the pharmacist must acquire new skills and expertise that can be obtained through a large variety of sources, such as special courses given by health-accessory distributors and manufacturers, professional associations, and some college or university-based programs.

The initial step in selecting the appropriate health product is a thorough evaluation of the patient's needs and then matching these needs to the available options. Note that the option may very well be referral to another source for care.

Age	Disability-related factors
Life-style	Patient and equipment measurements
Diagnosis	Patient ability for self-care
Prognosis	Reimbursement sources

Each of these factors should be considered when selecting the most appropriate health accessory for the patient. It is often necessary to verify insurance coverage, including whether particular equipment is mandated by an HMO and which equipment will be considered for reimbursement by Medicare, Medicaid, or insurance companies. Although a standard "prescription" may not be required, most third parties will expect some indication that the product/service is a medical necessity to be reimbursed.

Other steps may include consulting with the patient, physician, and family; selecting the accessory from stock or ordering it from the manufacturer or distributor; and checking the accessory to ensure that it meets the appropriate specifications. Usually, follow-up adjustments or modifications are necessary.

Useful forms (eg, certificates of medical necessity CMN), disability analysis, measurement, prescription and ordering forms—are usually available from health-accessory manufacturers, insurance companies, and government agencies. In fact, some insurance companies and government agencies may mandate the use of their special forms. Documentation of patient analysis, measurements, and what was sold/dispensed is an essential part of record keeping, especially in this litigious society.

WHEELCHAIRS

Wheelchairs range from the most simple self-propelled devices used to provide independence of movement for a person temporarily inhibited in walking,to specially built models. The battery-powered "scooter" has become quite popular, especially because the development of longer lasting battery chargers. There are literally hundreds of different wheelchairs to serve the patient's different needs. Figure 110-1 shows one example. The importance of an individualized prescription cannot be overemphasized. A carefully prescribed chair has a prolonged and useful life and promotes the patient's maximal physical independence.

The general loss of body functions in aged or infirmed patients serves as a guide to providing the best chair for their needs. They may have less strength and endurance than a younger or healthier person and, therefore, may require safety and convenience features. This point reemphasizes the general rule when fitting any wheelchair: the primary considerations in fitting are the user's physical limitations and lifestyle.

MEASUREMENTS—Following the disability analysis, the measurements of the patient and the chair should be considered when preparing a prescription for the proper chair.

The Patient—Ideally, the patient should be sitting when measured, preferably in a chair that allows good body alignment.

Side-to-Side (widest area of hips while sitting)—It is important to determine the chair seat width. To avoid pressure on the hips or thighs, yet help maintain good seating posture and stability, the chair-seat width should be 2 inches more than the width straight across the hips.

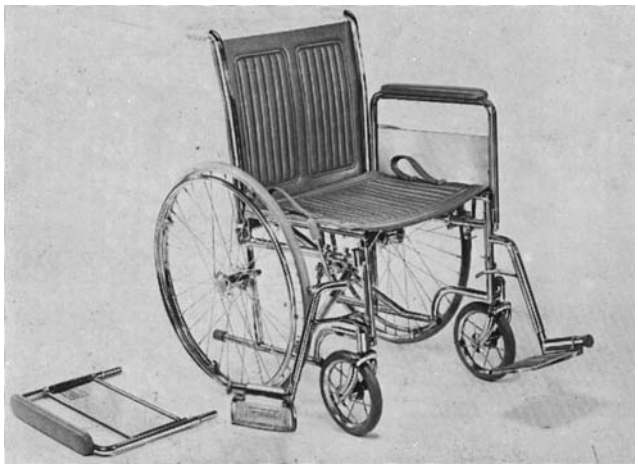

Figure 110-1. Adult wheelchair with full-length, removable arms and swing-away, detachable footrests (courtesy, Everest & Jennings).

Knee-to-Hip—This measurement is critical to determine the actual chair-seat depth. Normally, the seat depth will be approximately 2 to 3 inches less than this measurement to provide adequate support, yet avoid pressure behind the knee. If a back panel or back cushion is to be inserted, its thickness must be considered.

Seat-to-Elbow—This measurement serves as an indicator for armrest height. Depending on seating posture, armrest height should provide proper body support. (*Danger signals:* drooping or hunched up shoulders when the patient's elbows are resting on the armrests.) It should be noted that an armrest height 1 inch more than the patient's seat-to-elbow measurement will force the patient's elbows slightly forward, providing a natural brace against forward body slumping, especially when descending ramps.

Floor-to-Knee—This measurement is used to determine footrest adjustments from seat level and/or special seat height. The minimum footrest adjustment should be at least 2 inches less than this measurement to avoid pressure against the underside of the legs. A good visual guide for proper footrest adjustment (especially when using a standard chair) is to make sure that the tops of the patient's thighs are horizontal and parallel to the floor. To obtain greater-than-standard maximum footrest adjustment, a special seat height must be considered. Sometimes the use of a solid insert seat and/or seat cushion will solve this problem, although it should be remembered that optimum seat height allows patients to place their feet on the floor without excessive pressure behind the knees.

Seat-to-Armpit—Used to determine back-upholstery height on standard-back chairs. This is important because many patients must be able to put their arms over the back upholstery and hook their elbows under the push handles to achieve leverage when reaching for things.

Other Measurements—May be required for more-involved or custom wheelchairs. Consult manufacturer product literature.

The Chair—Certain wheelchair dimensions (Fig 110-2) are important in preparing an individualized prescription. The following are some of the components and measurements that should be considered.

Arms—Full-length, nondetachable arms are available. Desk- or full-length detachable styles are needed if the user must do a lateral transfer. Because detachable arms are offset from the main frame of the wheelchair, they also provide 1 1/2 to 2 inches of additional seat width. Thus, a wheelchair with 18 inches of upholstery and detachable arms actually yields 19 1/2 to 20 inches of seat width. Just as this feature widens the seat, it also widens the overall width of the wheelchair. If this additional overall width results in an architectural restriction, *wraparound* or *space-saver* arm styles must be considered. They are mounted behind the back uprights instead of between the uprights and the rear wheel. This design allows the additional seat width and removable convenience but keeps the overall width to that of a standard-frame wheelchair.

Another consideration of the arm is its height in relation to the seat. Standard arm height is approximately 10 inches. The arm can be manufactured to any specified height; however, a more convenient option is the adjustable-height arm, which is available in the detachable styles.

Seat and Back Width—A determination of seat and back width is the most important and fundamental part in selecting the proper wheelchair. A standard adult wheelchair has an 18-inch seat and back upholstery. Wheelchairs are typically available in 2-inch increments from 12 to 24 inches. When considering seat width, remember the effect of detachable arms. A wheelchair that is too wide will promote leaning to one side or limit the ability of the user to propel the chair. Too narrow a wheelchair can result in pressure sores.

Foot Supports—There are two basic types of foot supports: the footrest and the elevating legrest. Both are adjustable in length. To determine which type would be more beneficial to the user, consider the condition of the legs. If there is swelling or infirmity involving the leg or reduced flexion in the knee, elevating legrests might be indicated. A new concept, the articulating elevating leg rest, extends automatically as the leg rest is raised, to fit the outstretched leg correctly (Fig 110-3). In most other cases the simple footrest will suffice. At this point, also consider options such as removable versus fixed assemblies, quad-release levers, heel-and-toe loops, and oversized or nonskid footplates.

Seat Height—The standard seat height is approximately 19 to 20 inches from the floor. Hemi- or low-seat wheelchairs run about 2 inches lower. Seat height is important to those users who propel the wheelchair with one or both feet. A higher seat may be required for users with long legs so the footrest-to-ground clearance will not be less than 1 1/2 to 2 inches.

Seat Depth—The standard seat depth is 16 inches. The seat should be deep enough to support the thighs properly without putting pressure on the back of the calf.

Back Height—The standard back height is 16.5 inches. A higher back height provides more support for a weak upper body. A lower back height provides less support but allows greater freedom of movement. To determine which is best, consider overall physical strength and lifestyle. Try to keep the height of the back to a minimum, i.e., high enough to provide adequate support, yet still allow upper-body mobility.

Wheels—Standard wheelchairs use a 24-inch rear wheel with an 8-inch front caster. Hemi wheelchairs have a 22-inch rear wheel. The rear wheel generally is aligned with the back upright. In the case of a reclining or amputee chair the wheels are set back to provide a larger base of support, which is needed to prevent tipping backward.

Note: Additional Precautions during measurement

1. When taking measurements and adjusting the wheelchair always consider the effects of cushions and body positioners if they are to be used.

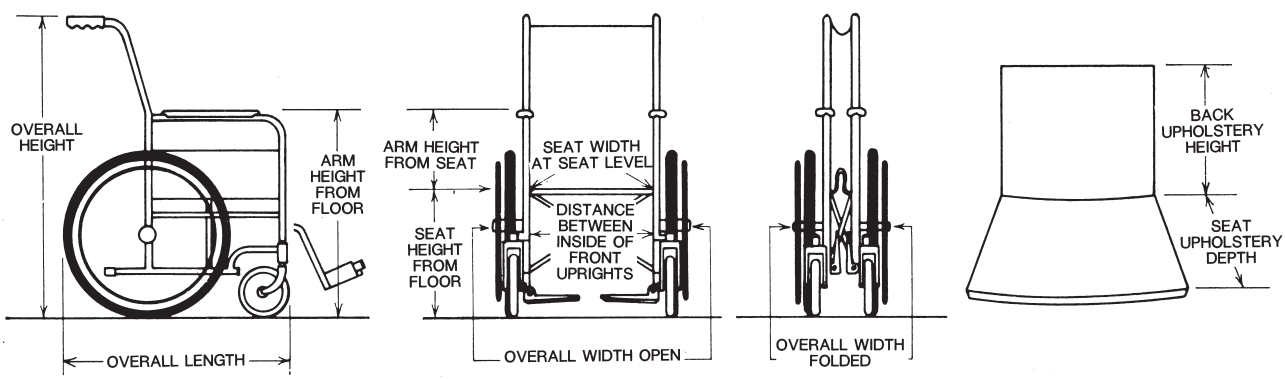

Figure 110-2. Key to wheelchair dimensions (courtesy, Everest & Jennings).

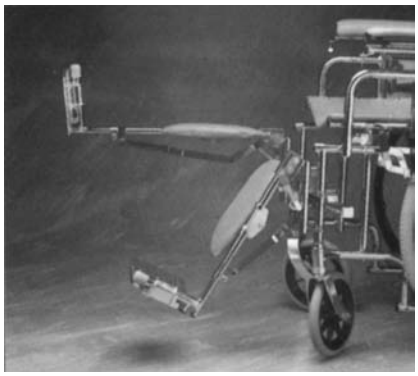

Figure 110-3. Articulating, elevating leg rest (courtesy, Invacare).

Figure 110-4. Action Jarsys weight-shifting tilt system moves the seat to optimize the client's center of gravity during the tilt cycle (courtesy, Invacare).

2. Always fit the wheelchair for the user's present condition. Make some allowances for progressive diseases but never overfit a wheelchair. Extra, added features add weight and can make the wheelchair cumbersome to its user.

When the pharmacist has completed the measurements and evaluations and actually has the patient sitting in the chair, there are three quick *hand checks* the pharmacist can make.

1. An extended hand should fit between the hip and the skirt guard of the chair.
2. Three or four fingers should fit between the seat upholstery and the back of the calf.
3. Three or four fingers should fit between the top of the back upholstery and the underarm.

This kind of a quick double-check is the type of professional activity that will differentiate a pharmacist as an authority on health accessories.

While most patients will be able to use the manually operated wheelchairs described previously, a growing number will need a battery- powered wheelchair. This will include some quadriplegics and any patients who lack the ability to propel a chair manually. In some cases when the patient has no hand or arm movement a chair can be operated by chin control or a sip-and-puff control, in which the controls may be operated by the patient inhaling or exhaling into a straw-like device. Recently, even dental controls have become available, and wheelchairs controlled by vocal commands are under development and may soon be on the market. For wheelchair-bound patients who do not have the ability to reposition themselves in the chair, tilt-in-space wheelchairs (Fig 110-4) are available. Shifting the weight-bearing areas of the body can provide relief from or prevent formation of decubitus ulcers.

Because patients using an electric wheelchair usually spend the major part of their waking hours in their chair, it is especially important that the chair and its accessories be fitted properly to them. Manufacturers can provide specialized measuring and fitting guides for power wheelchairs.

One other health-accessory product that may be included in the wheelchair category is the three- or four-wheeled, battery-operated scooter. These are often useful for people with limited mobility. Persons who can walk a short distance in the home environment may be unable to spend several hours on their feet in a shopping center or on a trip to a museum or zoo. A battery-operated scooter may be the perfect answer to such a situation, and many health-accessory dealers include three- or four-wheeled scooters in their product mix (Fig 110-5).

CUSHIONS AND SUPPLIES FOR PRESSURE SORES

Many types of cushions are available for a variety of purposes. Some are used to simulate a hospital bed's gatch spring. These enable the patient to eat and work in bed in relative comfort, while others are used to bolster the patient's legs to achieve flexion of the lumbar spine during traction. The most important use is to protect the patient from bruises and prevent the occurrence of pressure sores (ie, decubitus ulcers, bed sores).

Pressure sores result from pressure at the thinly covered bony prominences of the body such as the sacrum, tuberosities of the ischium (below the buttocks), heels, elbows, shoulder blades, and ears and back of the head in children. When pressure interferes with the normal circulation of capillary blood in the tissues, it can cause localized ulceration and gangrene.

A pressure sore begins as a reddened area that, if left untreated, will develop into an open sore; if not corrected early, surgery may be the only feasible remedy. The best cure is prevention. According to Richard M Meer, Founder and Executive Director of the Center for Tissue Trauma Research and Education (Jensen Beach, FL), "all pressure sores are preventable," a notion that unfortunately still is denied by some health professionals in institutions where pressure sores continue to occur. As health-care consultants to their customers, community pharmacists are in a unique position to facilitate an understanding of pressure sore–prevention techniques that can be used in the home-care environment.

Pressure sores most commonly occur after long-term confinement in either a bed or a wheelchair. In institutions where nursing services are provided or at home where family members are available, the following measures will prevent their occurrence:

1. Keep the bed dry and clean.
2. Thoroughly pat the skin dry.
3. To increase circulation, regularly and gently massage the skin.
4. Change the position of the patient in bed as frequently as possible, at least a minimum of every 2 hours.
5. Relieve pressure as soon as the first signs of redness appear.

Figure 110-5. Three- and four-wheeled scooters (courtesy Pride Health Care).

6. Expose the reddened area to the air and reduce pressure by using commercially available items (ie, cushions) to increase circulation.
7. Maintain proper nutrition.

It has been said that any type of treatment will be of some benefit, because it takes the patient off the sore.

Wheelchairs should never be used over an extended period of time without some kind of seat cushion. The most frequent occurrence of pressure sores in wheelchair users is at the ischial tuberosities. Pressure sores also result from a chair that is too wide or too small or whose footrests are adjusted improperly. Footrests that are too low cause the patient's legs to hang off the front edge of the seat upholstery, thus interrupting circulation to the lower legs, and also cause some patients' knees to come together, increasing the possibility of pressure sores between the knees. Footrests that are too high force the patient's knees up in the air and take body weight off the back of the thighs, resulting in all of the patient's body weight being focused directly on the ischial tuberosities.

There are literally scores of wheelchair cushions on the market, ranging in price from under $20 to over $1000 for custom, adaptive-seating arrangements. The most commonly used types include:

Sheepskin Cushion (or Pad)—A standard cushion used in hospitals for decades, in wheelchairs and in hospital beds, is the natural sheepskin cushion. Its fluffy, thick hair provides good relief from pressure. While it still is used in bed, it is inadequate for the wheelchair by itself. A drawback for the use of natural sheepskin is that it is more difficult to clean and keep odor free.

Today, there are several manufacturers of synthetic sheepskins that are superior to natural sheepskin because their polyester fibers will not support bacterial growth and their porous back permits adequate drainage and airflow. The synthetic sheepskin is helpful to the wheelchair user if placed on top of another cushion and works best when in direct contact with the skin.

The usual solution for pressure sores occurring on the elbows and heels is either a large synthetic sheepskin or individual heel-and-elbow protectors. These incorporate the sheepskin into a plastic holder that straps to the foot or elbow.

Foam Cushion—The most common wheelchair cushions are made of different densities of foam.

Convoluted Foam Cushion—The top surface of this foam cushion consists of rows of cones, giving it an egg-crate appearance. It remains popular in retail stores and many nursing homes but has yet to be used extensively in the rehabilitation setting.

Coccyx Cushion—This is an effective modification of the foam cushion, with a cut-out in one side. It usually comes with a board insert that provides stability in an inherently unstable cushion. This cushion is ideal when pressure sores exist or are anticipated at the base of the patient's spine and also is used postsurgically for hemorrhoidectomies and patients who have suffered a fracture of the coccyx.

Inflatable Ring Cushion—The wheelchair-size inflatable ring cushion also may be effective providing it is neither underinflated (permitting the patient to bottom out) nor overinflated (making it hard and nonresilient). For most adults a 16-inch cushion with a 4.5-inch interior diameter (ID) is usually preferred.

Silicone Gel Cushion—The purpose of a silicone gel cushion is to simulate adipose tissue (body fat) and so perfectly distribute body weight that decubitus ulcers will be nearly impossible. While it is an excellent cushion for many patients, it has a drawback in that the loose gel permits some roll and creates a shearing effect which is injurious to some patients with tendencies toward the development of pressure sores. Less-expensive gel-type cushions are now on the market.

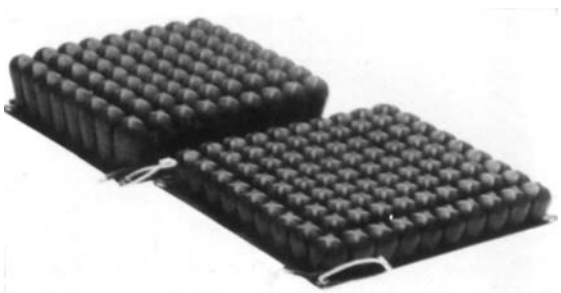

Figure 110-6. Balloon cushion (courtesy, Roho).

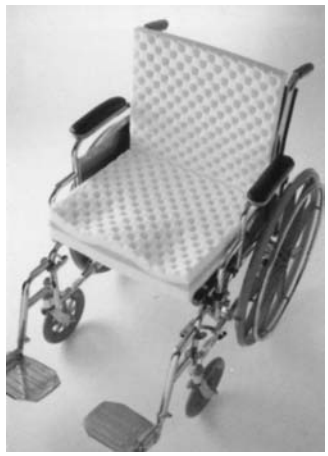

Figure 110-7. Iris wedge cushion (courtesy, ER Carpenter).

Roho Balloon Cushion—Rows of inflatable balloons make up the surface of this cushion. A pressure gauge is used to adjust the pressure of the balloons (Fig 110-6).

Newer cushions on the market include cushions that combine decubitus care and body positioning.

A new look at advanced flotation therapy to prevent and manage skin breakdown can be found in the Iris product line by E R Carpenter. This new technology uses an outer surface produced from Omalux, a densified, high-resiliency foam which has a dimpled, flat surface for improved flotation. The high-performance foam in the inner core provides optimal support, while the Omalux layers mold to body contours. Together these work to reduce pressure. A tough but supple nylon-taffeta fabric is available to envelop this system, which is highly resistant to moisture and microbial contamination. This system is available as a mattress overlay and as a wheelchair cushion (Fig 110-7).

CANES AND CRUTCHES

Canes

Although walking canes are very simple devices, they are misused and misfitted frequently. The problem stems from a lack of basic knowledge as to what a walking cane is supposed to do and how it should be used properly.

A walking cane serves two important functions:

Weight Transfer—It provides a means to transfer weight off the weak limb. To accomplish this, weight must be put on the cane. A patient who carries the cane on the side of the weak limb and puts 50 lb of weight on it transfers 50 lb off the weak limb. The same is true if the cane is carried on the strong side. While the choice of carrying hand has nothing to do with weight transfer, it is crucial for proper balance.

Balance—Good balance in walking is no more than keeping one's center of gravity over the supporting limbs. If one suddenly lifts his/her feet off the floor, one reduces his/her base of support to one foot, one's center of gravity is outside the base of one's support, and the person falls. People who walk with legs apart tend to waddle, as they must move their centers of gravity from one foot to the other to avoid falling. Fashion models avoid waddling by learning to place one foot directly in front of the other so their centers of gravity move forward rather than side to side.

If a patient carries the cane on the same side as the weak limb, the base of support will be narrow (ie, the distance between the cane tip and the weak limb is small), and the patient will have to transfer his or her weight from side to side, increasing the possibility of falling. A narrow base of support makes it difficult for a patient to keep the center of gravity over that base. A patient who is instructed to carry the walking cane on the side opposite the weak limb will have a wide base of support and the center of gravity can move primarily forward rather than side to side. The patient uses the cane together with the weak limb, alternately swinging the strong limb through for the next step.

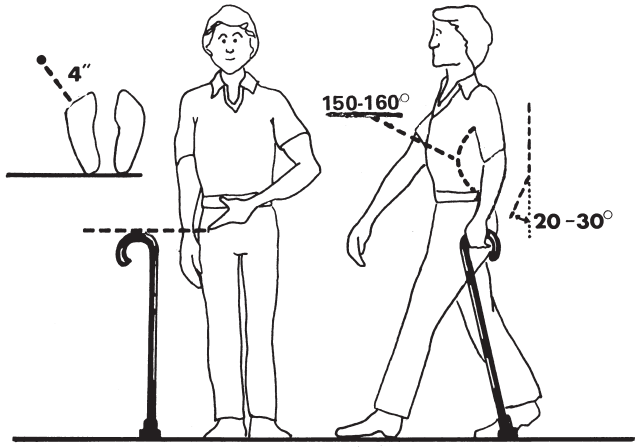

Figure 110-8. Proper fitting for canes, walkers, and crutches.

Again, this kind of instruction in *simple* aids is the type of professional activity that will differentiate a pharmacist as an authority on health accessories.

Unless specifically instructed by a patient's physician or physical therapist to the contrary, *always instruct patients to carry the walking cane on their strong side.*

Fitting—A cane should be neither too long nor too short. Each one must be adjusted or cut to fit the patient. Fitting a cane is quite simple. Most schools of physical therapy recommend that a walking cane should fit so that the patient's arm makes a 150° to 160° (from vertical) bend at the elbow; this places the muscle groups in the arm in the best position for firm support. The cane tip should be placed 4 inches in front of the toe at about a 45° angle; angle the cane back to the hanging arm, and the handle of the cane should be at the crease in the wrist. Then, when the patient lifts his or her hand up to the cane handle, the elbow will form the desired 20° to 30° bend automatically (Fig 110-8).

If a patient normally has one shoulder higher than the other, such as when the patient has scoliosis (an S-shaped curvature of the spine), no effort should be made to straighten the patient for the fitting. One cannot measure one side of the patient and then use that measurement for the other side. Each side must be measured separately. The arms should be made to hang normally. A patient who has trouble standing without support should be backed up against a wall during the fitting. The back of a chair can be used effectively for support. Rather than measuring at the top of the cane for an indication of where to cut it, turn the cane upside down for the fitting.

These rules apply in the fitting and use of all ambulatory aids including quad canes, forearm crutches, axillary crutches, and walkers.

Walkers

The most common walker in terms of sales and rentals continues to be the adult, folding, adjustable walker. A basic inventory of walkers in any pharmacy should include

1. Child adjustable walker.
2. Youth adjustable walker.
3. Adult adjustable walker.
4. Hemiplegic walker.

Proper use is the same for all nonwheeled walkers. Patients are instructed to lift the walker, place it in front of them, and walk to it. With this method, the walker is firmly on the floor when the patient is moving. A walker should never be carried by a walking patient; if a patient is able to do this with relative ease and security, a cane probably would suffice.

A frequent problem is that patients tend to lean into the walker while walking up to it. The danger is that they may lose their balance and push the walker over, as it is relatively light. This tendency can be overcome by lengthening the front two legs of the walker by one adjustment, making the walker tilt back. This should not be a routine adjustment for all walkers, however; instead, it should be a response to a specific tendency of a patient to lean into the walker.

The safest wheeled walker is one with a braking mechanism that will stop it if the patient trips or loses his balance. The braking mechanism should work when the patient's weight is increased on the normal hand holds.

There are a variety of wheel options available for walkers, including 3- or 5-inch fixed wheels, as well as 3- or 5-inch swivel wheels. It is recommended that all of these wheel options be used in conjunction with glide-brake attachments. Proper application of wheel options should be evaluated by a durable medical equipment technician or physical therapist depending upon the individual client's disability and environment for best results.

Yet another ambulatory device being widely prescribed is a rollator walker, technically referred to as a heavy-duty, multibraking system, variable wheel–resistant walker. This item is generally equipped with 7.5- to 8-inch wheels. A hand-brake system is incorporated into this structure, with adjustability to control the ambulatory gait of the user. Some units are available with seats for intermittent resting and basket or tray accessories to carry items for daily living needs. Generally, Rollator walkers are recommended for, but are not limited to, an individual's need for mobility outside the home environment, where a variety of surfaces require greater versatility (Fig 110-9).

As in the case of walking canes, each walker should be adjusted for its user.

To fit a walker properly the patient should stand normally against a wall, if necessary. The legs of the walker are adjusted so that the top of the handgrips come to the patient's wrist. On raising his or her hands to the walker handgrips, the patient's elbows will form the proper bend. When it is also necessary to lengthen the front legs of a nonwheeled walker, the wrist-crease length should be accurate for the walker's rear legs. The front legs of the walker then will be 1 to 2 inches longer, depending on the extent to which the patient leans into the walker.

In terms of support, a walker can best be compared with the simple cane. While a walker does provide a steadier support for the patient, like the cane, it requires reasonably good arms, wrists, and hands.

A patient with a disability or injury involving the hand or wrist making it non-weight-bearing may need a platform at-

Figure 110-9. Folding wheeled walker (courtesy, Etac).

Figure 110-10. Walker with platform attachment (courtesy, Invacare).

tachment that allows the forearm to bear the weight instead of the hand or wrist (Fig 110-10).

Crutches

FOREARM CRUTCHES—Neither walking canes nor walkers provide support to the patient's wrists and elbows. The forearm crutch, however, is designed specifically to provide such support in that it has a vertical member that extends above the wrist and is secured reasonably well to the fleshy part of the forearm by a collar or cuff.

The term forearm crutch is generic. They commonly are referred to as Canadian crutches or Lofstrand crutches. All can be recognized by the collar or cuff that encircles the patient's forearm. The cuff usually is open, and the opening may face either the side or front. It is important that the cuff be open so the crutches may be thrown out of the way if the patient falls. The handgrip projects from the main shaft, and unless specifically instructed by the physician or physical therapist to the contrary, the patient should be instructed to hold the handgrip so that it points forward.

If only one crutch is used, it should be used on the side opposite the weak leg. When two crutches are used, the patient should be instructed to step forward with the right leg and the left crutch, followed by the left leg and right crutch, and so on. Commonly known as the two-point gait, it is recommended for persons using forearm crutches unless, of course, the physician or physical therapist suggests a different gait.

In fitting the forearm crutch, the patient should stand normally erect, with arms at the sides. The forearm cuff is flipped back out of the way, and the handgrip is brought to the crease in the wrists by adjusting or cutting the main shaft. The length of the vertical member between the handgrip and the forearm cuff also should be adjusted so that the cuff comes to the middle of the patient's forearm, usually over the fleshiest part. Care should be taken to make sure that the cuff does not interfere with the elbow when it is fully bent. The cuff can be opened or closed by bending and shaping by hand, with very little effort. Patients should be shown how to do this as they may want the cuff larger or tighter, depending on their clothing.

AXILLARY CRUTCHES—More common than the forearm crutch is the ordinary wooden or aluminum underarm crutch—the axillary crutch. It provides more support than the forearm crutch because it braces both wrist and elbow.

Adjustable crutches are preferred, as they offer better and easier fitting. First, the patient should stand normally erect with arms at the sides. The crutch is placed under the arms, with the crutch tip on the floor at a point approximately 6 to 8 inches ahead of the patient's toes and 6 to 8 inches to the side. The main shaft is lengthened or shortened so that the top of the crutch is about 1.5 inch (two finger-widths) from the armpit. This fitting should be done with crutch tips and axillary cushions in place on the crutch.

The second step is to adjust the position of the handgrip on the crutch so that it comes to the crease in the wrist. The crutch should be in the same position for this handgrip adjustment as it was during the fitting of its entire length. The arm then is brought out alongside the crutch for the handgrip adjustment.

A flexed elbow is important when using an axillary crutch. If the handgrip is not positioned at the wrist so that the elbow bends when the patient takes hold of the handgrip, the tops of the crutches would push up into the armpits with each swing. But with the elbows bent initially, the crutch tops are safely below the armpits, since the patient must straighten his or her arms on the swing through. When underarm crutches are fitted properly, there is little or no danger of injury to the lymph glands, blood vessels, or radial nerves in the armpits, which can lead to *crutch paralysis.* The primary danger signal is an elevation in the patient's shoulders with each swing through the crutches. When that happens, it is clear that the patient's weight is bearing on the crutch tops and not on the handgrips as it should be.

There are several axillary crutch gaits. The safest, most stable, and most common is the four-point gait. The patient begins by moving the left crutch forward. Next, the patient moves the right leg forward. The right crutch then is brought up to the right foot, and finally, the left leg is brought up to the left crutch.

The two-point gait, the principal gait used when two canes are employed, is also used commonly with forearm and axillary crutches. Simply, both the left crutch and right leg are brought forward; then the right crutch and left leg are brought forward.

The three-point gait has two variations: the swing-to gait and the swing-through gait. In either form, the patient begins by moving both crutches forward simultaneously. In the swing-to gait, both feet (or one foot for an amputee or when one leg is in a non-weight-bearing cast) are swung to a point between the two crutches. In the swing-through gait, the feet (or foot) are swung through the crutches to a point ahead of the two crutches—it helps to visualize a triangle made by the two crutchtips and foot, and flipping that triangle end-over-end.

Another common crutch gait is the hemiplegic gait. It is nothing more than the use of a single axillary crutch in exactly the same manner as one would use a single cane. The crutch is carried on the strong side and is moved forward together with the weak limb, alternating with the good leg.

Accessories

TIPS—The most important accessory is the tip, which makes contact with the floor. No cane or crutch should ever be sold or rented without a good tip. Safety requires that cane and crutch tips have the following minimum characteristics: they must fit the cane or crutch shaft snugly, have a suction-grip bottom, and have a flexible neck so the bottom of the tip will stay in complete contact with the floor when the cane or crutch

rocks through a gait. The suction-grip bottom of a crutch or cane tip should be as large as possible—the more rubber in contact with the floor, the less chance of slippage.

AXILLARY CUSHIONS—These are designed to protect the underarm from bruises and inhibit slippage of the crutch top from under the arm. They should not be weight-bearing, as the top of the crutch should be fitted to be 1 1/2 inches from the armpit.

HANDGRIPS—These are more varied in type and style because they are designed for various purposes. The most common kinds of handgrips are dense foam-rubber sleeves that fit over the standard crutch grip. The split handgrips should be used for nonadjustable crutches only, as they tend to slip around the handgrip. Taping them tightly will secure them somewhat. The nonsplit, often called closed, handgrip is better for the patient, but it requires removal of the crutch's handgrip to put it on.

Other contoured handgrips and *palmgrips* are available. Because the natural palm line is not horizontal, they are designed to alleviate problems such as hand discomfort and wrist soreness associated with the traditional horizontal crutch handgrip.

SEAT-LIFT CHAIRS—Another aid to mobility being used in homes today is chairs with electrically powered seat-lift mechanisms. Designed for the patient who can ambulate (often only with the assistance of a cane or walker) but is unable to get out of a chair unassisted, the seat-lift chair can add greatly to the independence and mobility of a patient at home. This may simplify the job of a primary caregiver, who may be a frail spouse who has great difficulty assisting the patient out of a chair (Fig 110-11).

STAIRWAY SYSTEMS—A home stairway system can aid a patient living in a two-story home who has difficulty using the stairs. Models are available for straight, angled, or curved stairways. Some models, such as the Electra-Ride II (Fig 110-12) are battery-operated and will continue to work even during a power outage.

Figure 110-11. Seat-lift chair (courtesy, Pride Health Care).

Figure 110-12. Electra-Ride II stairlift (courtesy, Bruno Independent Living Aids).

COMMODES

A commode is little more than a portable toilet, and yet there are a variety of different types. More than a convenience, a commode can mean the difference between coming home or staying in the hospital. Whenever the patient is unable to ambulate from the bed to the bathroom or to be transported via wheelchair, there is a need for a commode.

Perhaps the most common type is the steel- or aluminum-frame commode with a toilet seat and cover plus a removable plastic pail and cover. Adjustable legs are desirable, since some patients need a rather tall one to aid them both in sitting and in getting up more easily. The *Drop-arm* commode enables easier lateral transfer to and from the commode seat. Some patients also find this innovation helpful when there is a need to insert suppositories. Depending upon the attitude of the patient and, more often, that of the family, an aluminum folding commode can be removed from view when it is not in use.

The common aluminum- or steel-frame commode uses its uplifted toilet seat cover as a backrest. Commodes are available with padded and nonpadded backs, an upholstered seat and armrests, and casters for moving about easily (Fig 110-13); others are made of wood and resemble furniture—eg, the disguised, Danish Modern commode. Some commodes are designed to be used both in the bedroom and in the bathroom. These are either backless or have a removable back, so as not to interfere with the toilet tank.

Although commodes may be rented in most states, it is unwise to reuse the commode pail; it should be sold to the customer during the first month's rental. It also is helpful to advise the patient's family that a pail filled to one-third with water

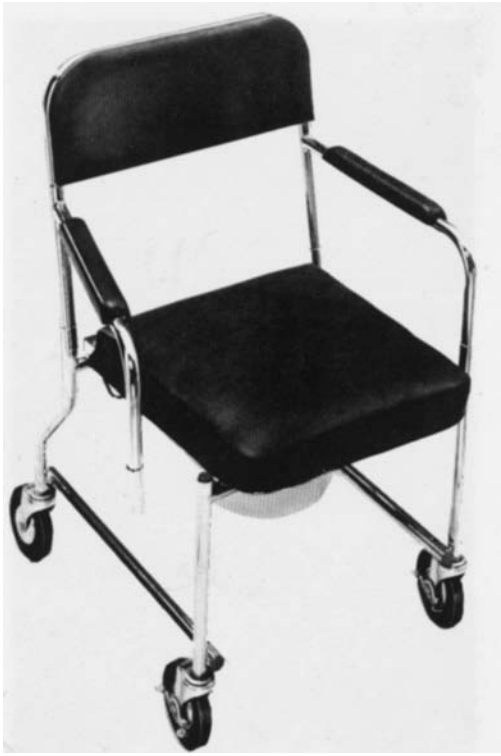

Figure 110-13. Padded commode on casters with pivot arms (courtesy, Lumex).

will be easier to keep clean. Deodorant tablets and drops are also appropriate as an accessory to any commode rental or sale.

A commode with wheels should be used with caution.

BATHROOM SAFETY AIDS

Before dispensing any bathroom safety aid that is weight-bearing (or for that matter, any medical equipment that is designed to support the partner's full weight), it is advisable to ask the patient's height and weight and document that information on the receipt, invoice, or intake sheet that is kept in the patient's file. Most bathroom safety aids list the weight capacity of that product on the package, on a tag, or in a catalog.

Safety in the bathroom primarily means safety in the tub or at the toilet. An elevated toilet seat makes it easier for patients to sit or stand and suggests the need for some kind of toilet guard rail. Attaching-type toilet rails can connect to the bowl with the regular toilet seat bolts. Some attaching types are designed with detachable sides, permitting the use of one side only, as well as easier cleaning of the rail in general.

Elevated toilet seats vary considerably with respect to the materials from which they are fabricated, whether or not they have full or partial splash guards, to what extent they are adjustable in height, and whether or not they are padded for softness or, like any normal toilet seat, quite hard. The full splash guard may be preferred by many people, but the pharmacist should keep in mind that persons without good legs and body control (paraplegics and quadriplegics, particularly) need the open sides that only the elevated toilet seat with the partial splash guard has, to administer to their personal cleanliness independently and to insert suppositories without assistance. The least expensive, and by far the most popular, elevated toilet seats are one-piece molded plastic. Combination elevated toilet seats with attached hand rails are available, but may *tip* if equal pressure is not applied to both sides when rising (Fig 110-14).

Figure 110-14. Elevated toilet seat with arm rails (courtesy, Invacare).

Safety aids for the bathtub include adhesive strips and spots for the tub bottom, mats for preventing slips, and a variety of tub seats and safety grab bars. Tub seats are either bench types with legs or seats that straddle the tub sides.

One type of bench has either fixed (standard)- or adjustable-height legs and is available with or without a back. A transfer bench (Fig 110-15) is used with two legs in the tub and two legs on the floor outside the tub. The patient can sit down on the portion of the seat that is outside the tub, swing his or her legs over the edge of the tub, and slide across the bench until the entire body is *inside* the tub. Transfer benches are available with solid seats or with a commode opening to facilitate perineal cleansing. Some models of transfer benches have suction-cup footpieces or clamp onto the side of the tube for security and stability and are available with a plastic or a padded seat for comfort and protection of skin integrity.

Another type of bath seat is powered by either water pressure or a hydraulic pump that actually raises or lowers the height of the seat from the height of the tub side to near the bottom. This seat also can be classified as a bath lift.

Bathtub grab bars range from those that attach to the side of the bathtub to wall-mounted grab bars. Perhaps the most frequently used type is one that extends high enough to give a

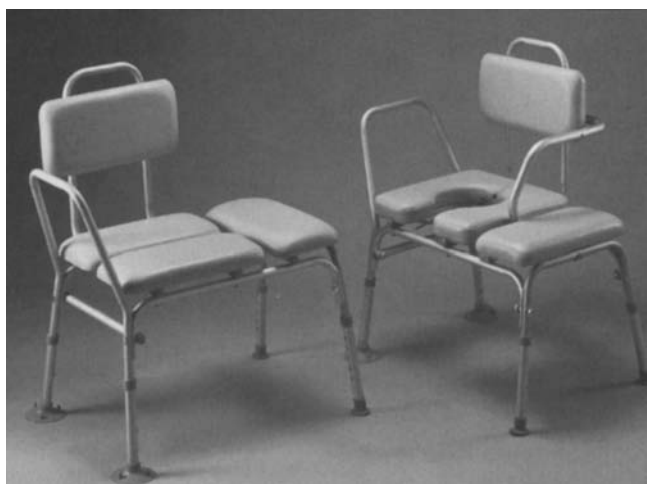

Figure 110-15. Transfer bath benches (courtesy, Lumex).

person standing outside the tub a firm support before stepping into the tub. Wall grab bars take a variety of shapes, angles, and lengths. Finishes of vinyl coating, smooth chrome, and a knurled texture for grip security are all available. True grab bars extend from the wall at least 4 to 5 inches, enabling a falling person to slip the forearm behind the bar and hook the elbow over it. Patient and/or family members should be cautioned to have the grab bars mounted to wood or metal studs within the walls. Using toggle bolts drilled in tile or plaster walls, but not securely anchored must be avoided at all costs!

Pharmacists should know how the bars they stock are mounted best for safety and either be able to instruct the customer in the mounting procedure, provide such service, or have someone who will provide installation services on call. Caution: be aware of liability when doing so.

HOSPITAL BEDS

The health-accessories department of a pharmacy also may have hospital beds for sale or rental, including manual or electrically operated beds. The bed can be either fixed or variable height, and its spring should have an adjustable head and foot section that raises the patient's knees as well as permits the feet to be elevated.

The electrically operated bed may be either the full-electric or semielectric type. The height of the full-electric bed is adjustable from the floor and permits positioning of both the head and foot sections. The semielectric bed may have a manual crank to adjust the height. Caution the patient or family member that electric hospital beds may not be reimbursable unless a clear indication of medical necessity can be determined.

MATTRESSES—Polyfoam mattresses with waterproof ticking are excellent for rental purposes, especially with split-spring hospital beds, as one person can handle them easily. An innerspring mattress should be used with an electrically operated bed or when the heavier mattress is preferred; however, not every innerspring mattress will work well on a hospital bed, since the springs must be hinged to have the mattress flex properly when the spring is adjusted. Sometimes the selection of the type of mattress is influenced by the diagnosis or the insurance coverage

Any mattress used for rental purposes should be constructed with a waterproof covering, and it is advised also to provide plastic mattress covers. The pharmacist should be aware of local or state regulations regarding the sanitizing of rental mattresses, as well as Occupational Safety and Health Administration (OSHA) regulations that might apply for infection control.

BEDSIDE SAFETY RAILS—It is recommended to stock three types of bedside safety rails, full-length and half-length rails for use on a hospital bed and the other for use on any kind of bed normally used in the home. Rails for use with a hospital bed have clamps that attach to the steel parts of the spring. Rails used on home-type beds are attached by connecting rods placed between the regular mattress and box spring. This *anybed* type of safety rail usually is made of aluminum, with crossmembers of steel. Hospital bed rails may be constructed of aluminum or steel. Bed rails used on home beds are to provide safety and should not be used as repositioning aids or transfer-assist devices.

BED HANDLES—A newer product to assist patients in getting into or out of their own beds is the Bedside Assistant *(Bed Handles, Inc)*. Installed by just sliding them between the mattress and box spring, they provide extra stability for anyone who feels dizzy or unsteady as they get into or out of bed (Fig 110-16).

ALTERNATING PRESSURE PADS—The alternating pressure pad (APP) is a thin air-mattress pad arranged in longitudinal tubes and connected to an air pump that alternately inflates and deflates alternate rows of tubes. To eliminate

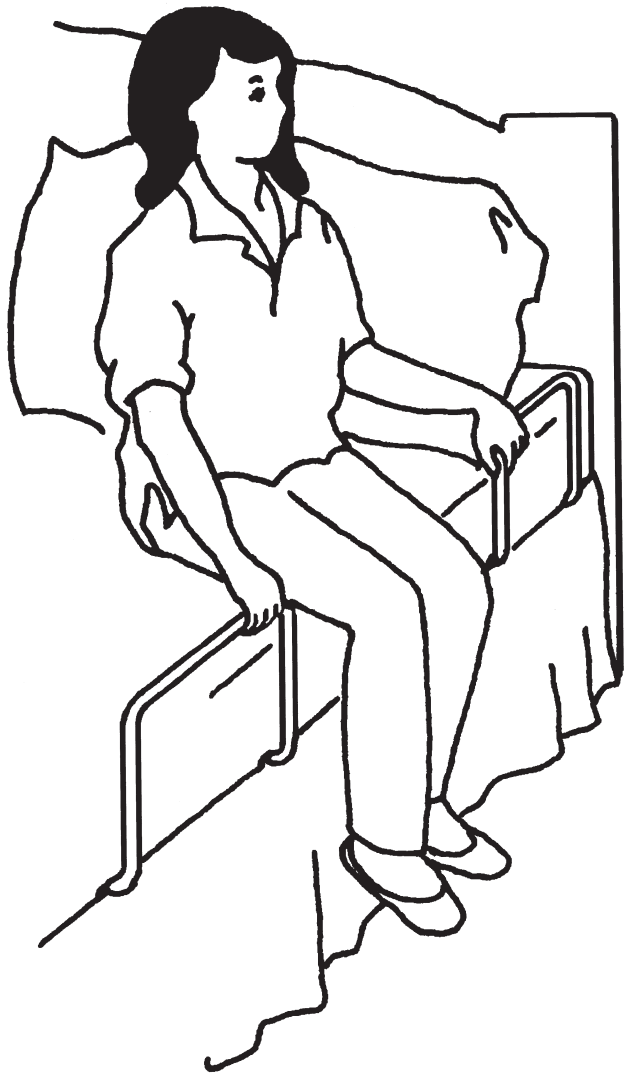

Figure 110-16. Patient using the Bedside Assistant (courtesy, Bed Handles).

counterpressure, sometimes created by the smooth long tubes in earlier APP pads, newer configurations may include small pillows arranged longitudinally in lieu of straight tubes. It works on the principle that circulation in the tissue occurs in the absence of pressure.

A newer product, the alternating pressure mattress (APM) by Invacare, features a full 7-inch-deep system with a variety of settings that can reduce interface pressure for treatment of Stage I through Stage IV pressure sores (Fig 110-17). A moisture-permeable covering also can help prevent skin breakdown by removing moisture from the skin.

TRAPEZE BARS—The typical overbed trapeze bar is used by the patient as an assist in sitting up and getting into and out of bed. It usually is made of steel and, by means of clamps, is attached to the headboard of a hospital bed. A trapeze-bar floor-stand, which enables the trapeze to be used over any bed, is also available.

Trapeze bars are adjustable in height, and some models also provide adjustability in the position of the bar over the bed. A special clamp permits the bar to be swung to various positions and locked for security. A pivoting trapeze bar should never be used with the floor stand, as accidents may occur unless the bar is suspended properly.

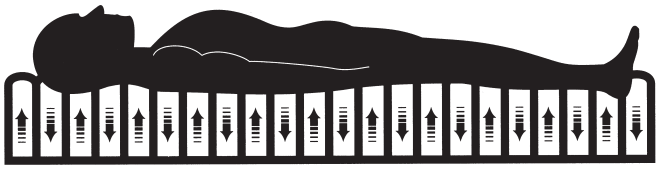

Figure 110-17. In alternating mode, the APM's 22 adjacent air cells alternatively inflate and deflate at 5-min intervals, which periodically redistributes the pressure against the skin to promote capillary circulation (courtesy, Invacare).

TRACTION

Overdoor traction sets provide for cervical traction at home, using any open door for the purpose of mounting the traction pulleys. Weight is applied to the cervical spine by a cord running over the pulleys and attaching to a halter that fits over the patient's head and applies pressure to his or her mandible and occiput. The weights may be cast-iron traction weights suspended on a traction-weight hanger or a graduated water-weight bag containing tap water in accordance with the weight-of-water markings on the plastic bag. An additional item in most overdoor traction sets is a metal spreader bar that spreads the top of the head halter to avoid pressure against the patient's ears.

Unless specifically instructed by the physician to the contrary, the pharmacist should tell the patient to use the overdoor traction set while sitting in a chair facing the door. When doing so, the patient's head will be pulled toward the front, bending the chin down and flexing the cervical spine.

Flexion generally is preferred over hyperextension in any type of traction. If the patient were to sit with his or her back to the door, as has been illustrated on the covers of overdoor traction sets for many years, the chin would be pulled up and the cervical spine would be hyperextended—usually an undesirable attitude during cervical traction.

Most patients who require traction will need it in a flexion posture; the rest need hyperextension. It may be dangerous to use flexion on patients who require hyperextension.

Any traction set—even the ordinary overdoor type—should be sold or rented only on the written prescription of a physician who specifies the frequency of treatment, the length of each treatment, the weight to be applied, whether the traction is to be static or intermittent, and special instructions as to positioning of the patient with respect to flexion and hyperextension. It is often necessary for the pharmacist or the patient to call either the physician or the physical therapist to clarify the amount of weight to be used or the length of time of each treatment.

TRACTION IN BED—While cervical traction may be given while the patient is either sitting in a chair or reclining in bed, pelvic traction is administered at home only when the patient is in prone position. There are two basic types of applied-in-bed traction sets: one is for use with a hospital bed and the other for use with any bed. The any-bed traction device has the typical vertical adjustments and pulleys and is mounted on a floor stand. Buck's extension traction or a mattress clamp set may require a sturdy headboard or footboard, as it has no floor stand. Either type is used for both pelvic and cervical traction.

When applying cervical traction to a patient lying in bed, unless specifically instructed by the physician to the contrary, traction pulleys usually are mounted quite high so as to develop flexion of the cervical spine and mildly depress the patient's chin.

When pelvic traction is applied, flexion is also important, and the pulleys should be mounted quite high to produce flexion of the lumbar spine. It also may be helpful to raise the head section of the hospital bed or bolster the ordinary bed with a wedge cushion or mattress elevator. Additionally, the patient's knees should be elevated either with the knee adjustments of the hospital bed spring or ordinary pillows placed under the knees. These recommendations must have the approval of the physician.

A complete traction department also will have pelvic traction belts in a variety of sizes, without which pelvic traction cannot be applied. A universal (one size fits all) belt with Velcro fasteners is also available.

PATIENT LIFTERS

Among a wide range of hydraulic and screw-type patient lifters, the floor-model hydraulic patient lifter is used most commonly (Fig 110-18). All lifters have an adjustable boom to which a patient-carrying sling or seat is attached. Lifter bases differ, though they are typically U-shaped and may be either adjustable or nonadjustable in width. The adjustable base may be spread wide and moved around almost any chair or commode so that the patient sling is suspended directly over the seat to which the patient will transfer.

Sling design is an important consideration when choosing a patient lifter. Slings in all fabrics come as one- or two-piece units, with and without head supports; they also may be had with a commode opening.

Positioning the sling under the patient who is in bed is accomplished in much the same way that bed linens are changed under a patient. The patient is rolled on one side while half the sling is folded accordion fashion and tucked up against him or her. The sling should be so positioned that on rolling back, the spine will rest on the middle of the sling. The patient is rolled back over the folded portion of the sling and to his or her other side while the folded part of the sling is unfolded; then the patient is returned to his or her back. Attention should be paid to the vertical positioning of the sling also—the bottom edge of the sling should not extend to the middle of the patient's knee, but rather should come just to the knee.

When the sling is placed properly under the patient, the lifter is brought to the bed, the chains or straps are hooked up, and the boom is raised slowly and gently until the patient is

Figure 110-18. Painted hydraulic patient lifter with nonadjustable base and two-piece canvas patient sling (courtesy, Ted Hoyer & Co).

lifted off the mattress. Patients should never take hold of the lifter chains; their arms should be safely inside the sling. To avoid swinging of the sling when moving the lifter, the attendant should cross the patient's ankles and hold the bottom heel with one hand while pulling the lifter with the other. Patients should always be facing the lifter when they are suspended by the lifter sling.

When a patient is ready to be lowered into a chair, commode, or bed, the attendant should release the hydraulic valve carefully and slowly, guiding the patient into position by the heel. A common mistake is to remove the sling from beneath the patient after transferring him or her to a chair or commode. It is considerably easier, and safer too, to let patients sit on the sling, and remove only the chains and lifter from their view.

When it's time to pick the patient up again, the lifter only need be brought into position, the chains hooked up, and the patient lifted slowly out of the chair.

A patient lifter with a special type of base must be used for bathtub transfers.

BEDPANS

Bedpans, used for the collection of feces, may be round but are predominantly oval and are constructed of plastic, stainless steel, enamelware, or porcelain. Single-patient-use plastic bedpans (nonautoclavable) are considerably less expensive than their metal and porcelain counterparts. Plastic, like rubber, also tends to be warmer to the touch and therefore much more comfortable than steel, porcelain, or enamelware. There is also available a smaller, sloping, flatter bedpan, called a fracture bedpan, for use, primarily for urine, with immobilized or overweight patients.

It is helpful to the patient for the pharmacist to suggest that when a hospital bed is available, the back rest and knee section of the gatch spring should be elevated when using the bedpan. The backrest should be elevated substantially while the knee section should be elevated only slightly. When a hospital bed is not available in the patient's home, four or five pillows behind the back will make using a bedpan much easier.

ACCESSORIES FOR THE BEDFAST PATIENT

Special tables and trays for spill-preventing, safety, and patient comfort are near-essentials in any sickroom (Fig 110-19). The common overbed table is an ideal accessory whether or not the patient has a hospital bed. Some overbed tables have a center section that can be raised to a slanted position for the support of a book or magazine; others have a vanity tray and mirror that slide out from beneath the tabletop for use by the bedfast patient. Sturdy breakfast trays that straddle the patient's hips while he or she is in bed, special folding tables, and trays with contoured fronts that enable the wheelchair user to get comfortably close contribute to the nonambulatory patient's comfort and convenience in the sickroom at home.

Easy-reachers are devices that enable the bedfast patient to reach out and pick up things normally beyond his reach.

A solid or inflatable plastic shampoo tray facilitates shampooing for patients who cannot leave their beds. The tray fits across the mattress where a pillow normally goes and is designed to carry shampoo water to a drain at the side of the bed, where it may be collected in a plastic bucket. The patient's head rests in the shampoo tray, which, though it has quite high sides, has a depression for the back of the neck.

Folding backrests with or without arms, wedge-shaped foam cushions, bedboards, and footboards with adjustable cushions for the prevention of foot rotation are additional articles for the comfort and convenience of the bedfast patient. When it is necessary to keep bed linens and blankets off the patient's feet and legs, a blanket support, sometimes referred to as a leg or body cradle, is desirable. Holding mitts, built-up forks and swivel spoons, food guards, feeding cups, pencil and cigarette holders, and simple drinking straws with accordion hinges that bend without collapsing are some of the devices that make patient home-care effective.

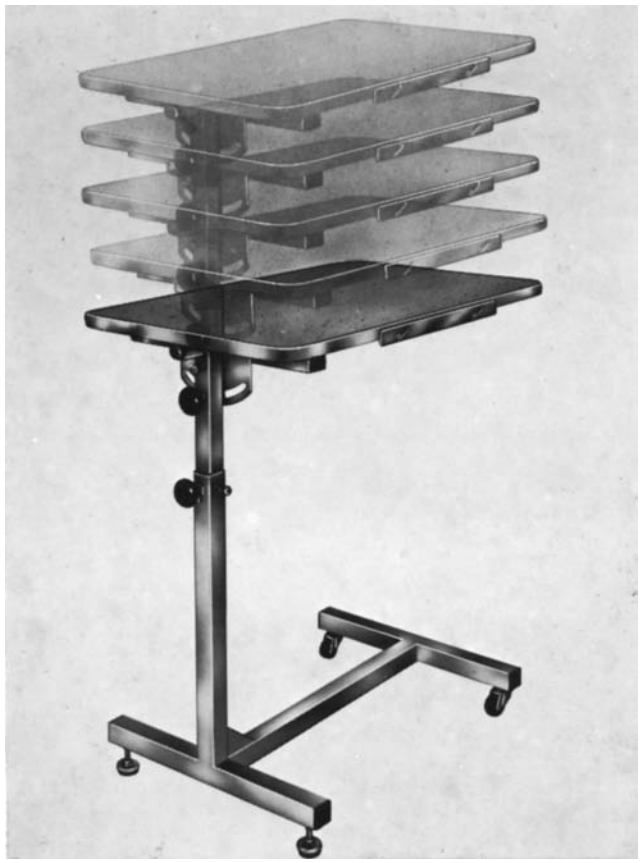

Figure 110-19. Adjustable overbed table with tilt-top for books or magazines (courtesy, Lumex).

Folding patient-privacy screens are a frequently requested sickroom accessory, especially when the patient will be using a bedside commode.

Finally, a health-accessories department also may stock a modest assortment of safety vests and belts, crib nets, and restraints for use by nursing homes and extended-care facilities, as well as by the patient at home.

RESPIRATORY THERAPY

STEAM VAPORIZERS—The modern steam inhaler is essentially the same as the now nearly forgotten croup kettle, except that it uses electricity to generate heat and steam. The advantage of this more modern adaptation lies in the attainment of a constant temperature. Also, most forms of this apparatus are equipped with a regulator so that when they run dry, the heating unit shuts off simultaneously. These are easier to handle in the home, especially at night.

The familiar vaporizer provides the conventional hot-steam therapy for the relief of upper respiratory illnesses. Physicians recommend it for colds, sinusitis, and similar ailments.

The portable room humidifier, on the other hand, provides a cool mist to compensate for the lack of sufficient moisture in the air and occasionally is used for its expectorant effect in liquefying tenacious mucus in the airway. An additional advantage is that since no heater is used, it is entirely safe for small children.

Vaporizers are used extensively in the home today to humidify bedrooms or chambers where patients suffering from various bronchial conditions may rest. Cool-vapor humidifiers provide effective high-humidity inhalation therapy for respiratory patients and can be used as well to restore proper humidity to rooms dried out by winter heating.

AIR PURIFIERS—The removal of dust, pollen, spores, secondhand smoke, and other irritants from room air by an air purifier can be a valuable adjunct to the treatment of many respiratory conditions. Models using a true HEPA (*high efficiency particulate arresting*) filter can remove up to 99.97% of all airborne room particles.

AEROSOL THERAPY AND NEBULIZERS—Instruments that generate very fine particles of liquid in a gas are called nebulizers. Medication compressors, such as the Pulmoaid (Fig 110-20) often are used in providing inhalation therapy. Other medicinal and pharmaceutical uses of aerosols are discussed in Chapter 69.

Many other types of high-tech respiratory equipment, such as continuous positive airway pressure devices (CPAPs) and ventilators, are available. While these may be a part of the pharmacy's health-accessory department, the actual setup, patient instruction, and equipment maintenance usually will be done by a respiratory therapist, who is on call 24 hours a day in the event of an emergency.

OXYGEN THERAPY—Providing oxygen therapy as an adjunct to a health-accessories department also should be done in conjunction with the services of a respiratory therapist.

Oxygen first became available as a therapeutic gas after the military developed an economical process to distill it in large quantities for use by the pilots and crew of high-altitude aircraft. Prior to this it was not economically feasible to provide oxygen in the quantities required to treat hypoxic patients. The primary commercial method of manufacturing therapeutic oxygen is by the liquification of air followed by fractional distillation.

Supplemental oxygen is used to treat various clinical disorders, both respiratory and nonrespiratory in nature.

Oxygen often is prescribed at a rate of 2 L/min for the relief of arterial hypoxemia and any of its secondary complications. Oxygen also has proved to be therapeutic in treating pulmonary hypertension, polycythemia secondary to hypoxemia, chronic disease states which may be complicated by anemia, cancer, migraine headaches, coronary artery disease, seizure disorders, sickle-cell crisis, and sleep apnea.

Some adverse effects and hazards of oxygen therapy include oxygen-induced hypoventilation, absorption atelectasis, and oxygen toxicity. Oxygen-induced hypoventilation is probably the greatest potential hazard of oxygen therapy.

In certain clinical situations the respiratory therapy drive that results from carbon dioxide stimulation of the respiratory center is blunted. This phenomenon may be the consequence of a drug overdose such as with a barbiturate or heroin or, more commonly, chronic hypercarbia. Hypoventilation is of particular importance in patients with severe chronic obstructive pulmonary disease (COPD) in which carbon dioxide retention and hypoxemia have developed over a long period of time. The respiratory drive of most of these patients results from hypoxic stimulation of the carotid chemoreceptors. Thus, the main stimulus for respiration is hypoxemia. If this hypoxic drive is relieved through the advent of excessive oxygen therapy, hypoventilation may occur, and further carbon dioxide retention with possible cessation of ventilation could result.

Figure 110-20. DeVilbiss Pulmo-Aide LT compressor (courtesy, Sunrise Medical).

Absorption atelectasis is the result of collapsed alveoli from a high concentration of oxygen in the inhaled air. Nitrogen, an inert gas that makes up 79% of our atmosphere, maintains the residual volume of space in the alveoli as the oxygen component of inhaled air is diffused through the pulmonary membrane and absorbed into the bloodstream. When a high concentration of oxygen is inhaled into the alveoli, the oxygen is absorbed rapidly into the blood, potentially leaving the alveoli empty and collapsed. This is particularly significant in patients with pulmonary disease that involves narrowing or obstructing the airways and a low ventilation-perfusion ratio.

Oxygen toxicity is not a significant hazard until oxygen concentrations are greater than 50% for prolonged periods of time. Oxygen toxicity can affect the pulmonary system, central nervous system, retina, and endocrine organs adversely. Pulmonary changes are usually the first to manifest, with increased permeability of capillary endothelial cells resulting in alveolar congestion, intraalveolar hemorrhage, and fibrinous exudation of the hyaline membrane. Normally, the first symptoms include substernal burning discomfort, cough, paresthesia, nausea, and vomiting.

A prescription of 2 L/min is generally considered sufficiently therapeutic without a great increase in risk of the previous hazards.

For the home-care patient on oxygen therapy, there are basically three different types of delivery systems available: the liquid system, compressed gas system, and oxygen concentrator. Each has its own distinct advantages and disadvantages. Choosing a system that is most applicable is based on the patient's needs, lifestyle, mobility, convenience, frequency of use, and volume of oxygen consumed. Reimbursement criteria set up by Medicare or an HMO also may dictate which type of system is used.

The oxygen in a liquid system has been compressed and cooled to −184.4° (−300°F). The resulting volume is less than 0.2% of an equivalent amount of oxygen at atmospheric pressure and temperature. The system consists of a large reservoir vessel and a lightweight portable unit. Both are designed to protect the extremely cold contents from heat and to regulate a consistent rate of evaporation from a liquid to a gas for subsequent use by the patient. Most large reservoirs will hold 75 to 100 lb of liquid oxygen and require filling once every week or so. Although considered stationary units, some patients have secured them in vehicles for travel. The portable unit is light enough, at approximately 8 lb when filled, to be transported over the shoulder by its carrying strap.

Compressed-gas oxygen systems consist of a basic high-pressure tank and a pressure regulator with an attached flow meter graduated in liters per minute. The most stable and reliable form of oxygen delivery and storage systems, it is most applicable for patients who predominantly are confined to their home with an occasional need for mobility or patients who require oxygen on an *as needed* basis. Compressed oxygen is available in a variety of tank sizes (Fig 110-21).

The largest, the *H* tank, holds 244 ft^3 or 6900 L of oxygen and is the standard stationary unit of the system. Smaller tanks, some of lightweight aluminum construction, are available for use as portable systems. The most common tanks are the *E* with 22 ft^3 or 622 L of oxygen, often used with a small pull cart, and the *D* with 12.6 ft^3 or 356 L of oxygen, easily carried in a shoulder bag.

Figure 110-21. Portable oxygen tanks (courtesy, DeVilbiss).

OXYGEN CONCENTRATOR AND ENRICHER—Electrically powered by standard 110-V household current, these devices pump in ambient room air and then preferentially separate oxygen from nitrogen and deliver approximately 95% oxygen at maximum flows of 3 to 6 L/min. Much improved in efficiency and reliability over the last few years, all concentrators still require inspection by a trained technician, preferably quarterly but at least annually, to verify the percentage of oxygen delivered and perform a scheduled, routine maintenance program. This type of system never needs refilling and is extremely convenient for the homebound patient. The disadvantage of older systems is that the system cannot store any oxygen for portable or emergency use during an electrical outage. Patients should be advised to have a separate source of oxygen, such as a compressed tank, available. Newer units actually are capable of filling portable tanks. One brand of concentrator (Fig 110-22) can produce a liter flow of 0 to 6 L/min and also can fill any backup tank at 3 L/min while still providing oxygen for the patient. The most commonly used backup tank, the *E* tank, takes about 2 hr to fill. The use of this type of unit, where practical, and the use of oxygen-conservation devices can reduce the number of service and delivery calls normally associated with providing oxygen therapy.

Figure 110-22. Venture HomeFill complete home oxygen system (courtesy, Invacare).

APNEA PROGRAMS

Sudden infant death syndrome (SIDS) is the number one cause of death in the US for infants under the age of 1 year. The relationship between SIDS and apnea (a pause in respiration of 15 to 20 sec or longer) is not exactly clear and is still somewhat controversial. However, a large portion of the pediatric medical community has begun home-monitoring in infants who have experienced episodes of prolonged apnea.

In the last few years a great deal of medical research has been devoted to improving understanding of the relationship between SIDS and apnea. This has resulted in the publication of a large number of journal articles about apnea and SIDS, the establishment of an annual medical conference on the subject, the startup of numerous hospital-based apnea programs, and a general increased awareness in the medical community about the problem.

As the interest in the medical community has increased, so has the number of physicians prescribing home monitors. Apnea programs were once the domain of a select few physicians and hospitals nationwide. Now, most hospitals with a Level II or III nursery have developed their own apnea-monitoring programs, staffed with a team of medical professionals. These programs evaluate infants at risk for apnea and prescribe the use of a home monitor. Typically, a neonatologist heads up the team and is assisted by nurses and respiratory therapists specializing in the treatment of infants.

The increased interest in SIDS and apnea by the medical community has stimulated tremendous growth in the number of home-health-care dealers offering apnea-monitoring programs.

PNEUMOGRAMS (PNEUMOCARDIOGRAMS)—Apnea monitoring has become much more sophisticated in the last few years. Very specific and detailed evaluation and screening programs have been established by hospitals to determine which infants will need to go home with an apnea monitor. Once in the home, more followup work now is being done. Historically, 12 hour recordings known as pneumograms were performed to evaluate an infant's progress in the home environment. Long-term event recordings are now commonplace for documentation of the types of alarms an infant is having and to determine the proper time for monitor discontinuance.

Pneumograms are two-channel recordings of heart rate (ECG) and respiration. Typically, these are performed in the home for a 12 hour period. These recordings then are printed out and analyzed by a physician or technician. The results are used to determine if the infant needs further study at a hospital apnea center or no longer needs to be monitored.

A 12-hour pneumogram is a *snapshot* recording of one night in an infant's life. The recording may include apnea events in combination with normal activity *(well information)* or it may include only *well information.* If an infant who previously has had a number of serious problems while being monitored has an unusual evening during a 12-hour pneumogram, with no events occurring, the physician has a recording that is not an accurate reflection of the infant's true condition.

An event recorder provides the caregiver with long-term information about the events that are causing the monitor to alarm. This provides the physician important documentation about the number and type of events an infant is having over a long period of time. An event recording provides a physician with a more realistic record of an infant's condition. The physician can alter the infant's monitoring program or discontinue monitoring altogether based on the results of the recording.

Event recordings, normally taken for a period of 72 hr or longer, are similar to two-channel pneumograms. They record heart rate and respiration data, but rather than continuously recording this information over a 12-hr period, they only record information when the monitor sounds an alarm. An event recording provides the caregiver with information about alarm events occurring in the home. This information is extremely valuable, particularly when evaluating problem infants or determining when to discontinue monitoring.

Traditionally, home pneumograms were made on small cassette-tape recorders. The recorders and tapes would be delivered to the home the day the recording was scheduled, and the readings were printed and analyzed the following day. Multiple-channel recordings are being used more widely, and improved electronic communication devices can provide physicians with results on a much more timely basis. Many units can be connected to store the data on a laptop computer or, through a modem, to transmit the data to a neonatologist at a hospital or directly to the physician's office.

PHOTOTHERAPY

The treatment of neonatal jaundice (hyperbilirubinemia) often involves the use of a phototherapy light. Phototherapy treatment also may be provided by a fiberoptic system, which consists of an illuminator, a fiberoptic cable, and a fiberoptic panel, which can be wrapped around an infant's torso (Fig 110-23). Phototherapy may be done in the hospital or, at the doctor's and parent's option, in the home. Home phototherapy costs can be a fraction of the cost of a hospital stay, and the financial resources of the parents or the mandates of an HMO may require home treatment. While the health-accessories pharmacist may stock and set up these units, a nursing service usually will provide the everyday blood-testing required.

LIGHT THERAPY—Studies have shown that during the winter months, especially in the northern climates, up to 20% of the population may suffer from sunlight affective disorder (SAD). Three-fourths of these will be women. By combining high-output fluorescent tubes with a parabolic reflector, one company has designed a light unit that can produce up to 10,000 lux (a unit of measure of light intensity) of light, similar to that of a very bright and sunny spring day (Fig 110-24). By contrast, normal indoor lighting levels may range from 200 to 700 lux. Usage for only 15 to 30 min a day may increase the sense of well-being for those affected by this disorder.

HYPODERMIC EQUIPMENT

Syringes are instruments intended for the injection of water or other liquids into the body or its cavities. They are classified according to differences in principle of action into three categories: *plunger syringes,* such as the hypodermic syringes; *bulb syringes,* of which the ear and ulcer syringes are one type, and *gravity syringes,* characterized by the fountain syringes.

HYPODERMIC SYRINGES—These syringes are used to administer medication *subcutaneously* (under the skin) or *intradermally, intravenously* (into a vein or artery), or *intramuscularly* (into the muscle).

Parenteral therapy or injection of medication under the skin and through tissues dates from the beginning of the 19th century. The first crude instrument of this type was a needle trocar, developed to deposit morphine in paste form. The principle

Figure 110-23. Wallaby phototherapy system (courtesy, Medical Products).

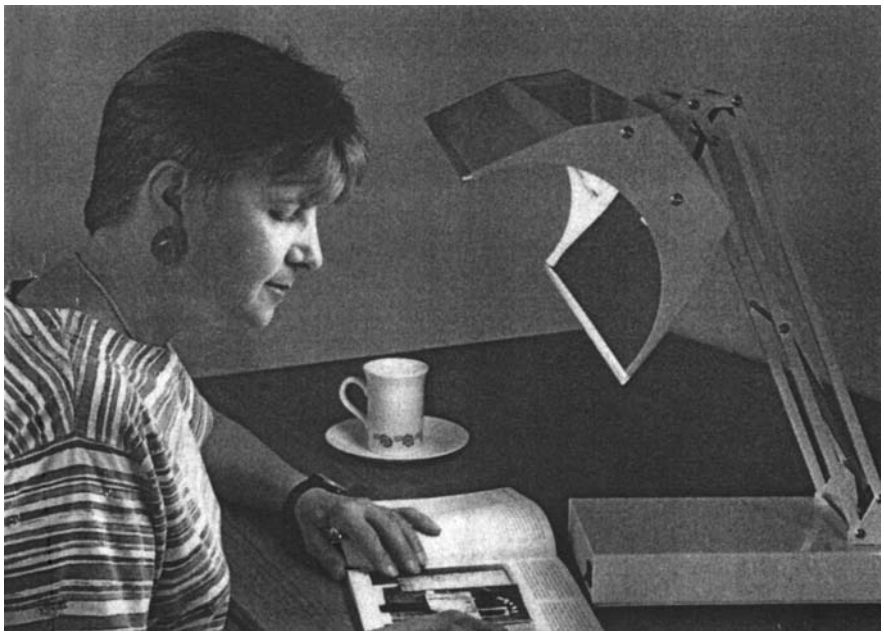

Figure 110-24. Satellite light system (courtesy, Northern Light Techologies).

of introducing medication under the skin, however, became popular in the first half of the 20th century.

Luer Syringes—The inventor of this type of apparatus, Dr Luer, patented his syringe; the letters patent have long since expired but today most hypodermic syringes of this style bear his name. The outstanding feature of the Luer syringe was its ground-glass surfaces. In many instances, the inside of the glass barrel and the outside of the glass plunger were ground individually. Later, they were ground together so that they would provide a perfect fit and prevent back leakage.

Hypodermic syringes are always of the plunger type, characterized by the type of piston and difference of size or capacity. The *tuberculin syringe* is a small syringe not exceeding 1 mL in capacity and graduated in 0.1- or 0.01-mL divisions. The *hypodermic syringe* is usually of 2- to 50-mL capacity. There are larger piston syringes, ranging up to 200 mL, for various purposes such as transfusions and in veterinary medicine. Graduations may be in fractions of a mL or in *minims*. Syringes also may be prepared with special graduations, such as *units* of insulin.

DISPOSABLE HYPODERMIC SYRINGES—Most hypodermic syringes used outside of a hospital setting are of the disposable variety. Various types of disposable hypodermic syringes, each carrying a single dose of sterile medication, now are supplied as a standard dosage container by many pharmaceutical manufacturers.

HYPODERMIC NEEDLES—Hypodermic needles used with Luer syringes are of metal and consist of a hub, which locks to the ground-glass tip by friction, and a needle point that varies in diameter and length. Needles also are called *cannulas*. Hypodermic needles have been made of stainless steel, hyperchrome steel, carbon steel, chromium, nickeloid, platinum, platinum-iridium, silver, or gold.

Hypodermic needles are characterized by their different points, which have a long, tapering reinforced point and beveled cutting edges of varying degree. A *long-bevel* or *long-taper* needle is used for local anesthesia, aspirating, hypodermoclysis, and subcutaneous administration. A *short-bevel* needle is used for intravenous administration, infusions, and transfusions. A *special short-bevel* needle is employed for intradermal and spinal administration (Fig 110-25).

Size—Selection of a size is governed by four factors—safety, rate of flow, comfort of patient, and depth of penetration. There are three standard dimensions—length, outside diameter of the cannula, and wall thickness. Regular needles are measured for length from where the cannula joins the hub to the tip of the point (hub not included).

The gauge of a needle is measured by the outside diameter of the cannula or needle shaft. The usual range of diameter for needles is from 13-gauge (largest diameter) to 27-gauge. Needles seldom are less than $\frac{1}{4}$-inch long or longer than $3\frac{1}{2}$ inches.

There are many special needles, designed for a variety of purposes. Various *biopsy* and *bone-marrow transfusion* needles range from 16- to 19-gauge and $\frac{1}{2}$to $3\frac{1}{2}$ inches long. They are characterized by their heavy-shaped hubs.

Needles for *local anesthesia* range from 26-gauge, $\frac{1}{2}$ inch to 20-gauge, 6 inch. *Intravenous, blood transfusion* needles, some with fitted cannulas, range from 19-gauge, $1\frac{1}{4}$ inch to 15-gauge, $2\frac{1}{2}$ inch.

There are also special needles and cannulas for *abscess, eye, hemorrhoidal, tonsil, laryngeal,* and *pneumothorax* use.

These many types of special-purpose hypodermic needles are of varying diameters and varying lengths. Examples of some of these are shown in Figure 110-26.

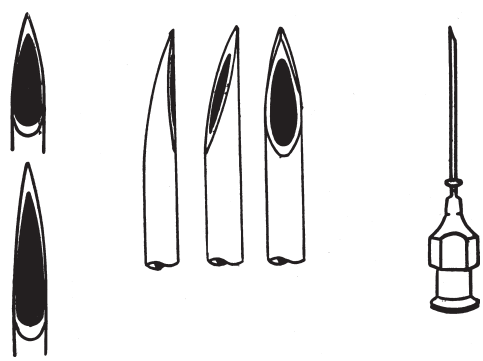

Figure 110-25. Hypodermic needles. *Left,* short-bevel and long-bevel needle points; *left center,* the Huber point with closed bevel and side opening to avoid producing tissue plugs; *right center,* regular point showing features that ensure less cutting, more distention of tissue, and reduced trauma, seepage, and after-pain; *right,* needle with security button that prevents a broken cannula from becoming lost in the tissues.

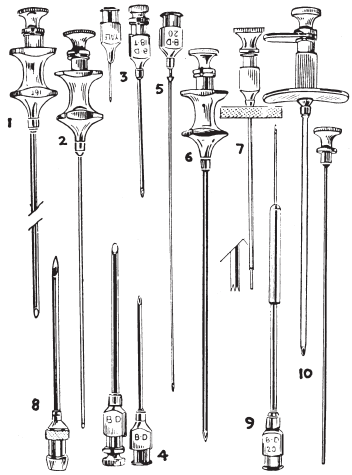

Figure 110-26. Special hypodermic needles. 1, caudal needle; 2, epidural needle for single-shot anesthesia; 3, intravenous anesthesia short-bevel and long needles (with vinyl tubing); 4, blood transfusion needles (with vinyl tubing); 5, short-bevel beaded local anesthesia needles; 6, spinal needle with large spool hub; 7, biopsy needle for bone-marrow aspirations; 8, infusion needle, with female Luer slip; 9, hemorrhoidal needle with threaded adjustable gauge to adjust depth of puncture; 10, cerebral angiography needle with thin-walled outer cannula, corrugated shield, and inner cannula (courtesy, Becton-Dickinson).

BULB SYRINGES

Bulb syringes frequently are preferred for use where sterility is not necessary or where plunger-type syringes, because of their force, would be dangerous to use. Bulb syringes are of particular value in the nose and ear and for wound and urinary irrigation.

These syringes customarily are known by the name of the part of the body for which they are intended.

Nasal syringes or *nasal aspirators* are soft rubber bulbs of about 1-oz capacity, with an acorn-shaped nasal tip to fit the nostril. The tip may be either glass, plastic, or hard rubber. A glass tip allows visual examination of the mucus removed from the nostril.

Ear syringes and *ulcer syringes* are one-piece molded bulbs of soft, flexible rubber, with long, narrow nozzles and are employed in treating the eye, ear, and nose and for irrigation of any open cavity or ulcer.

If necessary, bulb syringes should be sterilized with germicidal solutions. Prolonged boiling will injure the rubber.

Rectal syringes are customarily of the bulb type, with a long narrow nozzle. They frequently are employed in the administration of enemas to infants. These are the safest and least expensive of syringes requiring minimal maintenance. Such syringes customarily are of 1- to 4-oz capacity. Although many syringes provide hard-rubber or vulcanite tips, the use of hard tips should be discouraged because of occasional injury to the soft tissues from their use.

Vaginal syringes, used for irrigation of the vagina, are 8- to 10-oz capacity bulb syringes with a large vulcanite or rubber spray tube. Pressure on the bulb forces the medicated or irrigating liquid through the tip of the syringe either in a direct stream or with a *whirling* motion. These syringes in white or various colors are provided with rubber, sleeve-shaped, round or oval shields to prevent leakage when in use. Caps sealing the nozzles are provided to avoid leakage or loss of the contents before use. One model has a convenient plastic stopper at the bottom of the bulb opening, with a removable strainer, which permits mixing of medications.

ENEMA SYRINGES—Fountain syringes consist of a reservoir with a capacity of 1 to 3 qt, a 5-ft rubber tube, and a vaginal or rectal nozzle. These are used for irrigation with water, salt solution, soap suds, or special medications.

Pharmacists should caution users of enema syringes as follows: the *drop* must not exceed 4 ft to prevent excessive gravity pressure, the fluid should be maintained at body temperature to avoid chills or burns, and the tube customarily is closed with a mechanical pinchcock. Before using the syringe, the cutoff should be released for a moment until some liquid issues from the nozzle. The user must be certain that no air remains that might be forced from the tube into the body cavity. Hard-rubber nozzles are supplied frequently with enema syringes, but as they may cause damage to the rectum, they preferably are replaced by catheters or tubes of soft rubber, about 3/16 inches in diameter and 15 inches in length.

Enemas—In simple constipation, whenever evacuation of the lower bowel is indicated, and when proctological examination or surgery is indicated, an enema customarily is given because of its local, comfortable, and safe action in a relatively short period of time.

Enemas should not be used when nausea, vomiting, or abdominal pain is present nor more often than necessary, to avoid dependence. Prepared enemas are available for use in simple constipation or whenever evacuation of the lower bowel is indicated, such as in proctological or sigmoidoscopic examinations; small, disposable units consisting of flexible plastic bottles of 6- to 50-mL aqueous or oil solutions, with self-fitted comfortable plastic or rubber tip are available.

DRESSINGS AND FIRST-AID SUPPLIES

Pharmacists are the proper distributors of sterile materials for treating wounds. Their training enables them to appreciate the care necessary in their handling and storage, and they often are called upon for advice or instruction on their use. The following items fall in this class: absorbent cotton, cotton balls and buds, sterile rolls and pads of gauze, elastic bandages, disposable fabric tissues and underpads, eye pads, sponges, tissues and towels, adhesive elastic bandages, aerosol adherent, spray dressings, first-aid kits, scissors, tweezers, and applicators. Various types of oxygen and moisture-permeable transparent dressings such as *Tegaderm* or hydroactive dressings such as *Duoderm* serve specialized needs.

The pharmacy with a comprehensive health-accessories department will stock bulk packages of these items for use by nursing homes, visiting nurses services, and patients who consume quantities sufficient to warrant their making larger purchases, in addition to the smaller packages for the pharmacy's usual customers.

THE FAMILY MEDICINE CABINET—There is a place in every home where medicines are kept. The medicine cabinet should be either locked or completely out of the reach of children. Every bottle or box within should be labeled clearly. Unused prescription medications, outdated over-the-counter drugs, and empty bottles do not belong in the medicine cabinet and should be removed. Some community pharmacists provide folders containing information on first-aid, poison antidotes, and simple home medication for use by their patients so that the pharmacy's name is always in view in the medicine cabinet. This also is accomplished by providing a gummed *family prescription record* for the inside of the cabinet door or an *emergency label* bearing space for entering telephone numbers for the doctor, pharmacy, hospital, and fire and police departments, to be attached to the telephone or telephone book.

In addition, the pharmacist should urge that every family car, camper, and boat be equipped with an adequate first-aid kit in addition to a flashlight, flares, and a hand-held fire extinguisher.

SNAKE-BITE KITS—Anyone in snake, bee, or wasp country should carry a snake-bite kit. Usually, these are available in a compact plastic or metal case containing a tourniquet rubber or other lymph constrictor, antiseptic, razor blade or knife, and one or more suction cups or syringes. These are available from Cutter or Becton-Dickinson. Many lives are saved each year by

prompt action at the spot where the snake attacks, and relief from the pain and swelling of severe insect stings is also important. Snake bites are medical emergencies that require immediate treatment.

Every hospital pharmacist should have a chart of disaster-unit equipment required for a hospital, and all pharmacists should be familiar with the requirements and needs of disaster units.

HOT-WATER BOTTLES—The best instruments for applying dry heat are the hot-water bottle and the electric heating pad. Hot-water bottles may be of the usual 2-qt size or of the 1-pt capacity in the form of a *face bottle* for neuralgia of the head and for infant conditions. Each hot-water bottle has an opening through which warm water is added and a stopper securely sealed with a washer. It is more convenient to attach the stopper permanently to the bottle to prevent its loss. Some have screw-stopper attachments that permit conversion of the bottle into a fountain syringe.

When filling a hot-water bottle, it should be held against the back of the hand or forearm to ensure that the temperature is not too high. The hot-water bottle should never be allowed to come in contact with the skin, or burns may result. Flannelette bags or even a towel wrapped around the hot-water bottle will give adequate passage of heat and comfort and convenience.

After use, the empty hot-water bottle should be hung by the tap at its bottom for thorough draining. Water of boiling temperature, oil, grease, alcohol, or turpentine should not be permitted to come in contact with the material of the hot-water bottle.

MOIST-HEAT PACKS—Various commercial moist-heat packs are in common use in hospitals and nursing homes and are also available for use at home. These steam packs appear as compartmented, cloth bean bags when new and are filled with tiny beads. When boiled in water or heated in a microwave oven, however, the beads become hydrated and combine into a gelatinous substance that has the unique property of holding its temperature far longer than any other pack—about 30 to 40 min.

Moist-heat packs such as these must be wrapped in layers of Turkish towel to prevent burns and should never be used in direct contact with the skin. They are available in a variety of sizes, including a contoured pack designed specifically for the neck and shoulders. The neck-contour steam pack, as well as others, also has optional terry-cloth covers, lined with foam rubber, which takes the place of layers of toweling. Heating units are also available, but the patient at home can prepare a steam pack in an ordinary pot of boiling water. They can be used over and over again without loss of effectiveness if care is taken to avoid dehydration—easily accomplished by wrapping the steam pack in a plastic bag and storing it in the refrigerator. For long-term storage, these packs can be kept in the freezer (ie, again, sealed in a plastic bag) to prevent drying out.

ELECTRIC HEATING PADS—The advantage of the electric heating pad over the hot-water bottle is that there is no possibility of leaking or spilling, and the temperature is controlled constantly and indefinitely. Most are wet proof for wet or dry application and have soft-foam padding and washable flannel covers. Most have adjustable heating elements that permit the temperature to be set at the desired level and an illuminated temperature-control panel. One of the more popular electric moist-heating pads is manufactured by Battle Creek under the trade name *Thermophore*. These are controlled by means of a handheld switch that automatically turns the unit off when released, eliminating the possibility of burns caused by a patient's falling asleep. The Thermophore heating pad creates moist heat without preboiling or using large amounts of water, hence, its desirability in the home environment. The unit's flannel cover is dipped into water and then wrung dry. Intermittent applications of heat create *fomentation,* or intense moist heat. The manufacturer recommends that treatments not exceed 30 minutes in length. Customarily, all such electrical devices are inspected to ensure safe operation. However, short circuits and breakage of the heating element may result from constant use.

Automatic heat bonnets for scalp treatments; heat bandages for sprains, bursitis, or arthritis; neck and throat heating pads for stiff neck or whiplash cases; sinus masks for heat therapy of sinus areas; and even thermal massagers are available. The pharmacist always should caution the patient *not* to sleep while using an electric heating pad.

Still another modality for providing heat therapy are systems that pump temperature-controlled heated water through a special pad or pads. The pads can be applied to the areas of the body that require heat therapy. A key-operated temperature set point maintains the circulating water at a constant, preset temperature (Fig 110-27).

PERSONAL HEAT WRAPS OR PATCHES–Personal heat therapy products are useful in the management of mild to moderately self-limiting sprains, strains, and chronic conditions. These products contain iron and other natural materials that undergo an exothermic oxidative reaction when exposed to air. These products have been shown to be useful in treating low back pain, neck and shoulder pain, wrist pain, and abdominal menstrual cramps.

PARAFFIN BATHS—Heat also can be applied uniformly to feet, hands, or elbows by using a paraffin bath. By dipping the foot, hand, or elbow into the warm paraffin a number of times, a soft *glove* is formed that will release its heat slowly and uniformly. After the treatment the *glove* is just peeled off (Fig 110-28).

COLD APPLICATION—In deep inflammation the effects of external application of either heat or cold are essentially similar, owing to reflexes arising from the stimulation of the nerves conducting temperature sensation. Experience has shown that there are some conditions (eg, appendicitis) in which the application of cold is more desirable.

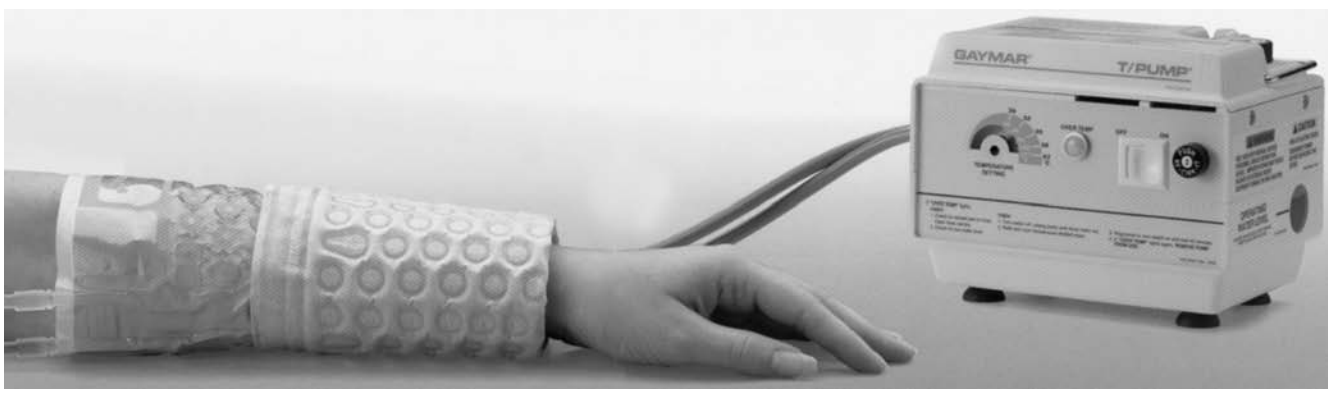

Figure 110-27. Gaymar T/Pump heat therapy system (courtesy, Gaymar Industries).

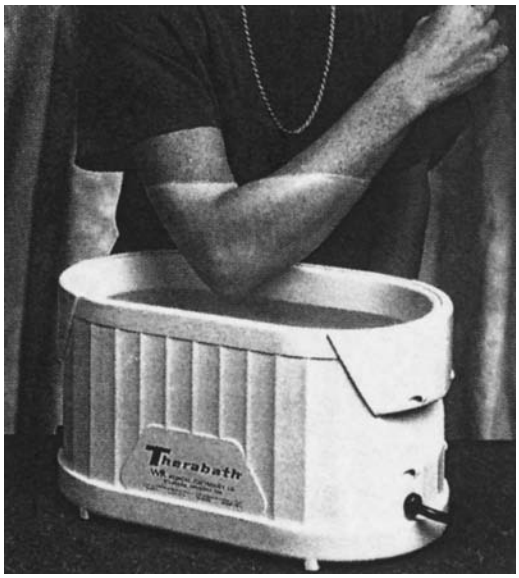

Figure 110-28. Paraffin heat therapy system (courtesy, Therabath).

Appliances for local application of cold are reusable cold packs and the familiar ice bag or ice cap (Fig 110-29). The latter is usually a circular rubber or rubberized cloth bag, circular in shape, with a large opening to admit cracked ice. Occasionally thick rubber, similar to that used in hot-water bottles, is employed. Usually, ice caps require a cover of some type to protect the skin. The contents of an ice cap are less flaccid than the liquid in hot-water bottles. Therefore, thin-rubber or cloth construction is preferable, to ensure better conformation with the body. The pleated shape common to many ice caps avoids bulginess and allows the introduction of large amounts of ice. The English Ice Cap is an example of an ice bag with an cloth, ornamental covering.

An adaptation of the ice cap is used for throat inflammation. It is the collar-shaped rubber bag known as a tonsillectomy bag. It fits snugly around the neck. Ice bags also are made in a long, narrow shape for use around the throat and along the spine.

COLD PACKS—Instead of using ice, some hospitals keep *redi-freeze ice packs* that are stored in refrigerators until needed and are exchanged for bags that have become warm in use. Thus, cold packs are immediately available at all times, and the liquid contents conform more readily to the contours of the body.

Ice packs of soft rubber or plastic, filled with a nontoxic solution of 10% propylene glycol and water, are available in the usual designs. When stored in the freezing compartment of the refrigerator, the contents freeze to a semisolid or slush that provides greater comfort in use and longer retention of cold temperature than ice cubes. Fitted with tabs and tie-tapes, these are available in throat and body shapes.

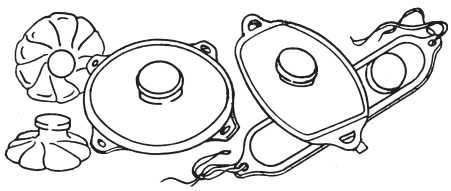

Figure 110-29. Ice caps and bags. *Left,* mackintosh cloth and rubber collapsible ice cap; *center,* ice bags; *right,* spinal and throat ice bags.

In addition, instant hot and cold packs are available that provide a portable modality for heat and cold therapy, ideal in situations when refrigeration or heating units are not accessible. To activate the packs, they are struck firmly, which breaks an inner packet containing an activating fluid. This fluid comes into contact with the base chemical, and the resulting chemical reaction is either endothermic, producing cold, or exothermic, producing heat. They maintain heat or cold for about 30 minutes and then must be discarded.

Another type of cold therapy circulates iced water through a special pad next to the part of the body being treated. Temperature control can be adjusted from 45° to 55°F for continuous use or below 45°F for sessions of 20 minutes or less.

THERMOMETERS

Hippocrates in 460 BC recognized that abnormal human temperature was a disease symptom. In 1610 AD Sanctorius developed the first clumsy oral thermometer. The thermometer was unreliable until 1714, when Fahrenheit developed the first dependable scale and instrument. It had standard gradations, and mercury was used as the heat-measuring liquid. In 1835, two Frenchmen, Becquerel and Breschet, established the mean, or average, temperature of a healthy man as 98.6° on the scale devised by Fahrenheit. A Hollander, Antoon Van Haen, in 1754 developed the first practical clinical thermometer. Thermometers were seldom depended on in medical practice until about 1865, when a Scottish physician named Aitken invented a self-registering thermometer.

THERMOMETERS FOR HOME USE—The types of thermometers usually employed in the home are the *household thermometer,* or common type for reading interior or outside air temperature, and *clinical* or *fever* thermometers (Fig 110-30). The temperature of the atmosphere at the surface of the earth varies more than 200°F, but man's body temperature rarely varies beyond 97° to 104°F, with the portent of danger at either extreme.

The change in temperature of the patient is one of the important symptoms upon which physicians base their diagnoses and treatments. The instrument employed for body- temperature determination is the *clinical,* or more popularly called *fever,* thermometer.

An abnormal temperature is nature's warning sign that something is wrong or amiss. A rapid rise or fall and substantial deviations from normal are danger signals. Every home should have a fever thermometer available at all times.

The essential difference between an ordinary thermometer and one designed for determining body temperature is the self-registering feature of the fever thermometer. When the mercury column has risen to the maximum temperature, it remains until shaken back into the reservoir at the bottom of the instrument. This is due to a constriction that acts as a tiny check-valve in the thermometer bore, just above the bulb, and permits

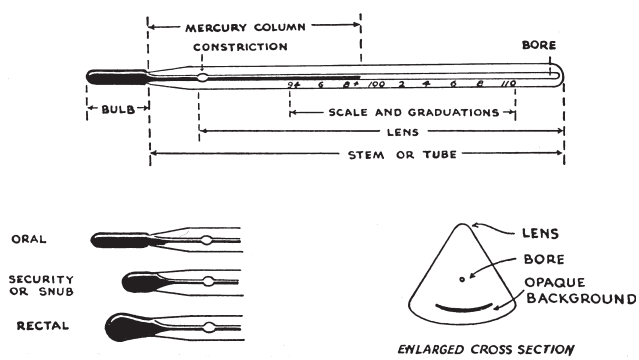

Figure 110-30. Diagram of thermometer construction.

passage of the mercury on expansion but does not permit its return on contraction.

CLINICAL OR FEVER THERMOMETERS—Three bulb types of fever thermometers are available:

The *oral type,* characterized by the slender mercury reservoir, is the most sensitive for mouth use.

The *rectal type* has a blunt, strong, pear-shaped bulb for safety and to ensure retention in the rectum.

A small, sturdy *universal, security, snub,* or *stubb* type with a short, stubby bulb, for oral or rectal use and safer for babies or irrational patients (Fig 110-30).

All fever thermometers have a magnifying-lens front that renders the mercury column visible against an opaque background. Some have a colored line that by reflection helps detect the mercury column, or guidelines that center the eye on the image of the column. Others are flat so that the markings are on the same plane as the mercury when the thermometer is held in normal reading position.

TAKING BODY TEMPERATURE—Fever thermometers should always be sterilized and shaken down below 97°F before taking a reading. For *oral* temperatures, the thermometer should be placed in the mouth, with the bulb under the rear edge of the tongue, and rotated once or twice to ensure complete contact. The transfer of body heat to the thermometer is speeded by then shifting the bulb to the opposite rear edge of the tongue. The lips should be kept closed, and the thermometer left in the mouth for at least 3 min. Regardless of length of initial oral exposure, it is always well after the initial reading to return the thermometer to the patient's mouth for another minute, to provide a check or verification of the original reading. Oral temperatures should not be taken for 30 minutes after exercising, smoking, eating, or taking hot or cold drinks.

Rectal temperature should be taken only with a rectal or stubby bulb thermometer. The bulb should be lubricated with a water-soluble jelly and gently inserted deeply enough to pass the constricting muscle, leaving about half the thermometer exposed. Babies should be held firmly face down, their buttocks separated with one hand, and the thermometer held in place with the other. The thermometer should be left in place at least 4 minutes.

A longer time may be necessary for temperature readings if the thermometer is cold or if the patient is anemic or aged, with poor blood circulation. Axillary (underarm) temperature measurement is not recommended except when all other methods are impossible.

NORMAL TEMPERATURES—The average normal oral temperature is 98.6°F, but some variations are natural. Healthy persons may have temperatures as much as 1°F above or below the average normal temperature. One's temperature may range from about 97.3°F at 2 to 5 am to about 98°F in the morning and to about 99°F in the late afternoon. One should determine his or her normal temperature by a series of readings while in good health, for comparison as a personal standard when one is ill.

Normal rectal temperatures are usually 1°F higher, or 99.6°F, though the *normal* mark on all types of fever thermometers, including the rectal type, is at 98.6°F.

BASAL TEMPERATURE GRAPH—A woman who wishes to become pregnant may increase her chances of conception greatly by having intercourse at the time of ovulation, or she may decrease the chance of contraception by avoiding intercourse then. She may use her knowledge of the fertile interval for avoidance of conception for some time by natural means, then use it for a planned pregnancy *(natural child spacing).*

Basal temperature graphs are helpful in determining whether and when ovulation occurs. Ovulation is the release of an egg (ovum) from the ovary; ordinarily it occurs only once in each menstrual cycle. Conception can take place only if intercourse takes place at or near this time, during the interval of transition between low- and high-temperature levels.

The basal temperature graph reflects slight body changes taking place during the menstrual cycle; charts for plotting the daily temperatures are available from Schering, Becton-Dickinson, and elsewhere. The *basal resting* temperature in the first part of the cycle is usually well below normal; in the last 2 weeks or so of the cycle the basal temperature is closer to 98.6°F. Most important, *the shift from the lower to the higher temperature occurs about the time of ovulation* (Fig 110-31).

The variations in the temperature before and after ovulation are slight, often only a few tenths to a half degree, so it is important that the temperature be taken carefully and recorded accurately. Special thermometers are available for this purpose. They record temperatures within the usual range of cyclic variations (from 96° to 100°F only) and are graduated in tenths of a degree and are easier to read than the ordinary fever thermometers, although the latter may be used.

TEMPERATURE COMPARISONS—Throughout the US the Fahrenheit scale still is employed, although the use of the Celsius scale is increasing rapidly in medical circles. Some hospitals and physicians prefer the latter scale, and clinical thermometers graduated in Celsius degrees are available. Normal body temperature on the Celsius scale is 37°. A comparison of temperature equivalents of the two scales, in the range of body temperatures below and above normal, is given in Table 110-1.

ACCURACY—The critical factors in obtaining maximum accuracy are that the thermometer must be designed properly, it must be sufficiently accurate to meet each specific requirement, and it must be used properly.

In general, the accuracy of fever thermometers is established either by federal standards, or by states, local authorities, and sometimes private institutions, usually operating for hospital groups.

Thermometers offered for sale that exceed the standards usually bear specific information on the certificate indicating special accuracy or selection for other factors beyond the minimum requirements. They are valuable for critical temperature use, such as in diagnosis of certain pulmonary diseases and infectious diseases, both surgical and medical, and for basal-temperature studies, now being used widely in the study of human fertility.

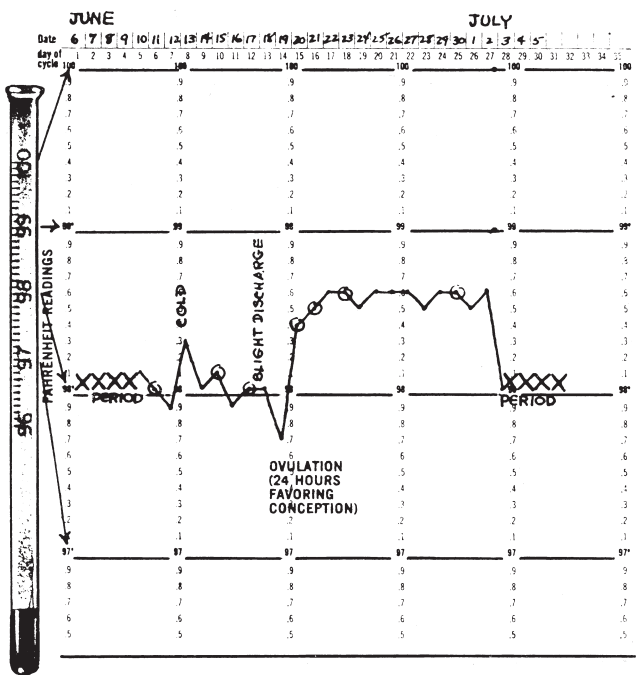

Figure 110-31. Basal temperature graph for determination of ovulation period in the female.

Table 110-1. Temperature Comparison

FAHRENHEIT	CELSIUS
96.0	35.55
97.0	36.11
97.6	36.36
98.0	36.65
98.6	37.0
99.0	37.22
99.5	37.50
100.0	37.77
101.0	38.33
102.0	38.88
103.0	39.44
104.0	40.0

READING THE THERMOMETER—Next to accuracy, the most important feature of a fever thermometer is its ease of reading. This is especially true for the inexperienced home user, who will appreciate being shown thermometers with easy-reading features, as offered by many manufacturers. Always demonstrate how to hold the thermometer for reading, which should be done with the back to good light and the instrument held horizontally in the right hand, about 12 inches from the eyes. The bulb should never be held while reading, but the thermometer may be steadied by the left-hand index finger placed behind it. With the markings to the front, the thermometer should be rotated slowly until the mercury is visible.

CARE OF THE THERMOMETER—After the thermometer has been read and the temperature recorded, it always should be shaken down so that it is ready for use the next time it is needed. In shaking down the mercury column, the thermometer should be grasped firmly between the thumb and the forefinger at the scale end and shaken vigorously by several snaps of the wrist until the reading is below 97°F. This is effective, and a good way to describe this method is to liken it to shaking water off the bulb, which the customer can visualize. The thermometer should *never* be held in the fingers while the hand is struck upon a solid surface to jar down the mercury column. Such rough handling is almost certain to cause a breakage or rupture of the constriction, even though it may appear unbroken. If dropped, even though apparently unbroken, the thermometer should be tested before using. Fever thermometers should never be exposed to heat, the sun's rays, or a heat unit or be displayed in a pharmacy display window.

Currently, there are also available a variety of low-cost, battery-operated electronic fever thermometers, with a visible gauge, that sell for under $10. The most popular is the digital type (Fig 110-32); however, models with analog indicators are available. This type of thermometer gives precise temperature readings within a minute and is safe to use. Most have a *peak hold* feature, so that the maximum temperature attained can be read, and use disposable probe covers for sanitation.

A thermometer designed to make quantitative temperature measurements directly from the surface of the skin has been developed at the University of Colorado, Craig Rehabilitation Hospital. Known as a temporal scanner, this instrument is accurate to within one-tenth of a degree when measuring the difference in heat generated by an arthritic joint and that generated by a healthy tissue. Its probe is about 6 inches long and has about a 5/8 inch diameter. Its hollow aluminum barrel holds a spring mechanism—like a ballpoint pen—that permits the user to exert uniform pressure when measuring skin temperatures.

The new tympanic thermometer (Fig 110-33) can be used on virtually every patient, newborn to elderly. The contoured safety probe of the thermometer is placed snugly into the patient's ear. A sensor on the tip of the probe measures the infrared emissions from the tympanic membrane. The thermometer converts this information into an accurate temperature reading and displays it on a clear liquid-crystal display (LCD) panel in approximately 3 sec.

Color-change thermometers are easy to use, but frequently inaccurate and unreliable. The thermometer is an adhesive strip placed on the skin, usually the forehead, and a heat-sensitive material in the strip changes color in response to the temperature gradient. Skin temperature does not always reflect core temperature, however, and may be influenced by a variety of factors such as the environmental temperature and skin perfusion.

BLOOD-PRESSURE MONITORS

While pharmacies near hospitals and in clinics or large professional buildings have long sold stethoscopes to doctors and nurses and sometimes to patients, increased public interest in health and fitness in general and hypertension in particular has created an ever-growing interest in blood-pressure monitoring devices. Once plain, nurses' stethoscopes now come in many colors and styles, and the sale of stethoscopes and replacement chestpieces, tubing, diaphragms, and eartips to nurses not only brings in additional revenue but also introduces them to all the other health-related accessories offered by the pharmacy.

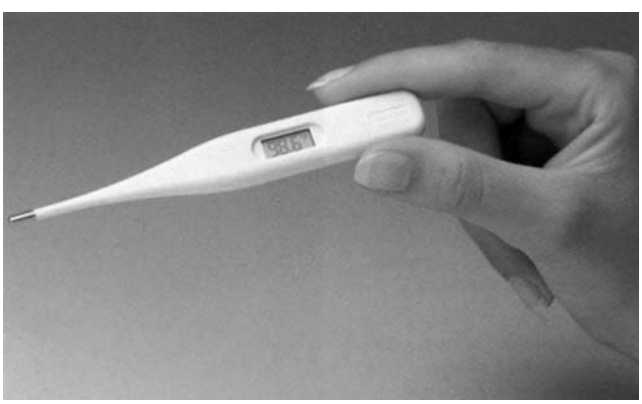

Figure 110-32. Digital electronic thermometer (courtesy, Omron Healthcare).

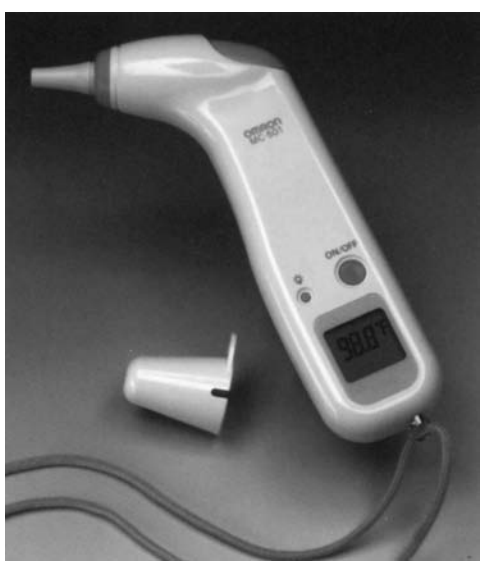

Figure 110-33. Tympanic thermometer (courtesy, Omron Healthcare).

Desk-type mercury sphygmomanometers are still used in professionals' offices, but aneroid models are much more popular. Inexpensive self-taking aneroid models can be purchased for home use. More expensive digital models are available and easy to use, and some even come with printers. Other digital models take systolic and diastolic measurements from the index finger or from compact wristband monitors (Fig 110-34).

A pharmacist can highlight the blood-pressure monitor department by offering free blood-pressure screenings, either on an as-needed basis or specifying a certain morning or afternoon each week. Training in proper techniques for measuring blood pressure may be offered by a local chapter of the American Heart Association.

After taking a subject's blood pressure, the pharmacist or a properly trained associate may choose to record the measurement on a folding wallet card (Fig 110-35). The patient can be advised to return at regular intervals for further readings or encouraged to consult a physician if appropriate. By having the pharmacy name and logo on the opposite side of the folding card, patients are carrying a reminder of the pharmacy in their wallets. Also, if patients show the readings to their physicians, physicians may become more aware of the professional level of services provided by the pharmacy.

Name _____

DATE	TIME	BLOOD PRESSURE	INITIALS
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Figure 110-35. Wallet blood-pressure record card.

BLOOD-GLUCOSE MONITORS

A pharmacy can expand its services to diabetic patients by offering blood-glucose monitoring devices and providing training in proper usage. Models are available that are inexpensive and easy to use at home. Ongoing purchases of the test strips and other supplies used with these monitors can provide opportunities for patients to return to the pharmacy on a regular basis. For more detailed coverage of these devices, their usee and maintenance, the reader is referred to Chapter 125.

TENS

Transcutaneous electrical nerve stimulation (TENS) is an electrical method of controlling pain. It is a safe, nonaddictive, and noninvasive alternative to drug therapy. A TENS unit delivers mild electrical signals through the skin to the underlying nerves to relieve pain by blocking the pain message before it reaches the brain or by causing the body to release pain-relieving endorphins.

A small battery-powered stimulator generates low-intensity electrical impulses to electrodes adhering to the skin. A physician or therapist will determine the stimulation parameters. The pharmacist (who has been trained in TENS usage) will instruct the patient in placement of electrodes and use of lead wires to connect the electrodes to the unit, give instructions on adjusting the level of intensity and the treatment schedule, and advise the client on proper skin care.

Also available are muscle stimulators, which use an electric current to stimulate an atrophied or weakened muscle. This should be done in conjunction with a physical therapist, under the direction of a physician.

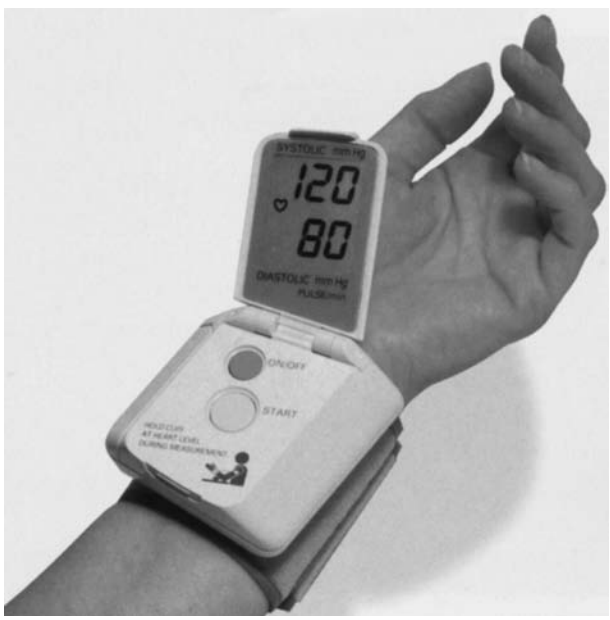


Figure 110-34. Wrist blood-pressure monitor (courtesy, Omron Healthcare).

BREAST PUMPS

Every year more working mothers who want to continue breastfeeding their babies when they return to work after maternity leave are learning of the availability and advantages of breast pumps. The emergence of women's health issues in the public consciousness has led many employers to accommodate the needs of new mothers who need to breast pump during the workday.

Breast pumps may be used occasionally, as in a day or evening away from the baby, or more regularly, as by a mother who pumps once or twice a day while at work. Babies who are unavailable for any feedings for a period of time (such as premature babies kept in the hospital after the mother is released) may necessitate the mother breast pumping until the baby comes home.

Simple manual pumps are available for occasional use. Electric pumps, including models with convenient compact carrying cases, are recommended for regular pumping. The electric models also can be used with time-saving double-pumping kits that pump both breasts at the same time (Fig 110-36).

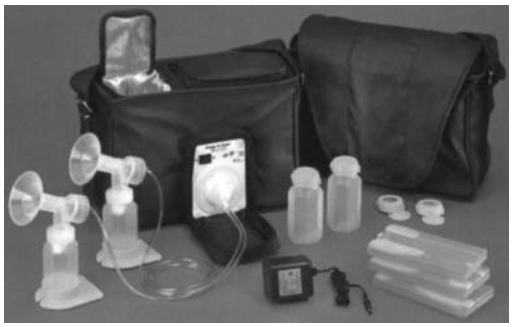


Figure 110-36. Breast pump (courtesy, Medela).

VACUUM CONSTRICTION DEVICES

A nonsurgical solution to impotence is vacuum constriction therapy. Many men are silent, embarrassed, or uneasy about discussing their impotence. Pharmacists can provide the confidential and professional advice essential for the successful use of these devices.

Impotence may result from inadequate blood flow into the penis and/or the inability of blood vessels to retain the blood flowing into the penis. *Osbon Medical Systems* defines therapy as follows: Vacuum constriction involves placing the penis in a patented vacuum cylinder. An erection is achieved by creating a vacuum that generates blood flow into the penis, causing engorgement and rigidity. Similar to the natural erection process, blood flow from the penis then is reduced, using a simple retention device. In this manner an erection can be maintained safely and easily for up to 30 min (Fig 110-37).

IV PHARMACY

Historically, parenteral preparations (see Chapter 41) and IV admixtures (see Chapter 42) were not a normal component of community pharmacy practice. With the rapid increases both in technology and in the demand for care in the home, many pharmacies now prepare and dispense enteral nutrient solutions and IV solutions such as antibiotics, TPN (total parenteral nutrition), biological modifiers, and other IV solutions.

Figure 110-37. ErecAid System Classic, ErecAid System Esteem battery and manual models, and Easy Action ring applicator (courtesy, TIMM Medical Technologies).

Because of technological advances, many of the functions of providing IV therapy that traditionally have been provided in a hospital setting can now be replicated in the home, up to and including the complex therapy required by a patient who has been discharged from a hospital after a bone marrow transplant.

Different types of infusion pumps also may be supplied by the pharmacist. Newer models are able to provide for continuous flow (hydration), intermittent flow, or PCA (patient- controlled analgesia). With an intermittent flow, the home-care nurse, on a once-a-day visit, could set the pump to provide a 1-hr medication flow every 4 or 6 hr, or however the physician directs, often with a *keep open* between treatments. Thus, exact treatment schedules set by the physician can be maintained. A pump with a PCA function also should have a lockout device so that patients cannot give themselves more than a specified number of doses within a predetermined time-frame. Some pumps can be connected to a modem so that a pharmacist or nurse off-site can change the dosage. Pumps may have video screens (which can be connected to a laptop computer or a printer) that can monitor how often PCA patients give or attempt to give themselves more medication.

Pharmaceuticals given IV always should be provided with the assistance of a home-care nurse (either on staff or from a home-nursing agency). It is essential that there are always open lines of communication between the physician, the pharmacist, and the home-care nurse.

OSTOMY APPLIANCES AND SUPPLIES

UNDERSTANDING THE OSTOMY—An ostomy is a surgical procedure whereby parts of the intestinal and/or urinary tract are removed from the patient, the remaining end(s) then are brought to the abdominal wall and a stoma (Gk, mouth) or artificial opening, is constructed surgically through which urine or feces will pass from then on.

It is estimated that more than 80,000 such operations are performed annually in the US, most resulting in the saving of lives. There are approximately a million Americans now living who have had such surgery, and each one of them is buying appliances and supplies on a regular basis.

Because the pharmacist will be called on to offer advice to ostomy patients as to the kind of appliance that will best serve their needs, and because there are many different kinds of ostomy surgery, each of which has its own special requirements as to the fitting and type of appliance best suited to it, it behooves pharmacists who wish to develop a successful ostomy section in their health-accessories departments to become familiar with every type of surgery and the idiosyncrasies of each.

One could develop three basic classifications of ostomy surgery: those that involve the intestinal tract, those that involve the urinary tract, and those that involve both.

Among the surgeries that involve the intestinal tract, there are two types. If the ostomy results from part of the colon being brought to the abdominal wall for the surgical construction of a stoma, the operation is called a *colostomy*. If, on the other hand, the ostomy results from part of the ileum being brought to the abdominal wall for the construction of a stoma, the operation is referred to as an *ileostomy*. The differences in the appearance of these two categories consist primarily in the sizes and locations of their stomas.

Stoma is the name given to the artificial anus on the abdominal wall; it has the appearance of a small bud. A good stoma stands at least 1/2 inch above the skin and is usually pink to bright red, although stomas vary in color and sometimes appear darker. While most stomas do not protrude more than about 1/2 inch, there are some that may have been constructed so that they protrude an inch or more. But a pharmacist who observes a stoma that protrudes more than 1 1/2 inch

should question the patient as to whether it was that long shortly following the surgery. In cases in which the length of the stoma has changed drastically since the surgery, the chances are that it has become prolapsed, and the patient should be advised to consult his/her physician for possible corrective surgery to avoid the potentiality of strangulation of the intestine. It also is possible for a stoma to *shrink* back into the body. When it becomes inverted, management can become very difficult, and corrective surgery may be indicated. Also, corrective surgery may be necessary if intestinal stomas become too small. An indication that this is happening might be a patient needing appliances with smaller and smaller openings.

Stomas appear red because surgeons invert the end of the intestine slightly when they bring it to the outside of the abdominal wall. After suturing the intestine to the abdominal skin, it becomes an integral part of the body wall, and all tissues live normally. Actually, the red surface of an ostomy stoma is the intestinal capillary bed; it stays red because blood continues to flow through it. As it is also a mucous membrane, it will continue to stay wet.

As most ileostomies result in the entire colon being separated from the small intestine at a point just behind the ileocecal valve (where the ileum joins the cecum), that is usually where the incision is made in the abdominal wall and where the ileum is brought to the outside of the body. The location of the ileocecal valve is near the appendix, in the abdomen's lower-right quadrant, and where an ileostomy stoma typically is located. Because the stoma in an ileostomy is constructed from the small intestine, it will be smaller than the colostomy stoma, which is made from the colon. However, it is important to note that the location of stomas on the outside of the body cannot be standardized as colostomy on the left side and ileostomy on the right side.

Placement of the stoma is determined by body folds, the waistline, bony prominences, old scar tissue, and the person's occupation. The fecal matter or output indicates what type of surgery was performed.

In a colostomy, only part of the colon is removed from the body. The types of colostomies depend upon where the diseased part of the colon is separated from the healthy part of the colon. When only the juncture of the sigmoid colon with the rectum and anus is involved, the surgeon brings the sigmoid colon to the surface of the abdomen and the surgery is termed a *sigmoid colostomy*. When the separation occurs along the length of the descending colon, anywhere between the splenic flexure (the bend where the transverse colon meets the descending colon) and the sigmoid flexure, the operation is called a *descending colostomy*. Accordingly, when the surgeon makes the separation along the length of the transverse colon anywhere between the splenic flexure and the hepatic flexure (where the transverse and ascending colon meet), the surgery is termed a *transverse colostomy;* an *ascending colostomy* occurs between the hepatic flexure and the cecum. Finally, when the stoma is constructed with that part of the colon called the cecum, the surgery is simply called a *cecostomy*.

These five surgeries, while they are all colostomies, are distinctly different from each other in that different lengths of colon remain in patients having different types of colostomies. Because a primary function of the colon is the removal of water from the feces as it passes through it, it is understandable that the feces produced at a cecostomy stoma will be quite loose and watery, while the feces produced at a sigmoid colostomy stoma are generally quite solid. Likewise, the ascending, transverse, and descending colostomies produce feces, within the extremes just described, of varying degrees of consistency. The additional fact that all colostomies, because of the reservoir effect of the colon still remaining, can be managed better than ileostomies in which there is no reservoir remaining has implications for the pharmacist with regard to the types of appliances that are best suited for each type of ostomy.

The implications are that different colostomies in particular, and intestinal ostomies in general, because of differences in fecal products, create nonidentical problems for the patient, i.e., not all colostomies can be irrigated successfully, they require different types of appliances, and they use different kinds of accessories. There is very little difference in the size of the stomas of each of the five colostomies, but they may be located on the abdominal wall differently. Colostomy stomas, which usually are located in the lower-left quadrant of the patient's abdomen tend toward more-solid feces, while those usually located in the lower-right quadrant tend toward feces that contain more water and are, therefore, of looser consistency. The most common reasons for performing a colostomy are cancer of the lower bowel, trauma, and ruptured diverticula.

When the entire colon must be removed, the surgeon performs an *ileostomy* by separating the colon from the small intestine behind the ileocecal valve. The result is a stoma much smaller than any colostomy stoma, located in the lower-right quadrant and producing fecal material that is always loose and watery. Most ileostomies are performed on people between the ages of 18 and 40 and are usually the result of an ulceration of the inner lining of the colon that is called ulcerative colitis.

There are several types of urinary diversions, the most common being those in which the patient's bladder must be removed. The preferred surgical procedure brings the two ureters together, implants them in an artificial bladder, and enables the patient to have but one stoma to manage and one appliance to wear instead of the usual two.

This operation is frequently referred to as an *ileal bladder, ileal conduit,* or *urinary diversion*. All three names indicate the same operation, however.

During this operation, the surgeon removes a piece of the healthy small intestine at the ileum and then performs a resection of the two ends of the ileum, joining them together again. The missing piece is usually between 6 and 8 inches and is a relatively insignificant loss to the small intestine, which measures nearly 24 ft in the average adult. One end of the piece of ileum is closed, and the other is brought to the outside of the body to become the single stoma. Once the two ureters are implanted in the closed end of the piece of ileum, that piece becomes a conduit for the urine—actually a substitute bladder. Because this conduit or bladder is made from a piece of the ileum, it has earned the names ileal conduit and ileal bladder.

The stoma has the appearance of an ileostomy stoma and, usually, is located within the same quadrant, the lower right, but its product is only urine. While most ileostomy stomas are located in the lower half of the lower-right quadrant of the abdomen, most ileal conduit stomas are located in the upper half of the lower-right quadrant. The only way to be sure which ostomy is which is to determine the nature of the waste product.

When the two ureters are severed or cannot be brought forward to the abdominal wall for any reason, the surgeon is forced to bring the ureters to the nearest outside surface—the patient's back. Stomas appearing on the dorsal side or openings through which renal catheters lead directly to the kidneys, indicate an operation called a *nephrostomy*. Persons with bilateral nephrostomies wear two appliances.

In a cystostomy, the bladder wall is brought to the skin, and a stoma is formed. This often is done for paraplegics and quadriplegics. The stoma is just above the symphysis pubis. The stoma for a vesicotomy, in which the urethra is brought directly to the surface of the skin, would be very similar in appearance to that of a cystostomy. Vesicotomies are often temporary operations and are rarely of concern to the pharmacist. There are two other ostomies that are temporary and with which the pharmacist should be familiar. One is a modified kind of descending colostomy in which the lower portion of the descending colon, sigmoid colon, and rectum are not removed from the patient. After the surgical separation is made, both ends of the colon are brought to the outside and two stomas are constructed, one active and the other inactive.

This operation, the *double-barrel colostomy,* results in two stomas, side-by-side, normally located in the lower-left quadrant and producing solid fecal material exactly like the or-

dinary descending colostomy. This condition may last from 1 month to a year or longer, depending entirely on when the surgeon is satisfied that a resection can be performed without further complication. Sometimes the double-barrel colostomy is performed in the hope that the lower bowel can be brought back to normal with treatment and rest. On occasion, a patient with a double-barrel colostomy must return to the hospital for a permanent colostomy.

The second kind of temporary colostomy is called a *loop colostomy*. Normally, patients who have a loop colostomy performed will have the colon repaired and back to normal within a few weeks and before they leave the hospital. Loop-colostomy appliances are applied during surgery by the physician and are the only ostomy appliances that are packaged sterile, besides the common postoperative drain. This ostomy gets its name from the fact that, unlike the double-barrel colostomy, the loop colostomy doesn't result in the complete separation of the intestine but, rather, a loop of intestine is brought through an incision and temporarily is secured to the abdominal wall by means of a plastic or silicone rod that is slipped under the loop and across the incision; the loop then is perforated surgically to relieve the impaction. The wound stays open, and the loop remains visible until the perforation in the intestine is closed and the loop is returned to its normal position within the visceral cavity. It is highly unlikely that a pharmacist will ever be called upon to fit a loop-colostomy appliance although he or she may still want to stock the appliances for use by the hospital.

CHOOSING THE RIGHT APPLIANCE—The various ostomies described above can be grouped into three major categories for the purpose of understanding which kinds of appliances are most appropriate for each.

1. Those ostomies that only produce solid waste at their stomas. They include the sigmoid colostomy, descending colostomy, transverse colostomy, double-barrel colostomy, and often the loop colostomy.
2. Those ostomies that only produce urine at their stomas. They include the cutaneous ureterostomy, nephrostomy, cystostomy, vesicotomy, and urostomy.
3. Those ostomies that, for one reason or another, produce liquid or semisolid fecal matter at their stomas. They include the ileostomy, cecostomy, ascending colostomy and sometimes the loop colostomy.

In real life, neat and perfectly reliable categories such as the ones just described do not exist. People differ, their digestive processes are different, and their diets are different. The consistency of the waste matter in any one individual also varies from day to day. Yet these categories are useful generally, and in addition, they point up the fact that an appliance should be chosen primarily for the nature of the waste matter it will have to collect.

Further, the groupings do indicate that among a host of ostomy appliances presently on the market from numerous manufacturers, there are just three basic types, categorized primarily by the nature of the waste material for which they are intended: those designed for pure urine, for semisolids, and for solid waste matter. Other considerations in choosing the right appliance for each patient include the size of gasket openings that fit around the stoma, method of attaching the appliance around the stoma, patient's financial resources (including what reimbursement limits may be placed either on types, quantities, or cost of appliances by government agencies such as Medicare and medical-assistance programs or by HMOs or insurance companies), and activities in which the patient engages at work or at play (Fig 110-38).

OSTOMY APPLIANCES FOR SOLID WASTES—The colostomy appliance, so-called because most colostomies are solid-waste-producing, is the appliance used for most colostomies. There are many types of colostomy appliances on the market, recognizable by larger-size gasket openings to accommodate the larger stomas characteristic of all colostomies and by detachable, throwaway pouches made of thin polyethylene plastic; some are sealed at their bottoms. However, some

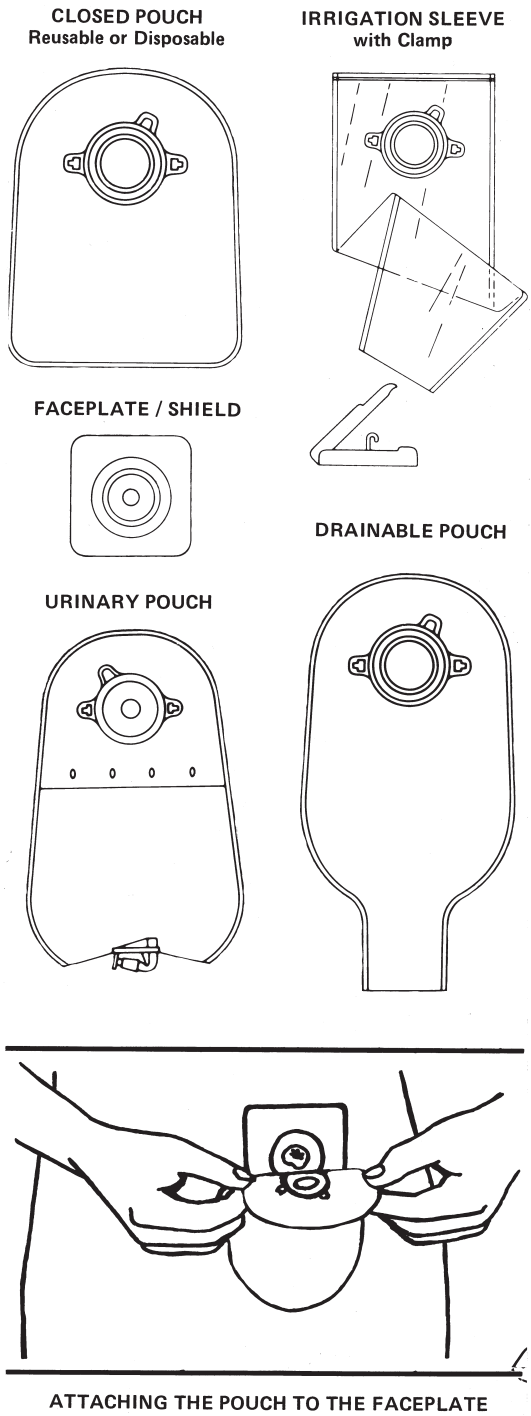


Figure 110-38. Ostomy appliances (courtesy, Convatec).

colostomates do use open-ended pouches. The fact that these pouches are sealed at the bottom and are disposable indicates the impracticability of bottom drains for solid wastes generally. By and large, colostomy appliances are not the permanent type, since the ostomies that produce solid wastes do not cause the problems with skin excoriation typical of the wetter ostomies.

The self-adhesive colostomy appliance is more of a collection bag with adhesive around the stoma opening than it is an appliance. The openings may be cut with scissors to fit the stoma precisely, though most manufacturers provide several sizes. The advantages with this type of appliance are that it is

lightweight and quite flat against the body so it is less likely to show through clothing. Those colostomates who irrigate regularly find this type of appliance perfect for safety's sake.

Some colostomates are urged by their physicians to irrigate on a regular basis. Irrigation is the process of administering an enema to the colon via the stoma for the purpose of establishing regular, conveniently timed, evacuation of the bowel—in other words, to become relatively stool-free. It is necessary just once a day at the most and may be scheduled in the morning before dressing or in the evening before retiring. It is a highly individual thing, and some persons need to irrigate only every other day or two to three times a week. Some persons have quite irritable bowels and cannot remain stool-free.

After irrigation, the colostomate can expect to have no bowel activity until the next irrigation, except perhaps for slight dripping now and then. Many ostomates, after irrigation, wear only a gauze pad over the stoma for safety and psychological confidence. The pad can be taped over the stoma or secured with a two-way stretch wraparound.

The irrigation process is quite simple and takes up to an hour for completion. The important steps include:

The stoma should be dilated with a gloved finger (finger cot) and a bit of lubricating jelly prior to insertion of the irrigator cone.

About 1 quart of tepid water (some patients add a couple of tablespoons of salt) is placed in the irrigating bag—never hung more than head high. About 15 min should be allowed before permitting evacuation; after the initial gush it normally takes another 20 to 25 min before the colon is really empty.

Most people close the end of the irrigating sleeve with a clamp and then shower or shave during this period.

Sometimes drinking a cup of strong black coffee or a glass of ice-cold water will start the intestinal peristalsis necessary for complete evacuation.

Irrigation is a technique for accomplishing regularity and security throughout the day but is only useful in those ostomies that produce solid wastes. Many physicians and enterostomal therapists now are recognizing the importance of diet in gaining control and regularity of bowel movements and irrigation. The question of whether or not a particular colostomy patient should irrigate should be answered only by the physician or enterostomal therapist (ET) nurse. Irrigation usually is not advised when the possibility of reconnecting the intestine at a later date exists.

APPLIANCES FOR URINE AND SEMISOLIDS—The appliances used for urinary diversions and ileostomies are both similar to the appliances used for colostomies (Fig 110-38). A notable difference is in the size of the stoma openings (because urostomy and ileostomy stomas are usually much smaller than colostomy stomas). Also, since the discharge from either a urinary diversion or an ileostomy is more liquid than that from most colostomies, there is more often a need for skin barriers and protectants such as karaya, Stomahesive, and similar products to maintain a waterproof seal.

The real difference between a urinary appliance and an appliance for semisolids is in their bottoms, however. Where the urinary appliance has a nylon twist-drain plug in the bottom, the *ileostomy* appliance merely narrows down to between 1½ to 2½ inches and is just open. The bottom is closed with a clip. To drain, the clip is removed, and the bottom of the appliance unfolded.

Different manufacturers make appliances that, although basically similar in design or function, differ with respect to method of securing to the skin. In the past, urinary and ileostomy appliances often were made of rubber and secured to the skin with adhesives. Periodically, these appliances had to be removed, often with the help of an adhesive remover. The appliances then had to be cleaned, dried out, and reapplied. Some ostomates still use permanent appliances of this type, but most new ostomates choose the disposable type.

OSTOMY APPLIANCE ACCESSORIES—Most popular among a host of accessories for ostomy appliances of all kinds are pectin-based or karaya gum washers, Stomahesive powder, and Stomahesive and similar barrier pastes. These pastes can be used to fill in irregularities in skin surfaces to protect against leakage.

Varieties of deodorant drops, tablets, and sprays are available; some are applied to the outside of the appliance, while others are dropped into the bag prior to applying it. Most ostomy appliances now have odorproof barriers. Silicone and benzoin tincture sprays also may be used to prepare the skin around the stoma. In addition, racks for drying an appliance after washing, abdominal dressings and cover sponges, gloves and wipes, and even zippered, purse-size pouches for supplies are available to make things easier for the ostomate. Some manufacturers now offer new easy-to-apply appliances featuring synthetic materials to reduce skin irritation and prevent leakage.

But perhaps the most helpful things that pharmacists can provide their patients who have ostomies are suggestions and ideas on how to manage themselves with a minimum of difficulty. Knowledge of these things will come from the ostomates themselves, and it is therefore wise to spend some time asking them questions. It is also important for a pharmacist featuring ostomy-care products to develop a good working relationship with an ET, a nurse specially trained in ostomy care. The ET can advise the pharmacist or the patient when unexpected problems occur. Membership in a local ostomy club or the United Ostomy Association is another way to increase your knowledge of the problems ostomates often encounter.

UROLOGY AND INCONTINENCE SUPPLIES

URINALS—These containers are employed to collect urine. They differ in shape according to male or female use. They ordinarily are made of white enamelware or plastic, which is by far the most common, especially for use at home. Plastic urinals come in two basic types: single-patient use or autoclavable.

CATHETERS—To collect urine from the patient unable to void naturally or when incontinence pants and external catheters are inadequate, indwelling catheters are employed.

The insertion of catheters is a dangerous procedure, customarily handled by physicians or trained nurses and orderlies. Serious infections of the bladder and damage to the urethral and bladder tissues may result from improper insertion.

Flexible soft-rubber catheters consist of small rubber tubes with a closed solid tip. At one end is a flaring funnel-shaped opening to facilitate attachment of the catheter to a plastic junction or another tube leading to a collection unit. At the inserted end is a wide opening that leads to the channel through which urine flows to the collection unit. This is referred to as a straight catheter, in contrast to the indwelling catheter, which is designed to remain in the urethra for long periods of time.

The indwelling retention catheter, or Foley catheter as it is commonly known, is characterized by a balloon at its insertion end (Fig 110-39). The balloon is designed to secure the catheter tip within the patient's bladder to keep it from slipping or being pulled out. There are two channels that run from the insertion tip to the end of the Foley catheter—one for the passing of urine and the other for the injection of sterile water that inflates the balloon.

Foley catheters are available with either 5- or 30-mL balloons. The 30-mL balloon catheter, which also is known as a hemostatic catheter, is used commonly in nursing homes for patients whose urethras have become dilated or for those patients who have pulled the 5-mL balloon catheter out. A common

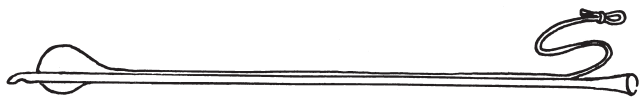


Figure 110-39. Balloon catheter, for prolonged insertion through the urethra into the bladder.

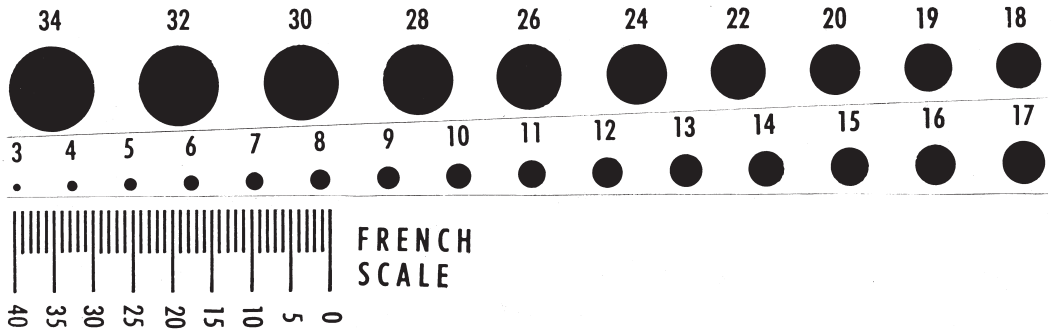


Figure 110-40. Standard French scale for hospital tubing and catheters as well as rectal and colon, stomach-feeding, suction, urinary drainage, and oxygen tubes (courtesy, Becton-Dickinson). To determine the French size if instruments are oval or other shape, use a strip of paper to measure the periphery—then lay on the scale at the left.

mistake in filling a balloon catheter is to use too little water. It takes about 10 mL to inflate a 5-mL Foley balloon because nearly 5 mL is held in the filling lumen that runs the length of the catheter. The diameters of the catheter also vary in size. Though their use is limited somewhat, 75-mL balloon retention catheters are also available. The French scale is employed most commonly (Fig 110-40).

Other innovations in the urinary catheter include a Foley catheter with its own supply of sterile water for balloon inflation. With these catheters, a valve is released following insertion of the catheter, and the sterile water, which is under pressure, runs up its channel and inflates the balloon. They are especially convenient, as there is no need to prepare a syringe for balloon inflation, but they are considerably more expensive than the typical Foley catheter. Another improvement is the silicone and Teflon coatings on the outside and inside of Foley catheters. Such coatings not only cut down friction during insertion and removal of the catheter, but also inhibit buildup of deposits on catheter walls, thus extending the time between catheter changes and reducing irritating infection and leakage problems. The newest improvement is the all-silicone catheter, now manufactured by Kendall, Bard, and others.

The pharmacy also may stock a variety of urine-collection units and catheter administration trays. The bladder-care tray, sometimes called a *cathtray,* is a sterile package containing the items required during the administration of a Foley catheter, packed sequentially with those things needed first on top.

Male condom catheters and female external catheters are designed to be worn by the patient. They allow mobility and discrete urinary collection without the use of pads or an indwelling catheter. These external types of collection systems are becoming more widely used and are available in a number of different styles. The style selected is usually a matter of personal preference, activity level, and size and capacity requirements.

The male condom catheter system consists of two parts: the penile sheath, which resembles a condom with a drainage opening, and a collection bag. The single-use condom catheter may be self-adhesive or attach with an adhesive foam strap. The reuseable style is secured with an adjustable rubber or foam strap worn over the catheter. These are not as secure, but are considerably more cost-effective.

External female catheters are not reliably successful in containing urine. The device consists of a pouch with a sticky wafer that is attached to the vulva; the end of the pouch is connected to a larger drainage bag.

Condom catheters have distinct advantages over other incontinence management methods. Since they are not inserted into the bladder, the incidence of infection is reduced greatly. And since the urine is conveyed to a collection bag, the problems of odor and skin breakdown associated with diapers and absorbent pads are minimized.

It is advisable for the pharmacist to inquire as to whether the patient has an allergy to latex. Finding the right urological products is a big problem for patients with latex allergies.

URINARY BAGS—There are two basic types of urinary bags: leg bags and night urinary collection bags. Both can be used with external or indwelling catheter systems.

Leg bags vary in size and capacity and are used by a patient who is ambulatory. The bag is connected to the catheter by a length of plastic or rubber tubing (usually sold separately). The bag itself is worn on the inside of the thigh or lower leg, whichever is most comfortable and least conspicuous. It is secured in place by use of adjustable elastic straps. A common error is to fasten the leg straps so they encircle the bag, thus restricting its volume.

Night urinary collection bags vary in style. The standard is a bag that hangs from the side of the bed or the back of the wheelchair. The standard capacity is 2000 mL. Night bags are also available in a cube or a bottle form.

INCONTINENCE PANTS—A variety of body-contoured incontinence pants are available for both men and women. Disposables are the most popular, with a variety of absorbancies being available.

Other products helpful for the incontinent patient include disposable underpads, adult diapers, rubber sheeting, silicone skin sprays, and body lotions and deodorants. Perineal washing solutions are available for cleaning skin. Their advantages are deodorizing, disinfecting, and maintaining the skin's normal acidity and moisture content and ease of use. The skin may be protected with skin barriers.

TRUSSES

Hernias and trusses are as old as mankind. A truss is defined as a supportive device, usually consisting of a pad with a belt, worn to prevent enlargement of a hernia or the return of a reduced hernia. A hernia is defined as the protrusion of an organ or bodily structure through the wall that normally contains it.

The first trusses were nothing more than a rope or strap and a rock. Celsus developed the use of a plate, and in medieval times a form of plaster and plate were used. The spring-and-belt-type truss, practically as it is today in principle, was developed by the Netherlands physician Camper in 1785.

There are several types of hernias. One is the protrusion of the intestine and its surrounding membrane, the peritoneum, through a natural opening in the abdominal wall and may be inguinal, scrotal or femoral, depending upon the site of the protrusion. Other hernias, incisional hernias, are the result of a protrusion through the muscles of the abdomen usually occurring at a point previously weakened. An incisional hernia occurs at the site of a previous surgical incision. The natural openings in the abdominal musculature through which a true

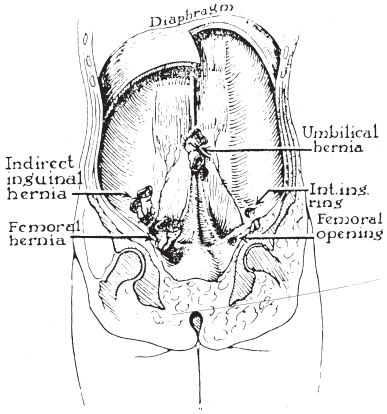


Figure 110-41. Looking toward the front of the abdominal wall, from within the cavity, showing the five congenitally weak points.

hernia may occur include the umbilical opening; the inguinal openings, through which, in the male, the spermatic cord passes, and in the female, the round ligament passes; and the openings for the femoral arteries (Fig 110-41).

Abdominal or umbilical hernias are common. Infants in the first year of life show an incidence of 19.6/1000. Between ages 20 and 24, the incidence is lowest, rising to 24.2/1000 in the 70- to 74-year age group.

Of all males afflicted with hernias, 96% suffer from the inguinal type. The corresponding incidence of inguinal hernias among females is just 44.3%. While surgery is the preferred treatment for all hernias, it is not always the best solution for all patients. Some will require trusses in lieu of surgery.

Hernia trusses of all kinds vary from soft-fabric supports (not actually capable of holding a true hernia!) to models containing a metal or steel band and requiring experienced judgment on the part of the fitter. The type and location of truss pads and the weight and build of the patient are important considerations in truss fitting. All trusses should be fitted while the patient is lying down and the hernia is reduced (the protruding intestine has been returned to the abdominal cavity) or the truss itself may cause strangulation.

A well-fitted truss, appropriate to the specific patient and the specific type of hernia, may be tested by having the patient bend, stoop, and cough. If the patient can do those things without having a protrusion of the intestine past the truss pad, it is likely that it is fitted properly. Finally, it is important for pharmacists to teach patients how to properly put on the truss and test its security while they are in the fitting room, so they can remove it with confidence when they are on their own.

FITTING SCHOOLS—The pharmacist who will be in charge of the truss and orthopedic department should attend a fitting school. This may require time and travel, but it basically trains the pharmacist in the anatomy involved, and appliance selection and fitting skills, which are absolutely necessary. Several good schools are conducted by surgical-appliance manufacturers and typically run 3 to 5 days. Such programs are presented by the Camp Institute of Applied Technology, Surgical Appliance Industry, Freeman, and others. Professional organizations such as the National Community Pharmacists Association (an ACPE provider) also conduct continuing education programs.

No pharmacist or pharmacy employee should attempt any truss or orthopedic fitting involving shaping metal without proper training.

Attendance at one of these schools provides background on the definition, location, varieties, frequency, symptoms, causes, complications, and treatment of conditions that could result in the use of these types of surgical appliances:

Orthopedic corsets
Spinal braces
Cervical collars and braces
Knee, ankle, and foot orthoses
Traction equipment
Compression hosiery
Trusses
Mastectomy prostheses
The interested pharmacist should refer to literature available from appliance manufacturers.

ORTHOPEDIC SUPPORTS AND BRACES

The spinal column can be divided into five major sections:

The cervical spine, consisting of 7 vertebrae, supports the head and is characterized by an anterior curve.
The thoracic spine, consisting of 12 vertebrae with a pair of ribs attached to each, is characterized by a posterior curve.
The lumbar spine, consisting of 5 vertebrae, is characterized by an anterior curve.
The sacrum, consisting of 5 vertebrae that are joined so tightly as to appear as one bone, is situated beneath the fifth lumbar vertebra and between the two innominate bones of the pelvis forming the sacroiliac joints and is characterized by a posterior curve.
The coccyx, consisting of 3 to 5 vertebrae is immediately beneath the sacrum and continues its posterior curve (Fig 110-42*A*).

Apart from the cervical spine, anomalies of the spinal column include lordosis, a hyperextension of the lumbar spine recognizable as swayback; kyphosis, a flexion of the lumbar spine and/or hyperextension of the thoracic spine, often appearing as hunchback; and scoliosis, an S-shaped lateral curve of the spine (Fig 110-42*B*). Each of these conditions, in varying degree, often requires use of supportive garments or braces. Sometimes ruptures of the intervertebral discs, the cartilaginous shock-absorbing cushions between separate vertebrae, interfere with the spinal cord or the nerves leading from it. An example is sciatica, in which a ruptured intervertebral disc causes compression or trauma at the base of the sciatic nerve resulting in extreme pain at the back of the thigh and running down the inside of the leg along the course of the sciatic nerve. This condition also may require the use of a spinal garment or brace and, occasionally, the occurrence of spondylolisthesis (the slippage of lower vertebrae usually against the sacrum) will bring the patient to the pharmacy with a prescription for a garment or brace-fitting.

These and other conditions create a need for spinal braces and orthopedic garments to limit motion in the spine and permit healing. While pharmacists should be knowledgeable about them, they should never diagnose such conditions or prescribe

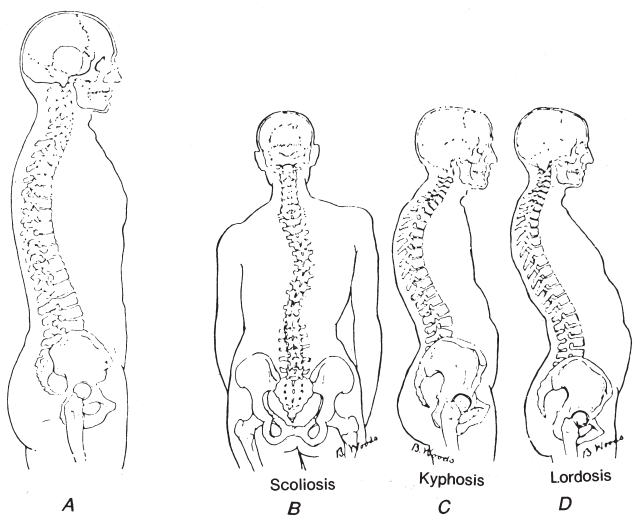


Figure 110-42. *A,* Curves of the normal spine; *B–D,* abnormal curves of the spine.

the wearing of an orthopedic appliance. That should be left entirely to the physician. Unhappy consequences can be avoided and the surgical-appliance business strengthened if the pharmacist will adhere to the simple rule of never fitting any brace or support except on the prescription of a physician.

The most commonly prescribed back supports fitted in a pharmacy setting are the industrial back supports made of neoprene or heavy elastic (sometimes with shoulder straps). They provide support to, and somewhat limit mobility of, the lower spine. Orthopedic back corsets have a back length of 12 to 15 inches and are made of heavy, cloth material or elastic (Fig 110-43). They often feature two or four rigid metal stays that the fitter will shape to the physician's order, usually to the contour of the patient's back. Readymade spinal braces often are similar in principle to corsets but are generally of heavier construction. Braces limit mobility to a greater degree than orthopedic corsets. A custom-made or fitted body jacket would limit mobility even more than a spinal brace. The proper fitting of spinal braces and body jackets would probably require the expertise of a skilled orthotist.

The procedures for fitting different orthopedic supports and braces are quite involved and are better covered in the week-long schools presented by manufacturers than in a few paragraphs in this text.

Conditions affecting the cervical spine often result in a prescription for a cervical collar or brace. The most popular type is a soft-foam collar with a *Velcro* closure. Unless the prescriber specifies flexion or extension, the fitter usually would select a collar that provided support to hold the head in a neutral position. A more rigid plastic collar (Philadelphia type) can be adjusted to the contours of the patient's neck, chin, and shoulders. This type will provide a greater degree of immobilization than a soft collar. Still more immobilization can be obtained by the application of a properly fitted metal cervical brace.

The use of cervical-traction devices also is specified often in the treatment of conditions affecting the cervical spine.

Supports for the knee can vary from a simple pull-on elastic type as found in many pharmacies, to 10- or 11-inch-long braces with shaped metal hinges and leather straps, to complex braces such as an ACL knee orthosis (Fig 110-44).

COMPRESSION THERAPY—Many types of compression hosiery are available in pharmacy health-accessory departments. Lightweight, fashion-sheer elastic hosiery is very popular but does not give as much support as heavier, surgical-weight hosiery. For severe or unusual conditions, custom-made elastic supports for arm or leg (such as Jobst, Fig 110-45) can be ordered. Antiembolism hosiery is intended primarily for bedfast patients.

Taking the patient into a private fitting room, measuring the limb, and then actually applying the hose are the professional activities that will differentiate qualified health-care-accessories pharmacists from their peers. It should be noted that the best time to measure and fit elastic compression hosiery is early in the morning when the affected limb is likely to be the least distended.

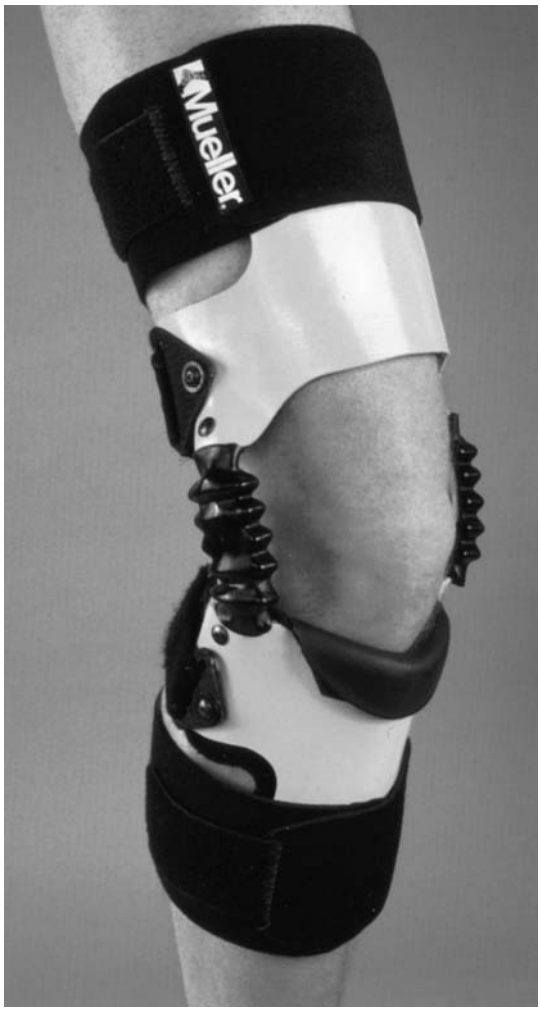


Figure 110-44. Magnum competition ACL knee brace (courtesy, Mueller Sports Medicine).

Figure 110-43. Lumbosacral support (courtesy, Camp).

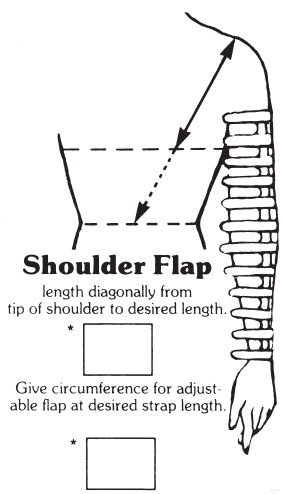
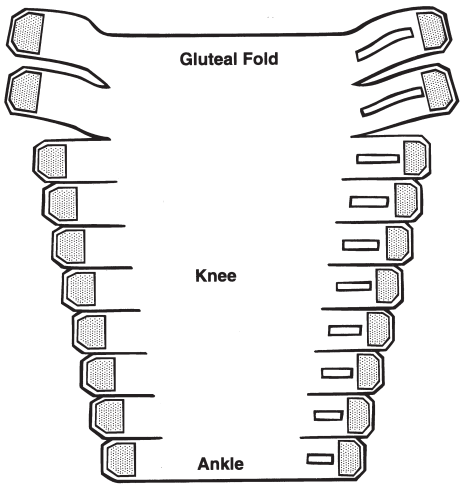
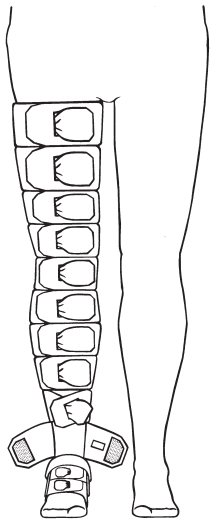


Figure 110-45. Custom-made elastic support (courtesy, Jobst).



Inside view
Quick-Fit Thigh-High Legging



Quick-Fit Thigh-High Legging
with Ankle-Foot Wrap

Figure 110-46. Circ Aid Quick-Fit thigh-high legging (courtesy, Circ Aid Medical Products).

A nonelastic form of compression therapy is the CircAid system of nonelastic, adjustable, interlocking bands that give patients the ability to maintain compression levels regardless of changes in limb size or physical ability (Fig 110-46).

Recent advances in the treatment and management of primary and secondary lymphedema with the use of multicompartmental pneumatic compressors has done much to improve the quality of life for people suffering from lymphedema. Pneumatic compression devices are designed to reduce lymphedema in the extremity by applying pressure sequentially through a multicell pneumatic arm or leg sleeve. The pneumatic sleeve inflates in a distal to proximal direction, promoting the flow of lymph fluid through existing lymphatics by exerting pressure on the interstitial tissue. Because the sequential milking pattern is soothing and comfortable, it results in excellent patient compliance.

To maintain the results obtained by home treatments with a multicell compression device, graduated compression hosiery is recommended. The lymphedema garments should be worn during periods of activity to prevent the rapid reaccumulation of lymphatic fluid. Patients should be measured after they have begun their treatments and have achieved some reduction in swelling. Periodic remeasuring is necessary to monitor further reduction.

In some cases, such as severe edema, the physician also may prescribe a lymphedema pump and sleeve to reduce the edema prior to applying compression hosiery. Usually, pumps are rented, although sales are not uncommon. Lymphedema pumps, particularly the sequential types, should be rented or sold only by qualified professionals who are very familiar with their uses and contraindications.

The Reid Sleeve is an alternative method of providing compression therapy. The Reid Sleeve applies a gentle gradient pressure with a unique, soft-foam insert. Compression is tailored to the patient's needs by a series of adjustable straps. The sleeve easily slides over the affected limb, and then the compression bands are adjusted. A specially designed gage is as easy to use as a blood-pressure cuff. This simple procedure ensures that compression applied to the patient's limb is applied consistently and in the proper range to provide optimal results. Patients can fit the sleeve in minutes without assistance and have the confidence of knowing they are applying the pressure prescribed by their doctor. As the patient improves, the Reid Sleeve can be adjusted to the new arm size, thereby maintaining the proper pressure range (Fig 110-47).

MASTECTOMY PROSTHESES—The fitting of mastectomy prostheses and bras is often a logical adjunct to an orthopedic corset and compression hosiery section in a pharmacy's health-accessories department. It is essential to have a female fitter for this department.

In most cases, breast surgery is the result of breast cancer. Some surgeries, such as a lumpectomy, remove only a portion of the breast. A *simple* mastectomy results in the removal of breast tissue. More-involved surgery results in removal of breast tissue and additional underlying tissue.

A variety of breast forms are available to fit a woman after each type of surgery, although it is often difficult to fit a woman after a lumpectomy. (Note: Male breast cancer, while rare, does occur.) The breast form is designed not only to help restore a woman's shape, but also to replace the weight lost and restore proper balance.

Although more women are selecting reconstruction each year, external breast forms remain a safe alternative. There have been many advances in the technology of manufacturing the forms, resulting in more-comfortable, natural-feeling breast prostheses. Although some forms are made with polyester fiberfill or foam, most are made with silicone. Conventional silicone forms generally are designed to be worn in conjunction with a specially designed pocketed bra that holds the breast form securely in place.

A new development in silicone breast prostheses allows the form to attach safely and securely directly to the chest wall by means of an adhesive skin support. This new option gives a woman greater freedom for an active lifestyle as well as fashion flexibility (Fig 110-48).

THE FITTING ROOM—For such a department, an adequate, private fitting room and stock space nearby are an absolute necessity. The fitting room need be no more than 8×8 ft but should be clean, be free of any stock or display, and have an inward-swinging door to shield the fitting table from view. The fitting room also should be soundproofed to provide privacy and enable a patient to feel comfortable discussing his or her condition. As many fittings are done with the patient in a horizontal position, a table 72 by 26 and 30 inches high, padded with moisture-proof vinyl and a pillow is needed, as well as a chair, coat hooks and clothes hangers, four-legged stool, small dressing

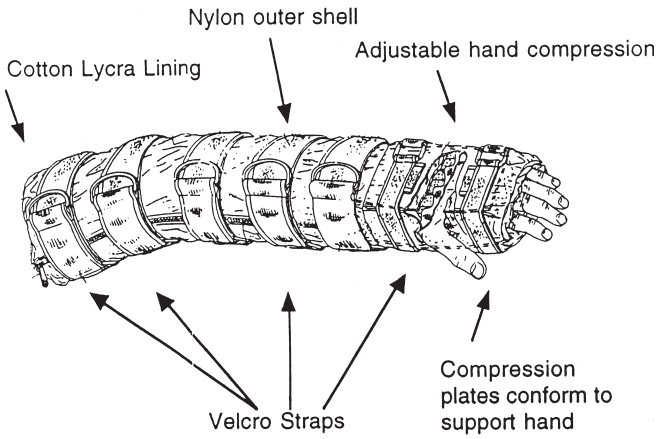


Figure 110-47. The Reid Sleeve (courtesy, Peninsula Medical).

table, and a full-length mirror. Professional simplicity and cleanliness are exceedingly important. The use of rolled paper on the table is practical and economical. If the pharmacy also has a comprehensive ostomy center, a second chair, so both the patient and the pharmacist can sit, is recommended. As a health-accessories department grows and prospers, more than one fitting room may be needed. Additional fitting rooms may not all need fitting tables, especially if a large portion of the expected clientele will be there for mastectomy or elastic hosiery fittings.

Conveniently near the fitting room should be the orthopedic inventory. It depends on the volume of sales, types and number of physicians prescribing appliances, and extent of the pharmacy's promotion. An estimate of the required initial stock space is about 30 to 40 ft^2. Also near the fitting room should be a sink with antiseptic soap and disposable paper toweling for use by the pharmacist before and after each fitting. Where ostomy fittings are concerned, it is advisable to have such a sink inside the fitting room.

Each pharmacy should keep a service record for each patient, with data on physician's instructions, appliances fitted, and any reorders.

WHAT TO STOCK

There are perhaps as many opinions as to which items should be represented within the pharmacy's surgical supplies and convalescent aids department as there are pharmacies, manufacturers, and wholesale distributors with experience in this field. Pharmacies differ, one from the other, in a multitude of ways. They face different limitations with regard to the available space within their pharmacies for the establishment of health-accessories departments. Their financial resources are different. The markets they purport to serve are different, with respect to both size and demographics. With regard to their drawing areas, differences exist due to various, specific economic factors reflecting distinctively different kinds of demand.

Figure 110-48. Breast form (courtesy, Amoena).

In an area with a heavy coal-mining industry, the market demand for respiratory therapy equipment might be very high relative to that in a rural farming community.

The extent to which hospital outpatient departments and home-care-oriented health agencies provide the thrust for a viable home health-care market within the community is vastly different from one town to another. Different pharmacies in different communities face widely divergent forms of competition, in both degree and kind.

All these considerations affect different pharmacies differently. Each pharmacist who contemplates the development of a surgical supplies and convalescent aids department must take these considerations into account when making decisions about what to stock. These are the issues that ultimately determine the optimum variety and depth of in-stock inventory for any given pharmacy.

Pharmacists must first decide which type or types of health accessories they want to specialize in handling. If they want to start with durable medical equipment such as canes, crutches, walkers, wheelchairs, commodes, and hospital beds, they should contact manufacturers of that type of equipment for advice on which products to stock. The same would be true for ostomy, urological, and incontinence supplies. Before opening a department for either orthopedic or mastectomy fitting, it would be necessary to attend a manufacturer's or wholesaler's school to obtain proper instruction. The manufacturer or wholesaler again would be a valuable source of information to assist in selecting those products best suited to an individual pharmacy. Before establishing a comprehensive respiratory-services department, it would be advisable to affiliate with a respiratory therapist who could assist in dealing with manufacturers in selecting the products most suited to a particular market area.

In many pharmacies, it is the actual experience of having capital tied up in slow moving inventory that has led many owners to the unfortunate practice of choosing a stocking inventory policy for health-accessories departments solely on the basis of the kind and number of requests received for various types of medical equipment in the past.

Thus, a vicious cycle ensues. For example, a pharmacist has no calls for specialized kinds of wheelchairs, and therefore, stocks only four or five basic wheelchair types. Then, when someone comes into the pharmacy for a wheelchair, because of a lack of wheelchair expertise and because more-specialized types of wheelchairs are not immediately available, he or she buys one of the wheelchairs that is in stock. Sometime then in the future, when visiting his or her physician or physical therapist, that person reports, often without realizing it, that the pharmacy was unable to meet his or her specific wheelchair needs. The result is that the physician or therapist will not send patients to the pharmacy for further wheelchair fittings.

From then on, the only persons who come to the pharmacy for wheelchairs are those who are either that pharmacy's regular patients or those who are largely uncounseled and self-initiate their visits to the pharmacy. And so, based on the past experience of not having had calls for specialized types of wheelchairs, the pharmacist concludes there is not much demand for them.

Without question, pharmacists who are interested in developing a successful surgical supplies and convalescent aids department within their pharmacies face a very serious dilemma. Either they play it safe and continue to stock those supplies for which they know they will have calls or they decide to expand

their inventory and expertise in an effort to become relatively sophisticated. By doing the latter, pharmacists run the risk of raising their operating costs in an industry about which, at the very least, they are uncertain.

Many pharmacists who are involved successfully in providing a comprehensive health-accessories service are discovering that when they give better service with the more specialized kinds of equipment, they also do better with ordinary kinds of equipment. That is because their pharmacies become recognized as *the* places where patients should be sent for a wheelchair, a walker, and other kinds of durable medical equipment and surgical supplies. It is also true that an improvement in health-accessories service tends to boost a pharmacy's prescription volume as well.

In preparation for the development of a list of inventory items for a health-accessories department, pharmacists should formulate guidelines for themselves that incorporate those variables discussed previously regarding space available within the pharmacy for such a department, financial resources, etc. It is also helpful to categorize the kinds of equipment and merchandise pharmacists might want to stock and then rank the various articles within each category as to the relative importance of each in meeting the health needs of their community.

One of the very first things pharmacists must do is to familiarize themselves with the industry's manufacturers and become knowledgeable about the products manufactured. While their local wholesaler may have many of the items they will need in their health-accessories department, pharmacists will have to establish direct-buying relationships to be able to obtain the scores of things their wholesaler does not stock. They should begin an alphabetical file of manufacturers' catalogs and price lists and develop an index that cross-references products with their manufacturers. An index of this type will save hours of time and possible embarrassment before their customers as well by enabling them to go quickly to appropriate information when faced with questions for which they don't have ready answers. Questions of this type will come frequently, and pharmacists will realize it as they become aware of how broad this field really is. Simply, too, pharmacists should admit an ignorance about certain products and be able to suggest to the patient where to go to have their questions answered and their needs addressed.

REIMBURSEMENT

A pharmacist would not accept a prescription for medication from a new customer without first asking if the patient is covered by an insurance plan. It is even more important to do this when dealing with health-care accessories.

Every year, more and more health-care accessories are being billed to third-party payers, and pharmacists providing these services must be sure to follow all the rules of the various government and insurance plans if they expect to be reimbursed for their services. The pharmacist must first determine whether the pharmacy can be a provider for the requested services under a particular plan. Then it must be determined if the patient is indeed a covered beneficiary under that plan. It is also often necessary to determine if the physician is an authorized prescriber for that plan. Finally, the pharmacist must verify that the prescribed item or service is indeed a covered benefit and at what level benefits will be paid.

Since Medicare and many insurances pay only 80% (or some other portion) of the allowed claim, it is often necessary to determine if there is a second or even third insurance and verify these benefits. It may even be necessary to check to be sure which insurance is primary and which is secondary. A retired patient on Medicare whose spouse is still working may have Medicare coverage that is secondary to the spouse's insurance coverage at work. The primary insurance coverage on a minor child is determined by which parent's birthday comes earlier in the year.

It is also necessary to have a qualifying prescription and/or Certificate of Medical Necessity (CMN) before submitting a claim. Medicare has developed CMNs which are required to be used for many products, a few of which are wheelchairs, hospital beds, seat lift chairs, and even oxygen. HCFA (the Health Care Finance Administration) has set up a system of HCPCS codes (the HCFA Common Procedure Coding System) for every item that may be considered for reimbursement by Medicare. These codes are matched with the diagnosis code (ICD-9), which must be included on the claim, and Medicare and many insurance companies will match the item being dispensed with the diagnosis code to help determine if coverage will be approved.

Sometimes Medicare or an insurance company will contact the doctor for further information before paying a claim. (This is called *developing the claim*.) Sometimes a claim will be down-coded to a code that results in lower payment. For example, a physician may prescribe a semielectric hospital bed but with documentation that only qualifies the patient for a manually adjustable bed. If the pharmacist dispenses the semielectric bed as ordered and submits a claim to Medicare for it, the claim may be down-coded to a manual bed and paid accordingly.

While some insurance companies still pay claims in full (or a fixed percentage of the claim) as billed, more and more insurance companies, HMOs, and PPOs as well as Medicare and Medicaid base their payments on fee schedules and/or maximum allowable payment levels. Routinely, many insurance companies will not pay full price for a brand-name drug when a lower cost generic equivalent is available. So too, they will not pay a higher price for items they consider "deluxe" or not medically necessary. An example is the hospital bed in the preceding paragraph. While the doctor, patient, and pharmacist may all agree that a particular product or feature is really medically necessary, the insurance company or Medicare may not agree.

It is very important that the pharmacist providing health-care accessories take the time to learn the intricacies of billing for these items and keep up with the constant changes occurring. As the pharmacy's business in health accessories grows, it is often advisable to have at least one person dedicated to obtaining proper prescriptions, billing, posting payments, billing secondary insurances, reviewing denied or reduced payments, and in general keeping up-to-date on reimbursement issues.

PROMOTION

The first form of promotion the pharmacist can use is a well-stocked and attractive floor display (Fig 110-49).

Prior to deciding on other kinds of promotion to undertake, pharmacists must determine from where most of their health-accessories volume is likely to come. Pharmacists who are involved successfully in comprehensive surgical supplies and convalescent aids departments are finding is that the greatest share of their surgical business is not done with their regular patients, but with new ones coming to their pharmacies specifically for medical supplies. There is little doubt that the reason most of these new patrons find their way to these pharmacies is that they were sent there by medical and allied health professionals in their own communities.

Referrals for wheelchairs, walkers, ostomy supplies, breathing equipment, and other health accessories come from physicians, hospitals, nursing homes, and a wide variety of community health professionals, among whom are therapists (physical, occupational, enterostomal, respiratory), nurses, medical social workers, social service directors, home-care coordinators, visiting nurses, and trainers in organized athletics. Physicians in most major specialties will make referrals. It is important that each health professional be approached about products or services relevant to his or her specific discipline. Organizations in which these and other health professionals can be found include hospitals and nursing homes, visiting nurse associations, private physical therapy associations, state departments of vocational rehabilitation, insur-

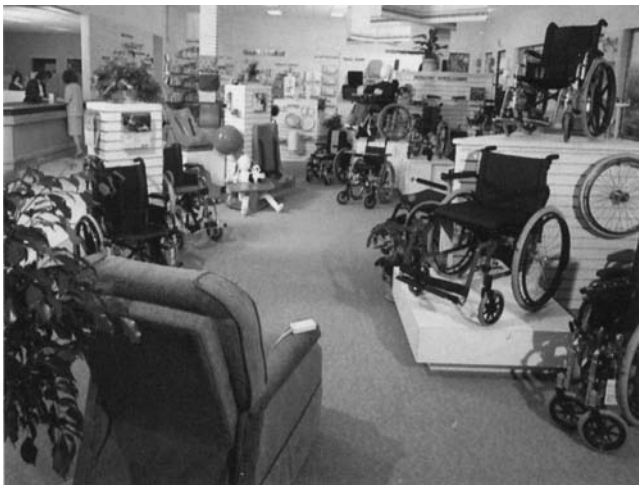


Figure 110-49. Floor display and wall space. This very common arrangement can be most productive. With the advantage of being able to display all the wheelchairs and walkers open, it gives the consumer a total and comprehensive picture of your home-care department at once.

ance companies, athletic departments in schools, commercial and manufacturing plants, rehabilitation centers, home-health agencies, clinics and agencies such as the Easter Seal Society, American Cancer Society, Multiple Sclerosis Association, Muscular Dystrophy Foundation, National Paraplegia Foundation, United Cerebral Palsy, United Ostomy Association, and many others. These, then, are the people and the organizations at which the pharmacy's principal promotional programs must be aimed. And while promotion to the general public is still very important, it is crucial that the pharmacist develop effective promotional programs aimed at the professional community.

Because it is quite common for many of these *new* patrons to begin to patronize their *new* pharmacy for other health needs, it is not surprising that the very existence of a comprehensive health-accessories department is regarded by the pharmacies who operate them as an excellent means for promoting the pharmacy as a whole.

Since the largest part of surgical supplies and health accessories volume originates with medical and allied health professionals within the community, the question must be asked: What prompts these professionals to recommend one dealer over another?

Aspects about the retail distribution of medical equipment and supplies that most concern a community's medical and allied health professionals are

1. That the supplier have the academic background and practical know-how to recommend the right equipment for each patient need and be able to show the patient how the equipment should be used.correctly.
2. That the supplier not practice medicine, physical therapy, etc, but call on practitioners of these professions for consultation and guidance when appropriate.
3. That the supplier have in stock an adequate inventory, in kind and quantity, to meet the immediate needs of his or her patients.
4. That the supplier, in addition to having ample stock, have access to wide varieties of medical equipment and supplies from numerous manufacturers, to service the special and unique needs of patients.
5. That the supplier distribute only merchandise of good quality and stand behind what he or she rents and sells. Many medical professionals are name-brand conscious also.
6. That the supplier have the capability of providing basic maintenance and repair services for what he or she sells and rents.
7. That the suppliers' equipment be priced competitively in rentals and sales.
8. That the supplier operate the business in an immaculate, well-organized, efficient, and thoroughly professional manner.

Advertising in professional journals, direct-mail campaigns, newspapers, and television commercials are all effective and commonly used methods of proclaiming that a pharmacy has the attributes that the professional community expects.

Attending and sponsoring meetings of groups, such as the local ostomy or diabetes associations, or working with public service groups, such as *Reach to Recovery,* allows the pharmacist to interact with health-care professionals and volunteers who are influential in these areas.

Sending a doctor or other referral source a written *Thank You* for each new referral also helps to remind the doctor of the professional services provided by the pharmacist. Even a simple note stating that a patient was fitted with a particular type of orthopedic support on a certain date as prescribed by the physician may end up in the patient's file where the doctor may see it several times.

One of the most effective ways of promoting a health accessories department, especially one that features the fitting of orthopedic and mastectomy appliances, is direct physician detailing. Calling on them in their offices is one sure way of promoting one's health accessories department. Even if it is not possible to visit the physician each time, contacts with his/her office personnel, especially a nurse, often can be very effective. Many times patients will ask the receptionist, while making the next appointment, where they can purchase or rent the item that has just been prescribed.

Another effective method to communicate that the pharmacy has the expertise and inventory to meet the community's health-care needs is by a developing a program of regular hospital displays. Further, in-service training classes for the staffs in hospitals and nursing homes as well as presentations at universities, social-service organizations, and special-interest groups are effective.

How better to demonstrate one's expertise in selecting, and when necessary measuring and fitting, health accessories than by providing instruction to groups of health professionals in a hospital or nursing home in the basic principles and proper use of the accessories, particularly those that serve as aids in convalescence or home care of the patient. Thus, for example, the important subject of walking aids—canes, forearm crutches, axillary crutches, and walkers—should include a discussion of the physiological factors of ambulation; the selection, measurement, and fitting of the devices to provide maximum leverage and comfort; and the manner of their use in walking on level areas as well as ascending or descending stairs. Many other subjects can be presented similarly by pharmacists knowledgeable in the use of convalescent aids and other health accessories.

Various equipment manufacturers offer in-service training programs that may be used as a guide to developing training programs for hospitals, nursing homes, visiting nurse associations, and schools.

With the advent of various managed-care programs, including plans for Medicare beneficiaries, another type of promotion has become necessary. Pharmacists may have taken many or all of the previous steps to promote their health-accessory department and still see meager results because most of the physicians who might recommend the pharmacy's services are required to refer to other providers who are in a particular health-care network, while the pharmacy is not. Pharmacists must actively pursue those health-care organizations for whom they want to provide services.

While some organizations deal only with capitated providers or may have an exclusive provider, many will work with several preferred providers. Often it is difficult to find the actual decision maker who may allow the pharmacy to become a preferred provider, but as the pharmacy becomes a provider for a few organizations, gradually other doors may be opened because of the excellent service provided. Often being exceptionally good in a small niche market may *open the door* to becoming a provider of other services as well.

All of the above-listed methods of promotion have one thing in common, relationship-building, a key element in forming a strong health-accessory department in the pharmacy.

PROFESSIONAL APPROACH

Pharmacists should not conclude hastily that they will be successful in this field, regardless of their estimate of the local market, their inventory, and their display facilities. Unless the pharmacist is willing to devote time and intelligent effort to the venture, he or she will fail. Pharmacists should be interested in helping the aged, the infirm, and the sick. Their attitude must be professional, and their approach to prospective referring physicians and the public must be made on that basis, not on mere availability or price. They must become knowledgeable in the areas of reimbursement and accreditation. Most important, they must have developed the expertise to recommend the right equipment and supplies and instruct their patrons in their proper use.

Pharmacists who seriously are considering developing this specialty will need to expand their reading list of relevant professional journals and periodicals. In addition to the major pharmacy journals, the following publications will broaden their knowledge and perspective concerning convalescent aids and surgical supplies: *HomeCare, HME News, Home Health Care Dealer, Medical Product Sales, Today's Home Healthcare Provider, Home Health Products, Ostomy Quarterly, The Journal of Care Management,* and journals in specialty fields such as physical therapy, occupational therapy, or respiratory therapy.

The National Community Pharmacists Association (NCPA) created a special division of Home Health Care Pharmacy Services. This division can provide additional information to pharmacists on changes in government programs that affect pharmacists providing home-health-care accessories. The NCPA publishes a newsletter, the *Alternative Pharmacist Monthly*. The NCPA, an accredited APCE provider, also provides educational programs concerning ostomy, incontinence, wound management, orthotics, and prosthetics. An advanced certificate program in orthotics and prosthetics is offered by the NCPA, and a number of other certification programs are available.

The surgical-supply department of the modern community pharmacy is recognized by physician and layman alike as a proper extension of the pharmacist's professional service. Physicians and allied health professionals quickly assess this new service as an important contribution to the health-team concept.

CERTIFICATION

Pharmacists who provide orthotic services should consider qualifying for credential, the Certified Orthotic Fitter, issued by the Board for Orthotists/Prosthetist Certification (BOC). Information regarding BOC certification may be attained from their website, www.bocusa.org. BOC Facility Accreditation is also available for pharmacies providing a wide array of Home Medical Equipment and services.

ACCREDITATION

The final step that pharmacists can—and should—take to demonstrate their competence as providers of health-care accessories is to become accredited. There are a number of accrediting bodies. The best known is the JCAHO (Joint Commission on Accreditation of Healthcare Organizations).

To become accredited, the pharmacy must, among other things, pass an on-site inspection in which the surveyor determines the firm's competency in such areas as:

1. Patient rights and responsibilities
2. Care, treatments, and service
3. Education
4. Environmental safety
5. Equipment management
6. Management of human resources
7. Management of information
8. Infection control
9. Quality assurance

The survey will include interviews with staff and clients, *riding along* on equipment deliveries, and spot checks of patient files. Accreditation extends for a period of 3 years, at which time the firm must be resurveyed.

The Accreditation Commission for Home Care, Inc, also can provide accreditation for firms that qualify. It has a specialty section dealing with the fitting of mastectomy prostheses. After successfully passing an on-site survey, a firm may be accredited for 3 years.

Other organizations that provide accreditation are CHAP (the Commission on Health Accreditation Programs), CARF (the Commission on Accreditation of Rehab Facilities), and NCQA (the National Committee for Quality Assurance).

THE FUTURE

Increased life expectancy has produced an increase in the number of aged persons and a corresponding increase in the number of ill and infirm persons in this segment of our population. The growing number of aged persons, the trend toward their greater subsidization, and the rapid increase in services from home-health-care agencies and hospital outpatient departments portends an ever-increasing number of potential candidates for surgical supplies and convalescent aids in the future. This is also true of many persons who are not aged but still are ill or infirm.

Though nursing homes do care for a substantial number of such patients, more of them want to remain at home and avoid the upward, spiraling costs of institutional care. Hospitals are reluctant to provide services to persons not in need of acute-care facilities, except on an outpatient basis, as it is too costly for both the patient and the hospital. As a result, the trend is to transfer the patient to home care as soon as possible. Encouraged to do so by the principal health-insurance companies such as Blue Cross and by developing home-health-care agencies, the demand for surgical appliances and medical equipment for use in the patient's home is growing daily.

This chapter was prepared as an overview of many, but not all, of the avenues pharmacists might take to expand their professional horizons. To be really successful in any, let alone all, of the areas, a sincere commitment of time, energy, and other resources may be required, but the professional rewards can make it all worthwhile.

ACKNOWLEDGMENT—The authors acknowledge the contributions of Barry N Eigen, MBA; Cindy Ciardo, Certified Fitter and BOC Orthotist; and Janet Lutze, RN, BSN, CETN to the development and enhancement of this chapter.