

INSTITUTE OF MEDICINE

Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations

Workshop Summary

Committee on Pharmacokinetics and Drug Interactions in the Elderly Division of Neuroscience and Behavioral Health Division of Health Sciences Policy INSTITUTE OF MEDICINE

> NATIONAL ACADEMY PRESS Washington, D.C. 1997

NATIONAL ACADEMY PRESS 2101 Constitution Avenue, N.W. Washington, DC 20418

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Support for this project was provided by the National Institute on Aging, National Institutes of Health, under Contract No. N01-OD-4-2139. The views presented are those of the Institute of Medicine Committee on Pharmacokinetics and Drug Interactions in the Elderly and are not necessarily those of the funding organization.

International Standard Book No. 0-309-05892-9

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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iv

Contents

1	INTRODUCTION	1
	Definitions,	2
	Demographics,	3
	Comorbidity and Polypharmacy,	4
	Report Outline,	5
	Acknowledgments,	5
2	WORKSHOP ON PHARMACOKINETICS AND DRUG	7
	INTERACTIONS IN THE ELDERLY AND SPECIAL ISSUES IN ELDERLY AFRICAN-AMERICAN POPULA-	
	TIONS	
	Physiology of Aging,	7
	Intracellular Responses,	13
	Chronic Use of Medications,	18
	Pharmacoeconomics,	22
	Clinical Trial Recruitment,	24
	Information Dissemination,	28
	Investigators,	29
	Summary of the Workshop,	31
3	CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS	35
	Research Needs and Opportunities,	35
	Summary,	41
	APPENDIX: Workshop Agenda, Speakers, and Participants	43

1

Introduction

Reports in the popular press about the increasing longevity of Americans and the aging of the baby boom generation are constant reminders that the American population is becoming older. Consequently, an issue of growing medical, health policy, and social concern is the appropriate and rational use of medications by the elderly.

Although becoming older does not necessarily correlate with increasing illness, aging is associated with anatomical and physiological changes that affect how medications are metabolized by the body. Furthermore, aging is often related to an increased frequency of chronic illness (often combined with multiple health problems) and an increased use of medications. Thus, a better understanding of the absorption, distribution, metabolism, and excretion of drugs;¹ of the physiologic responses to those medications; as well as of the interactions among multiple medications is crucial for improving the health of older people.

In 1996, the National Institute on Aging and the National Institutes of Health (NIH) Office of Research on Minority Health requested that the Institute of Medicine (IOM) conduct a workshop study to examine research opportunities and barriers to research on pharmacokinetics, pharmacodynamics, and drug interactions in the elderly with attention to elderly African-American populations. In addition, the workshop was intended to update a 1990 report by the IOM Forum on Drug Development, *Drug Development for the Geriatric Population.* In response to this request, the IOM formed a Committee on Pharmacokinetics and Drug Interactions in the Elderly and selected members with expertise in the relevant disciplines including basic science and clinical pharmacology, geriat

¹ Note: The terms *drug* and *medication* are used interchangeably throughout this report.

rics, drug development, and drug use policy. The committee met twice during the course of the 10-month study and held a scientific workshop at Xavier University of Louisiana College of Pharmacy in April 1997. This report highlights the workshop presentations and summarizes the committee's conclusions regarding future research directions.

DEFINITIONS

A starting point in most discussions on aging populations is the definition of the terms *aging* and *elderly*. In cellular and animal models, aging is measured by replicative senescence or chronology (e.g., 40–50 replications of fibroblasts; 24–28 months of age in rats; 3–4 years in rabbits; and 8–10 years in dogs). Although gerontologists view human aging as a continuous process, no two individuals age in exactly the same manner; consequently there is considerable heterogeneity² in the elderly population, with wide variance in physical health and cognitive function. However, for societal, demographic, and measurement purposes, there is a need to define the term elderly based on chronological age. Geriatricians and gerontologists often use the following construct to subdivide the population:

20–39 years	adult,
40–59 years	middle age,
60–74 years	young old,
75–85 years	old old, and
>85 years	very old or oldest old.

Diverse levels of physical health and overall well-being make it difficult to categorize what constitutes "normal aging." Within each of the subgroups of people over 60 years of age, individual biological responses to aging are affected by a range of physiological, genetic, socioeconomic, and environmental factors including nutrition, access to medical care, smoking, and weight. Further, the over-60 subgroups vary widely in physical, emotional, and mental health, social function, activity levels, and overall vitality.

Definitional issues also surround the terms *race* and *ethnicity*. Although this report discusses aging issues related to race and ethnicity, particularly in elderly African-American populations, the committee acknowledges the complexities and limitations of racial categories. Individuals may be categorized into a particular group for purposes of identifying a study population; however, there may

² The elderly population encompasses a range of people including those who have aged successfully, those with few health conditions and risk factors, and those with health conditions and disability (Wenger, 1993).

not be important biological significance to the categorization. There is a great deal of genetic heterogeneity within broad racial categories (IOM, In press), even though they are used as discrete variables in many surveys including the U.S. Census. It is important to remember that immigration and the rapid rise in the number of interracial marriages are resulting in a U.S. population that is increasingly multiracial, comprising individuals of mixed heritages from a number of racial and ethnic groups. In addition, racial categories that are currently in use may include people from widely different geographical locations and sociocultural backgrounds that have great genetic diversity (e.g., the term *Hispanic* may be used to include people of Caribbean, Mexican, and Central and South American descent). Thus, grouping people along racial and ethnic lines to study functional differences in their drug-metabolizing capacity or to interpret results of research and clinical trials relating to various drugs has proven to be complex and challenging. These definitional issues extend far beyond the committee's charge and are noted here to acknowledge the complexities involved in the study of diverse aging populations.

The task of this committee primarily relates to pharmacokinetics (defined in its simplest form [Benet, 1996] as "what the body does to a drug") and the age- and ethnicity-related changes in drug disposition. Pharmacodynamics (in its simplest form "what the drug does to the body" or the consequences of drug dosing) must also be considered. However, little work has previously been undertaken in this area, and changes in pharmacodynamics that cannot be explained based on age-related pharmacokinetic changes are less well known. The identification of purely age-related pharmacodynamic changes will not easily be understood until the areas of future research summarized in Chapter 3 of this report have been substantially addressed.

DEMOGRAPHICS

Declining fertility and mortality rates, lengthened average life spans, and the aging of the baby boom generation are all factors in the changing demography of the U.S. population. In 1994, the 33.2 million Americans aged 65 or over constituted 12.5 percent of the population; the U.S. Bureau of the Census (1995) estimates that by the year 2050, the number of elderly persons will more than double to about 80 million, or approximately 20 percent of the total U.S. population (Table 1.1).

The portion of the population aged 85 and over (the "oldest old") is the most rapidly growing elderly age group, and this group typically has the highest incidence of chronic disabling diseases and the highest health care expenditures. It is expected that this age group, which numbered 3 million in 1994 (making up 9 percent of elderly Americans and over 1 percent of the U.S. population), will

increase to 19 million in 2050 (making up 24 percent of elderly Americans and 5 percent of the U.S. population).

	1994	Projected for 2050
Number of Americans age 65 or older	33.2 million	80 million
Percentage of the U.S. population age 65 or older	12.5	20
Number of Americans age 85 or older	3 million	19 million
Percentage of the U.S. population age 85 or older	>1	5

TABLE 1.1	Projected Demo	ographic Statistics
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SOURCE: U.S. Bureau of the Census, 1995.

The elderly American population will also be more ethnically and racially diverse in the future. In 1994, 1 in 10 Americans was identified as being of a race other than Caucasian; demographers project that this ratio will change to 2 in 10 by the year 2050. By that time, the number of elderly African Americans will more than triple (to constitute over 10 percent of the elderly population) and the elderly Hispanic population will increase from less than 4 percent of the elderly population to nearly 16 percent.

COMORBIDITY AND POLYPHARMACY

Despite the great heterogeneity in health status and functional levels within the elderly population, aging generally increases an individual's risk of illness and, subsequently increases use of medications. Community-dwelling elderly persons over age 64 take an average of two to three prescription medications, whereas older elderly persons (>80 years), elderly hospitalized patients, and elderly patients in long-term care facilities on average take significantly more medications (LeSage, 1991; Chutka et al., 1995). Cardiovascular drugs, antihypertensive medications, analgesics. antiinflammatory drugs, sedatives, and gastrointestinal medications are the medications most commonly used by elderly Americans (Hale et al., 1987). Although persons over age 65 represent nearly 13 percent of the total U.S. population, it has been estimated that they consume nearly one third of all medications in the United States (Avorn, 1995). Of the \$36 billion spent on prescription medications in the U.S. in 1991, it is estimated that the elderly population spent between \$12.7 billion and \$14.3 billion (Long, 1994). The frequent presence of coexisting illnesses and the use of multiple medications by the elderly increases the potential for drug interactions. Thus, enhanced understanding of the issues involved in research on pharmacokinetics,

REPORT OUTLINE

This report provides a summary of the presentations and discussions of the IOM Workshop on Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations (Chapter 2) and presents the committee's conclusions on future directions for research on pharmacokinetics and drug interactions in the elderly (Chapter 3). Many of the issues presented in this document have been the subject of recent IOM reports. These issues include gender-specific issues for elderly women (IOM, 1994e, 1996b); careers in clinical research (IOM, 1994b) and specifically in geriatrics (IOM, 1993, 1994d); recruiting minorities into the health professions (IOM, 1994a); and confidentiality of patient information (IOM, 1994c); as well as recent reports on health care for the aging population (IOM, 1990b, 1991, 1996a).

ACKNOWLEDGMENTS

The committee appreciates the assistance provided by Stanley Slater of the National Institute on Aging and John Ruffin of the NIH Office of Research on Minority Health. In addition, the committee extends its appreciation and thanks to Marcellus Grace, Burde Kamath, and many other individuals on the staff of Xavier University of Louisiana who helped plan the IOM workshop and who graciously welcomed the committee, the workshop participants, and the workshop attendees (see Appendix). The workshop speakers shared their extensive expertise with the committee, and the committee appreciates the informative presentations. This report is presented to stimulate discussions on this important topic and to provide useful directions for future research on pharmacokinetics and drug interactions in the elderly. The report highlights and summarizes only the topics presented by the speakers and discusses the committee's conclusions based on the workshop presentations.

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Workshop on Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations

This chapter summarizes the presentations made at the IOM workshop and the discussions that took place among the speakers, committee, and participants (see the Appendix for the workshop agenda and lists of the speakers and participants). Each speaker was asked by the committee to address issues related to the effect of age, gender, race, ethnicity, and the environment on the topic of his or her presentation.

PHYSIOLOGY OF AGING¹

Multiple parameters at the cellular and system levels change with age (Table 2.1), and many of these changes have pharmacokinetic and pharmacodynamic implications. Although it is thought that drug absorption is not markedly altered by age, drug distribution, excretion, and metabolism can be affected by a number of the physiological changes associated with aging. For example, age-related changes in body composition with loss of lean body mass and decreased total body water can lead to decreased volume for the distribution of some drugs. These changes can be exaggerated in the presence of disease. The most consistent age-related change affecting drug excretion is the decrease in

¹ This section is based on workshop presentations by Drs. Jane Cauley, Keith Ferdinand, Jeffrey Halter, and Fran Kaiser.

and Composition	
Autonomic nervous system	
Peripheral	
	↓ Baroreflex responses
	↓ Beta-adrenergic responsiveness, ↓ receptors
	↓ Signal transduction
	↓ Muscarinic parasympathetic responses
~ .	Preserved alpha responses
Central	
	Dopamine receptors
	Alpha responses
	Muscarinic parasympatienc responses
Body composition	\downarrow Lean body mass
	\downarrow Muscular mass, \downarrow creatinine production
	↓ Skeletal mass
	\downarrow Total body water
	\uparrow Percent adipose tissue (until age 60, then \downarrow)
Cellular	DNA damage and \downarrow DNA repair capacity
•••••	↓ Oxidative capacity
	↑ Fibrosis
	Lipofuscin accumulation
Ears	Loss of high frequency hearing
Endocrine	Menopause, \downarrow estrogen and progesterone secretion
	\downarrow Testosterone secretion
	\downarrow Growth hormone secretion
	\downarrow Vitamin D absorption and activation
	↑ Incidence of thyroid abnormalities
	\uparrow Incidence of diabetes (decreased insulin sensitivity
	or increased insulin resistance)
	↑ Bone mineral loss
Eves	\downarrow Lens flexibility
	↑ Time for pupillary reflexes (constriction, dilation)
	↑ Incidence of cataracts
Gastrointestinal	↓ Henatic mass
	↓ Hepatic blood flow
	↓ Splanchnic blood flow
	↑ Transit time
	· · · · · · · · · · · · · · · · · · ·

TABLE 2.1 Selected Physiological Age-Related Changes in Body Function and Composition

9

Heart	 ↓ Intrinsic heart rate and maximal heart rate ↓ Diastolic relaxation ↑ AV conduction time ↑ Atrial and ventricular ectopy
Immune system	↓ T-cell function
Joints	Degeneration of cartilaginous tissues Fibrosis,↓ elasticity
Nose	↓ Smell
Pulmonary	↓ Vital capacity ↓ Lung elasticity
Renal	 ↓ Renal blood flow ↓ Renal mass ↓ Glomerular filtration ↓ Renal tubular secretion and reabsorption ↓ Ability to excrete a free-water load
Vasculature	↓ Endothelin-dependent vasodilation ↑ Peripheral resistance ↑ Systolic pressure

renal drug clearance resulting from decreased blood flow to the kidneys and decreased renal mass. Data on age-related changes in hepatic drug clearance have been less consistent and may be more complex.

Researchers still do not fully understand the physiological mechanisms of aging or the interaction of age-related changes with drug actions (see, e.g., Box 2.1). Moreover, investigators are only beginning to explore variations among individuals and the role of numerous environmental and genetic factors including gender, race, socioeconomic status, physical activity, and other modifiers that interact with the physiological aging process and affect pharmacology.

Research on the physiology of aging is complicated by difficulties in distinguishing the effects of normal aging from the consequences of coexisting diseases. There is significant variability among individuals (in physical and mental health status and a number of other parameters) that increases with age, and researchers must determine whether the variability is due primarily to disease or to an effect associated with normal aging. At the cellular level, changes due to aging may appear distinct (e.g., increased collagen cross-linkage, decreased elasticity, and alteration in DNA degradation) while in the whole organism, changes due to normal aging are often difficult to separate from disease processes.

BOX 2.1: HOMEOSTATIC CONTROL SYSTEMS

Age-related changes in homeostatic control systems present a challenge to the study of the physiological effects of drug therapy. For example, aging has a number of effects on the autonomic nervous system including increased circulating adrenergic catecholamines, decreased resting parasympathetic nervous system tone, and downregulation of peripheral adrenergic receptor function and vasomotor responsiveness, all of which may contribute to the age-related impairment of baroreceptor function. Because the autonomic nervous system plays an adaptive role in modulating the overall body response to a variety of medications, the interaction of age-related changes with drug effects must be considered.

An example of this interaction is the use of diuretics or potent alphablocking vasodilators for hypertension. Because diuretics can decrease fluid volume, people with baroreceptor dysfunction, such as elderly persons, may be at increased risk for developing postural hypotension during diuretic therapy. Similarly, blockade of alpha-constrictor effects in the presence of blunted heart rate responses (and decreased intravascular volumes) may predispose to postural hypotension. In fact, most symptomatic orthostatic hypotension occurring in older adults can be directly traced to medication use.

In addition, there are a number of areas in which research is beginning to challenge previous assumptions about aging. For example, osteoporosis, long thought of primarily as a disease risk for Caucasian and Asian women, has become a concern for African-American women as well (with the onset occurring approximately 10 years later than in other elderly female populations). Elderly men are also at risk for osteoporosis, although little is known about the extent of this risk. Research on changes in the endocrine system has in the past primarily focused on women and the relationship between loss of estrogen and bone disease, and more recently, cardiovascular disease. There is still much to be learned about changes in the level of testosterone in men during the aging process (Kaiser and Morley, 1994). Preliminary intervention studies show positive benefits for testosterone replacement (Morley et al., 1993). Studies are ongoing to compare the effects of endogenous versus exogenous hormones (Box 2.2).

The significance of distribution of body weight is of increasing research interest, and the implications of poor nutrition and weight loss are only beginning to be explored in elderly populations (Clarkston et al., 1997). It has been noted that high waist-to-hip ratios are associated with a higher prevalence of diabetes, hypertension, and coronary artery disease. The Baltimore Longitudinal Study on Aging found that, with aging, there is an increase both in upper and central body fat distribution, with most men having a higher waist-to-hip ratio than most women of comparable age (Shimokata et al., 1989).

BOX 2.2 BIOLOGICAL EFFECTS OF ENDOGENOUS AND EXOGENOUS HORMONES

Hormone replacement therapy is widely used in the United States, particularly for its protective effects in reducing the incidence of osteoporosis in postmenopausal women (Cauley et al., 1995). One area of ongoing research is a comparison of the physiological effects associated with endogenous hormones versus exogenous hormone administration. For example, blood concentrations of serum estrogens after estrogen replacement therapy at currently recommended doses are in the range of 153 pg/mL of estrone and 40 pg/mL of estradiol. This contrasts to physiological levels among postmenopausal women, not on hormone replacement therapy, in the range of 30 pg/mL of estrone and 8 pg/mL of estradiol.

Estrogen replacement therapy also appears to be associated with significant reductions in the risk of coronary death and death due to stroke. The mechanism of this protective action has not been fully elucidated or separated completely from the selection bias of socioeconomic status found in retrospective studies to date, but potential mechanisms include effects on metabolic processes that produce beneficial changes in lipids and lipoproteins, as well as direct effects on the arteries themselves to improve arterial function. Although there is a strong association of exogenous estrogen administration with reduced cardiovascular disease in women, preliminary research has found no association between endogenous estrogen levels and heart disease in women (Cauley et al., 1994). Studies of the relationship of breast cancer and uterine cancer with endogenous or exogenous estrogens are ongoing.

This area of research is one example of the numerous avenues for research on pharmacotherapy in the elderly. Pharmacotherapies such as hormone replacement therapy, raise a number of important questions including the consequences of long-term exposure to medications and the most appropriate methodologies for studying the effects of these drugs on older persons. Observational studies are an appropriate design to use in evaluating long-term exposures, since randomized clinical trials over 10–15 years are inappropriate for this age group.

Issues in Elderly Minority Populations

Although the disease burden falls heavily on elderly minority populations, researchers have not fully explored the pathophysiology of disease processes in various minority populations. Health-seeking behavior, socioeconomic status, nutrition, physical and economic access to medications, adherence to prescription regimens, and access to medical care all play a significant role in the prevalence and treatment of diseases in the minority elderly (Figure 2.1). Research is needed to more fully understand the variations between ethnic and ra



FIGURE 2.1 A framework for understanding the relationship between race and health. SOURCE: King and Williams (1995). Reprinted by permission of Oxford University Press. 12

cial groups in the time of appearance of disease, the disease processes that dominate, and the effectiveness of treatment interventions.

Hypertension, diabetes, renal disease, and their complications are generally more prevalent in elderly African Americans than in elderly Caucasians. In addition, African Americans frequently have more severe sequelae of hypertension, with higher rates of cardiovascular morbidity and mortality. Isolated systolic hypertension is disproportionately prevalent in African-American women. The cardiovascular risks associated with systolic hypertension have only recently been recognized. The Systolic Hypertension in the Elderly Program (SHEP), a multicenter study of community-based ambulatory elderly patients, has shown that treatment of isolated systolic hypertension can significantly improve cardiovascular survival and decrease risk of stroke in elderly patients (SHEP Cooperative Research Group, 1991). However, as in many studies, there was not significant representation from minority patients.

Studies indicate an earlier onset of hypertension in African Americans and suggest differing responses to antihypertensive medications. Recent studies have shown that African-American hypertensive cohorts had a higher response rate to treatment with calcium channel antagonists and diuretics and a lower response rate to treatment with ACE (angiotensin-converting enzyme) inhibitors and beta-blockers (reviewed in Jamerson, 1993). Possible physiological explanations include variations in the regulation of salt and water balance, variations in the angiotensin-renin system, differing sensitivities to the vasodilator bradykinin, or angiotensin-converting enzyme polymorphism. Thus, further research is needed to optimize the development of effective clinical therapeutic regimens.

INTRACELLULAR RESPONSES²

Pharmacokinetics

The therapeutic effect of a drug will be produced only when the appropriate concentration of the drug is present at its site(s) of action. Many medications act by binding to receptors at the cell surface; other medications require intercellular transport. Transport across cell membranes may occur through passive diffusion or facilitated diffusion (i.e., carrier-mediated transport in which there is no input of energy) or active transport through carrier-mediated membrane transport. At this time there are few data that examine the effects of age, sex, or ethnicity on transport mechanisms.

² This section is based on workshop presentations by Drs. Darrell Abernethy, Grant Wilkinson, and Kurt Rasmussen.

In addition to the transport of the drug to the site of action, drug concentration also depends upon the extent and rate of drug absorption, distribution, protein binding, and elimination. Important age-related changes in body composition and functioning (see Table 2.1) are relevant to drug disposition and, in turn, affect drug concentration. These changes have significant implications for clinical therapeutics in the elderly (Scharf and Christophidis, 1993).

The absorption of drugs (which affects the duration and intensity of drug action) does not generally appear to be significantly impaired in the elderly; however, the distribution of drugs may be affected. Certain physiological and physiochemical properties including cardiac output and regional blood flow will determine how a drug is distributed through the body. The drug is distributed to the heart, liver, kidney, brain, and other highly perfused organs during the first few minutes after absorption. Delivery to muscle, viscera, skin, and fat occurs later and at a lower level (Benet et al., 1996). In addition, distribution may be limited to the vascular compartment by the drug binding to plasma proteins, particularly albumin and alpha1-acid glycoprotein. As the production of albumin by the liver generally declines with age, there may be an age-related rise in the free fraction of any highly albumin-bound drug. Although this change does not by itself cause an increase in the drug concentration, it may be a marker for other alterations that may be associated with increased drug sensitivity. As lean body mass falls and total body water falls, both in absolute terms and as a percentage of body weight, the volume of distribution of highly lipid- or water-soluble drugs will be affected.

Altered drug elimination is also a consideration in the elderly. Drugs are eliminated from the body either by metabolism (primarily by the liver) or by excretion (primarily by the kidney). Drug metabolism in the liver occurs by a variety of reactions such as oxidations, reductions, or hydrolytic processes. In addition, drugs may be metabolized by conjugation reactions, such as acetylation, glucuronidation, or sulfation. There is evidence to suggest that oxidative metabolism decreases with age, whereas conjugative metabolism appears to be less affected by aging (Scharf and Christophidis, 1993). It is known that liver mass decreases with age, as does hepatic blood flow (see Table 2.1). Additionally, oxidative metabolism may also be influenced by smoking, genetics, gender, concurrent diseases, and frailty.³ Renal function also declines with age, as reflected by declines in creatinine clearance. When creatinine clearance falls below 30mL/minute,⁴ the excretion of drugs that are eliminated mainly by the kidneys decreases significantly and

³ In general, frailty is the term used by health professionals to describe elderly persons who require assistance with mobility and activities of daily living, have abnormal laboratory findings, and suffer with co-occurring medical conditions including Alzheimer's disease, multi-infarct cerebrovascular disease, Parkinsonism, osteoporosis, or healed fractures (Scharf and Christophidis, 1993).

⁴ Normal creatinine clearance in a young adult is 100–120 mL/minute. After age 40, creatinine clearance on average falls by 10 percent for every decade of life (Lee, 1996).

the risk of accumulation of the drug and its metabolites increases (Lee, 1996). Although measures of creatinine clearance provide dosing guidelines for drugs that are excreted exclusively by the kidneys, changes in hepatic metabolism with age and pathology are more difficult to estimate quantitatively.

Inter- and intraindividual variability in the pharmacokinetics of many drugs is largely determined by variations in hepatic drug clearance as described by the parameters of hepatic blood flow and metabolic capacity. These parameters may be altered as a result of liver disease, genetic differences in enzyme content, and drug interactions. Several metabolizing enzymes have been identified and characterized at the gene, mRNA, and protein level, as have their substrate specificities, including Nacetyltransferase (NAT) and isoforms of cytochrome P450⁵ (e.g., CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A). Some of these isoforms (e.g., NAT2, CYP2C19, and CYP2D6) exhibit genetic polymorphism such that there are subpopulations that may include a small group of people (3 percent-10 percent) who are homozygous and have the poor metabolizing phenotype (i.e., they have an impaired ability to metabolize specific chemicals or drugs) or the extensive metabolizing phenotype, which consists of both the homozygous and the heterozygous genotypes. In many different ethnic and racial groups (e.g., African Americans, Caucasians, Asians, Native Alaskans, and North Africans) there are differences in the frequency of the deficient alleles. For example, in African Americans, the frequency of the poor metabolizing allele for debrisoquine sulfate (an antihypertensive drug that is a specific substrate for CYP2D6) and for over 40 cardiovascular and central nervous system drugs is lower than in Caucasians. Thus, in populations of African Americans the proportion of people who cannot metabolize these drugs extensively is smaller. Asians also exhibit a significantly lower frequency of the poor metabolizing characteristic (~1 percent) than Caucasians (~7 percent) for CYP2D6 substrates.

Studies of the effects of physiological aging on the distribution and elimination of drugs in representative populations of the elderly are complex. Multiple confounding variables (e.g., gender, race, ethnicity, body weight, and exposure to caffeine, nicotine, and alcohol) and concomitant diseases, increase the difficulty of understanding the implications of age-related changes on clinical therapeutics in the elderly population.

⁵Cytochrome P450 (CYP) is a primary component of the oxidative enzyme system. Individual differences in enzyme activity and susceptibility to induction are genetically determined. Rates of biotransformation (which fosters elimination of drugs) may vary significantly among individuals.

Cardiovascular Physiology

Cardiovascular disease is the single largest cause of death in the elderly. Although basal cardiac output is maintained in the elderly by an increase in ventricular size and greater stroke volume than in the young, maximal- and stress-related responses are decreased. With regard to cardiac and arterial function, the following changes are also characteristic of aging:

- · decreased intrinsic heart rate,
- impaired diastolic function (e.g., slowed cardiac diastolic relaxation),
- increased atrial and ventricular ectopy,
- prolonged AV conduction times and increased repolarization times,
- · decreased elasticity of the aorta and large vessels,
- · impaired baroflex function, and
- impaired vascular endothelium-mediated function (Stolarek et al., 1991; Lakatta, 1993; Lakatta et al., 1987, 1993; Craft and Schwartz, 1995).

The physiology and pharmacology of the autonomic nervous system and the sympathetic regulation of the cardiovascular system are clearly affected by aging. Normally, stretch receptors in the systemic and pulmonary arteries and veins monitor intravascular pressures; the resulting afferent impulses alter sympathetic activity. An increase in blood pressure stimulates arterial baroreceptors, which results in the inhibition of central sympathetic outflow. In the opposite manner, when blood pressure falls, decreased afferent impulses diminish central inhibition, resulting in an increase in sympathetic outflow, withdrawal of parasympathetic tone, and a rise in arterial pressure. Thus, baroreceptors play an important role in blood pressure regulation. However, baroreceptor reflex activity appears to decline with age.

There appear to be significant age-related changes in adrenergic receptors.⁶ Although circulating norepinephrine levels increase in the elderly, there is no change in the sensitivity to the vasoconstrictor alpha1-adrenoceptor while there is evidence for both a decline in peripheral beta-adrenoreceptor numbers and decreased activity of the G-coupled protein complex and related intracellular second messengers. Age-related changes in central nervous system adrenoreceptor responses are less clear (White et al., 1994).

⁶Alpha-adrenergic receptors (there are distinct alpha₁- and alpha₂-receptor subtypes) mediate vasoconstriction, intestinal relaxation, and pupillary dilation. Beta-adrenergic receptors (the three distinct subtypes are beta₁, beta₂, and beta₃) stimulate heart rate and increase contractility, vasodilation, bronchodilation, and lipolysis.

Neurotransmitter Receptors

The brain is one of the most complex organ systems in terms of drug actions and disease. Research on the mechanisms of signal transduction, or intercellular communication, in the brain over the past two decades has shown that simple models of synaptic transmission (involving the release of neurotransmitters, which bind to specific receptors and either stimulate or inhibit neural activity) are not sufficient to explain all of the effects of neurotransmitters on neurons. It has been observed that a medication that acts at one or more neuronal receptors may also change neuronal activity by more than one mechanism depending on prevailing conditions at the receptor site. ⁷ However, the biological significance of having varied mechanisms of intracellular communication among neurons in the brain also depends on the part of the brain involved and its complex connections and pathways to other brain regions, as well as on the composition of neurotransmitters and receptors present in specific brain regions.

These varied mechanisms of neural activity underly both long- and short-term responses of neurons. For example, short-term effects may include inhibition or excitation of neuronal activity affecting the release of neurotransmitters along brain pathways (chains of neurons comprising subsystems with specific functions). However, research has identified a variety of subtypes of many neurotransmitter receptors (e.g., dopamine and serotonin receptors) that function differently and exhibit different pharmacological responses. In addition, some neurotransmitters exert effects by binding to receptors coupled to ion channels (proteins that regulate the flow of specific ions, e.g., chloride and sodium), and many neurotransmitters affect a cascade of intracellular chemical reactions that, eventually, lead to changes in gene expression in the neural cells. Such long-term effects of neural transmission are often mediated by proteins in neuronal membranes coupled to receptors and a variety of so-called "second messenger" molecules that act inside cells to regulate many cell processes including changes in gene expression. All of these reactions may be affected by aging; however, they also provide targets for therapeutic interventions.

Neurological diseases present important challenges to medication development and use in the elderly. Two neurological disorders often associated with aging are Alzheimer's and Parkinson's disease. Alzheimer's disease is clearly age related (it is uncommon in young or middle-aged persons) with a prevalence as high as 47 percent in people over 85 years, and this disease is the leading cause of cognitive impairment in the elderly population. The pathological features of Alzheimer's disease include neuritic plaques, neurofibrillary tangles, and the death and disappearance of nerve cells in the cerebral cortex. The densities of forebrain

⁷Similarly, it is by means of different receptors that norepinephrine can cause constriction in vessels of the skin and dilation of those in muscles. Acetylcholine too has an excitatory function, but it can also be inhibitory,

depending on prevailing conditions at the receptor site.

cholinergic neurons are markedly decreased in cortical and hippocampal (but not striatal) areas in Alzheimer's disease; however, there does not seem to be a corresponding decrease in postsynaptic receptors. Thus, the preserved postsynaptic receptors provide a target for therapeutic intervention.

Parkinson's disease is a disorder of middle or late life that involves the nigrostriatal dopaminergic system and is characterized by changes in the aggregates of melanincontaining nerve cells in the brain (the substantia nigra and locus coeruleus) (Isselbacher et al., 1994). The dopamine carrier (dopamine uptake complex) is involved in the uptake of the dopamine released into the synaptic cleft at the level of nigrostriatal dopaminergic neurons. With increasing age, the number of dopamine terminals in the striatum decreases. Clinical symptoms in Parkinson's disease do not appear until almost total depletion of dopamine has occurred in the striatum. In fact, it appears that Parkinsonian symptoms become apparent only when there is at least 80 percent degeneration of the dopamine terminals. That suggests the existence of either a compensatory mechanism to offset the loss of nigrostriatal dopaminergic neurons or a significant basal excess of terminals (Anglade et al., 1995). In addition, positron emission tomography (PET) scans suggest that there are fewer postsynaptic dopamine receptors. The depletion of postsynaptic receptors coupled with the degeneration of the dopaminergic pathway provides a significant challenge to the development of a pharmacotherapeutic intervention.

CHRONIC USE OF MEDICATIONS⁸

Treating the health problems of older patients presents a number of challenges, as these patients frequently have multiple health problems. For example, elderly patients who survive a myocardial infarction may have chronic ischemic heart disease, hypertension, and other related chronic conditions such as diabetes. Each of these conditions may require one or more medications, thereby increasing the risk of drugdrug interactions as well as the side effects of each of the drug therapies. This is complicated by the recent trend toward the use of multiple drug regimens as the most efficacious way to treat a variety of common chronic conditions (e.g., osteoporosis, hypertension, coronary artery disease, diabetes, congestive heart failure, and chronic lung disease). In addition, these conditions may be chronic, requiring long-term use of the medications. The duration of therapy and the effect of chronic use of medications are areas of increasing concern. As life expectancy lengthens, there will be increased older persons with chronic conditions numbers of who might require pharmacotherapeutic treatment for decades. Further, many patients also use over-thecounter

⁸ This section is based on workshop presentations by Drs. Louis Lasagna, Bruce Pollock, and Wayne Ray.

medications and a wide range of dietary supplements, vitamins, and other nutraceuticals for which the physiological actions and interactions with medications are largely unknown.

Measuring Drug Use

It is important to be able to measure past and current drug exposure when treating multiple comorbidities in the elderly and when enlisting elderly participants into clinical trials on drug effects and outcomes. However, it is often difficult to measure drug exposures accurately.

There are a number of complexities in measuring medication use. First, the information collected about the medication must be very specific. Within the same class of drug compounds there can be wide differences in adverse effects. Product formulations can vary between manufacturers, and information on the formulation is needed to distinguish various dosage forms and their respective effects. Second, information is needed on the timing of drug use and the subsequent occurrence of adverse effects. Acute effects, such as psychomotor impairment associated with psychotropic drugs, occur while the medication is in use, whereas other adverse effects may occur once drug use has stopped. Third, the dose is an important measure because many adverse and beneficial effects of drugs vary with dose—for example, the risk of serious peptic ulcer disease associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

The three techniques most commonly used to measure drug exposure are biologic measurement, interviews, and the use of pharmacy or other medical records. Each of these methods has its strengths and weaknesses in terms of obtaining valid data, particularly on the chronic use of medications. Current biological measurements (e.g., blood or urine tests) provide precise data; however, it is difficult to get people into the laboratory to take these tests and the cost of the tests may be a prohibitive factor. Additionally, biomarkers are needed to determine long-term past exposures.

Interview techniques generally provide accurate data on current medication use, particularly when combined with inspection of medication containers. However, retrospective drug use is more difficult to recall and document. There also appears to be a confounding issue related to the responses made by well and sick individuals about past medication use.

Pharmacy records provide a reasonable surrogate for drug exposure and are often the best method for assessing the history of drug use because they allow detailed tracking over time. Additionally, these records are relatively free from information bias. Unfortunately, the dispensing of medications does not necessarily correlate with actual drug use, and compliance is difficult to measure with this method. Moreover, pharmacy records have their own inherent weaknesses: patients do not always get their medications at the same pharmacy, outpatient and inpatient pharmacy record systems are rarely integrated, and most pharmacy records do not contain information on nonprescription medication use.

Chronic Drug Use

As the average lifespan of the population increases, it becomes important to shift focus from the acute effects of medications to their chronic effects in older patients. Some medications that are now prescribed for the elderly may be used for 20–30 or more years (e.g., antihypertensives, hormone replacement therapy, antidepressants, NSAIDs).

Depression, for example, is a relatively common condition in the elderly that is associated with considerable medical and social morbidity (Ruegg et al., 1988; Stewart, 1993). Although the prevalence of depression has not been found to differ by race, there are some indications that depression is an undertreated problem among African Americans (Brown et al., 1995). Pharmacotherapeutic treatments for depression must be carefully monitored in elderly patients because the consequences of treatment failure due to undermedication and the risk of drug toxicity resulting from overmedication may be more severe in older patients than in younger adults (Salzman, 1993; Pollock, 1996). One class of medications, selective serotonin-reuptake inhibitors (SSRIs), are increasingly prescribed to treat depression. However, the SSRI clinical trials were conducted primarily in younger patients, and there is a paucity of data on the effects of SSRIs on elderly patients. There is some preliminary data, however, showing that adverse effects in the elderly (e.g., insufficient antidiuretic hormone secretion, weight loss, extrapyramidal symptoms) differ considerably from those seen in younger persons, although the effects of chronic use of pharmacotherapeutic treatment of depression in the elderly are largely unknown. Maintenance doses of antidepressants have been shown to be effective in delaying the relapse of depression in elderly patients (Katz and Alexopoulos, 1996), but studies are needed on the long-term effects of these medications (Leo, 1996). Recent data on the prospective use of neuroleptics raise concerns about the extreme susceptibility of older patients to both acute and chronic neurological side effects. In particular, African Americans and patients with diabetes seem to be at increased risk for tardive dyskinesia (Pollock and Mulsant, 1995).

There are a number of additional areas in which ongoing research has been inconclusive about the risks and benefits of chronic drug use. For example, it has been found that there is a lower relative risk associated with fractures and heart disease among women who initiated estrogen replacement therapy within 5 years of menopause and who continue long-term use. However, there are unresolved questions about the possibility of an increased risk of uterine and breast cancer due to estrogen replacement therapy. Treating high cholesterol levels late in life has raised questions, inasmuch as there is some evidence that low choles

terol levels are associated with lowered serotonin function and greater risk of symptoms of depression.

Another issue to be considered in the chronic use of medications is the impact of medications with longer half-lives (e.g., alendronate, a new treatment for osteoporosis with a terminal half-life of approximately 10 years). Postmarketing surveillance will be important for evaluating the long-term effects and adverse outcomes of drugs that are used over long periods of time.

Use of Nutraceuticals

In addition to prescription and over-the-counter medications, there is a diverse group of other substances of interest-nutraceuticals. The term *nutraceuticals* is relatively new and is typically used to encompass dietary supplements, vitamins, herbal medications, sport drinks and energy bars, and herbal teas (DeFelice, 1991). These products have not been considered drugs, and most have not been examined with regard to their safety and efficacy. There are concerns about nutraceutical use by the elderly that relate to cost, unsubstantiated health claims, toxicity, and nutrient-drug interactions (Geriatrics Newsletter, 1996). However, neither the academic research community nor the food industry has made funding research and development a priority for this growing class of compounds. It has been difficult in the past to obtain persuasive data about traditional herbal remedies. In addition, there is disagreement over terminology (Are these products foods, supplements, drugs, etc.?), the dose that distinguishes a "food supplement" from a "drug," the data required by the Food and Drug Administration (FDA) to support health claims, the regulatory authority of the FDA over many of these products, and the manner in which nutraceuticals should be regulated. Further, the panoply of nutraceuticals has resulted in a deluge of information regarding their utility, with a paucity of research to support the claims of benefits, cures, or preventive effects. This situation, coupled with the often-held belief that the American diet is nutritionally adequate and a lack of knowledge regarding nutritional factors and malnourishment in the elderly, result in confusion regarding the status of nutraceuticals in the diet of elderly persons. What is known, however, is that the potential risks and benefits to the elderly resulting from the use of various nutraceuticals beyond current recommended doses are controversial. Very high amounts of these substances can interfere with normal metabolism, clinical laboratory tests, and with the action of prescribed medications. These reactions may cause serious problems for the elderly, particularly for those people with deteriorating health and inadequate nutrient intake. It has been suggested that elderly or chronically ill persons should not use high-potency nutraceuticals without medical supervision (Geriatrics Newsletter, 1996).

PHARMACOECONOMICS9

Increasingly, health care decision makers are insisting on having better information about the cost-effectiveness of pharmacotherapies. In addition to clinical and quality-oflife outcomes, clinical trials sponsored both by the pharmaceutical industry and the federal government are integrating analyses of the cost-effectiveness and cost consequences of pharmacotherapy as outcome variables.

The elderly population was estimated to spend an average of \$500 per capita for prescription drugs in 1991 (Long, 1994). This spending is disproportionate within the elderly population, with approximately 11 percent of the elderly population accounting for nearly half of the expenditures on prescription drugs (Long, 1994). The cost of medications is of concern to older persons, many of whom live on fixed incomes. Approximately 45 percent of the elderly population do not have insurance coverage for prescription drugs (Long, 1994), and many elderly people with insurance coverage cannot afford the high copayments, coverage limits, or both, for prescription medications. Medicare does not cover payments for outpatient prescription drugs, and as a result there is a piecemeal, inconsistent approach to prescription drug coverage that includes Medigap policies, Medicaid, other state assistance, retirement programs, and health maintenance organizations. Restrictive formularies, limited participation of pharmacies, and caps on reimbursements are other issues that many elderly persons face as a result of piecemeal prescription drug programs.

The economics of pharmacotherapy for the elderly encompass many factors beyond the direct cost of drugs including transportation costs, paid and unpaid assistance in the home for managing health care problems, and the cost of hospitalizations. The potential loss of earned income or productivity may also be an issue among those age 65 or over, and it is important to consider the intangible costs of pharmacotherapy, particularly on quality of life. In addition, there are costs associated with drug-related morbidity and mortality,¹⁰ which may result from treatment failures due to noncompliance or undercompliance with prescription regimens or adverse drug reactions, including those due to interactions with other medications, nutraceuticals, or foods. The fact that adverse drug reactions are more prevalent in the elderly population is in large part attributable to the increased number of medical problems they face, particularly chronic conditions in older patients and their increased use of medications. A further cost to society, which has not been well studied, is the undertreatment of medical conditions, which can have economic consequences by leading to inappropriate treatments or to the eventual presentation of more severe symptoms (an

⁹ This section is based on the workshop presentation by Dr. Andy Stergachis. ¹⁰ Drug-related morbidity and mortality for the entire U.S. population has been estimated to cost \$76 billion (Johnson and Bootman, 1995).

example of this is the undertreatment of glaucoma in elderly African Americans). The prevalence and cost of undertreatment are not well understood relative to pharmacotherapy.

Pharmacoeconomic research focuses on the economic savings resulting from use of medications—i.e., the relative trade-off between spending on pharmaceuticals and subsequent savings in medical care costs. There has, however, been little research focused on the cost-effectiveness of therapies that stratifies cost-effectiveness ratios by age. One study that has used this approach examined the cost-effectiveness of thrombolytic therapies and found the lowest (least favorable) cost-effectiveness ratio in younger patients and the most favorable in older patients (Mark et al., 1995). More studies are needed that stratify pharmacoeconomics as an endpoint not only by age, but also by other factors, such as quality of life, in an effort to provide the most cost-effective treatments.

There is a paucity of information regarding drug utilization among minority elderly persons and even less research on the economics of drug utilization among groups according to race and ethnicity. Fillenbaum and coworkers (1993) found a lower utilization of prescription and nonprescription drugs among African-American elderly populations than among Caucasian elderly populations. In both groups, health status and use of medical services were found to be the strongest predictors of prescription drug use. This contrasts somewhat with the 1987 National Medical Care Expenditure Survey, which found no significant differences in the percentage of African-American and Caucasian Medicare beneficiaries who received one or more drugs.

Few differences have been found in the percentage of elderly Americans with insurance coverage for prescription drugs by race or ethnicity; however, the type of coverage generally varies. Medicaid is more predominant among African Americans; employer-provided retirement assistance programs are more common among the younger old (age 60–74 years), particularly among Caucasians. A recent survey found that African Americans reported having more financial problems than Caucasians in covering their medical care expenses, including prescription drugs (Blendon et al., 1995). Research is needed to better understand the relationship between race and ethnicity and the economics of pharmacotherapy. It is, however, important to remember that there are other confounding variables within the heterogeneous elderly population.

Recent trends in health care delivery may have a significant impact on pharmacoeconomic studies. Increasing numbers of not only Medicaid recipients, but also Medicare enrollees, are moving to managed care plans, with the greatest growth occurring in Medicaid-based managed care plans. Many managed care plans currently provide prescription drug coverage for the elderly, but it is too early to evaluate the extent of coverage, the time frame for coverage, and its relative effect on the health of this group. State Medicaid databases are an important source of data for research on pharmacoeconomics, and there is concern that managed Medicaid plans will result in the loss of access to data on drug utilization and health outcomes. The unintended result of that would be to limit studies on pharmacotherapy in elderly populations.

CLINICAL TRIAL RECRUITMENT¹¹

Clinical trials are conducted to establish the safety and efficacy of drugs. There are several phases of clinical development of a drug. Phase I studies are usually conducted to establish a drug's safety. These are small trials that typically involve only healthy volunteers to determine pharmacokinetics and overall safety. Phase II studies establish a drug's pharmacological actions and note adverse reactions in individuals affected by the disease or condition for which the drug is targeted. Phase III studies evaluate a drug's benefits and risks in larger numbers of patients and in special populations. The data collected in Phase III studies help to better define safety and efficacy and provide important information to enable physicians to use the drug effectively. Phase IV postmarketing studies generally evaluate the drug under normal use conditions (OTA, 1993).

Until recently, most of the volunteers who have enrolled in clinical trials have been young Caucasian men. It is only in the past few years that citizen groups have pointed out this deficiency and ground rules for participation by women of child-bearing potential have been established, allowing their rather common inclusion in clinical studies. The elderly typically have not been recruited for clinical trials because of their multiple comorbidities, high prevalence of chronic illness, and chronic medication use (Wenger, 1993). As a consequence many studies have age-based exclusions (Gurwitz et al., 1992). However, the systematic exclusion of elderly populations from clinical trials leaves many questions unanswered with regard to age-disease interactions, diseasedisease interactions, disease-drug interactions, and age-drug interactions. These questions remain unanswered for elderly minority populations as well. Yet, increases in the size of the elderly population, increases in the range and extent of health problems associated with aging, and subsequent increase in the use of medications by the elderly (Chapter 1) make it imperative to study the safety and efficacy of drugs in this population. It has been estimated, for example, that if an effective medication could be developed to produce a 5-year delay in the age of onset of Alzheimer's disease, it would reduce the prevalence of this disease by 50 percent in one generation. If, for all diseases, the postponement of dependency for 1 month could be achieved for all people over 65 years of age, the cost savings would be approximately \$5 billion per month, or \$60 billion per year.

¹¹ This section is based on the workshop presentations by Drs. Richard Corriveau, Gregory Sachs, Nanette Wenger, and Jackson Wright.

A few additional demographic points that make pharmacotherapeutic research for the elderly imperative include

- the size of the population of the oldest old is increasing markedly;
- health status will decline and comorbidity will increase progressively with aging; and
- almost one half of the current U.S. population can anticipate living to age 80.

Given the statistics and demographics regarding the elderly, the FDA issued a guideline in 1989 for testing drugs in the elderly. The guideline was intended to encourage routine and thorough evaluation of the elderly in an effort to provide physicians with sufficient information regarding the use of drugs in older patients. The guideline states that, "there is no good basis for the exclusion of patients on the basis of advanced age alone, or because of the presence of any concomitant illness or medication, unless there is reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study. Attempts should therefore be made to include patients over 75 years of age and those with concomitant illness and treatments, if they are stable and willing to participate (FDA, 1989)." Although the FDA guideline is useful in providing a message that exclusion from a trial because of chronologic age is not appropriate, researchers are not legally required to follow the guideline (Gurwitz, 1993).

Nevertheless, there remain significant barriers to the inclusion of the elderly in clinical trials. Paradoxically, however, the barriers to their inclusion in trials are also the reasons to study this population. The barriers include

- the complexity of the elderly population, which can confound the study interpretation because of multiple diseases and therapies and coexisting psychological and social problems;
- differing physiology and pathophysiology in the elderly as compared to younger populations;
- problems with obtaining proper informed consent in those elderly patients who are confused, who are demented or become so during the study, or who have declining or fluctuating cognition; and
- the costs associated with recruitment and surveillance of the elderly, and the need for a larger sample size.

There are methodological issues, however, that can be utilized to overcome some of the barriers. With regard to the effects of heterogeneity and the associated increase in variability in response, trials can be stratified by clinically meaningful parameters such as the number of co-occurring illnesses, the number of drugs, measures of health status, and general measures of disability. Stratifying by those parameters can limit the effects of heterogeneity. Stratification may include groups that age successfully, groups that demonstrate typical aging (with illness and disability), and the frail elderly (i.e., those with multiple illnesses and severe disability). Outcomes that either maintain or enhance independence and functional status may be assessed, and outcomes that address prevention or complications of existing disease may be considered. In addition, a variety of endpoints should be examined other than mortality. More appropriate endpoints to consider in this population may include morbidity and functional status, quality of life, impact on coexisting illnesses, and costeffectiveness.

Other aspects of methodology that need to be explored include the selection of a subpopulation of older persons for a trial based on the purpose of that trial (e.g., a drug intervention trial may more appropriately involve a heterogeneous group of elderly to test efficacy in a broad sample, whereas targeted interventions may involve a more homogeneous subpopulation). Selection of the subpopulation of elderly persons may condition the intervention (e.g., the specific design of an exercise intervention is unlikely to be similar for healthy and ill older persons). Finally, selection of the subpopulation may affect the generalizability of the results (Harris, 1993).

Ethical considerations may need to be broadened with regard to the participation of elderly persons in clinical trials. Whereas previously the emphasis was on symptomatic relief, it may be important to include quality of life and prolongation of life as issues that should be considered in future studies. In addition, there may be a need to identify population subsets with the greatest potential for benefit or for harm from an intervention.

Complicating the ethical issues related to this group is the number of elderly persons with dementia. The capacity to make decisions and give informed consent is a difficult issue. Statistically, the elderly are more likely than the young to be affected by dementia or to be cognitively impaired. Furthermore, this population more frequently suffers from delirium and psychiatric illnesses than do younger cohorts. All of these conditions raise questions about the ability to give consent to participate in studies. There is also a concern about nursing home residents and their ability to give consent free from coercion. Further, elderly persons may be subject to abuse by others and are more likely to be impaired by the toxic metabolic effects of illness. Nonetheless, research with elderly persons who are capable of making decisions is governed by exactly the same principles and processes as clinical research with other age cohorts. The researcher clearly has an obligation to investigate and determine the cognitive capacity of each potential study participant (Dubler, 1993).

The recruitment of elderly minority populations into clinical trials, especially African Americans, has proved to be difficult. A variety of factors have contributed to this situation:

- occurrences of research exploitation of minority populations (e.g. sicklecell screening programs, involuntary sterilization, and the Tuskegee syphilis experiments);
- the limited access of many minority persons to health care (including high-technology and costly interventions);
- a lack of trust placed in the medical community (e.g., the view of AIDS as being a genocidal plot);
- frustration over an inability to have access to costly pharmacotherapeutic interventions once medications are chosen as the therapy of choice;
- a poor understanding of the need for clinical trials;
- a poor understanding of the safeguards in place in human subject research; and
- difficulty in getting to the site of a trial.

Yet it is important to include minorities in drug trials, as there may be significant differences in drug metabolism and therapeutic outcomes between ethnic groups. Crosscultural validation of quality-of-life measures and utility measures (i.e., patient preferences and values) are also important in assessing the efficacy of drug therapies.

Several mechanisms have been suggested to overcome some of these difficulties. It is important to obtain the endorsement of community physicians and leaders within the African-American community. Additionally, clinical trials should be advertised at cultural events and community gathering places (e.g., churches, barber shops). Ensuring that study participants are treated with dignity and respect is another critical factor. Other mechanisms to increase African-American participation in clinical trials include

- the association and collaboration of universities and historically African-American colleges in administering trials;
- educating individuals and communities about the benefits of participation in trials and about the safeguards in place for human subject research;
- recruiting minority researchers and staff to enlist patients into clinical trials;
- educating and disseminating information to the community about the knowledge that will be gained from the study and its potential impact on disease prevalence within the minority community; and
- providing transportation (or reimbursement for travel) to the study site.

The ability and commitment of researchers to accommodate the study population will affect success in minority recruitment. This issue is important both to ensure equal generalizability in populations that may demonstrate differences in drug metabolism from those seen in other ethnic groups and to validate cross-cultural quality-of-life measures.

INFORMATION DISSEMINATION¹²

Disseminating the immense amount of frequently changing and technically detailed information about pharmacotherapeutic interventions in a timely manner presents an ongoing challenge. The targets for this information—physicians, pharmacists, other health professionals, and patients—each have their own set of information needs and ways they access information.

Physicians and Pharmacists

Information on new medications and on drug interactions changes rapidly. As a result, some of the biggest challenges facing physicians and pharmacists concern updating existing information and accessing new information. Health professionals are trained to remember large amounts of information, unfortunately, they find it difficult to forget outdated information. Having an efficient way of delivering information so that it reaches health professionals at the time they are making decisions about drug therapy and writing or filling a prescription is a key need. Information is also critically needed when patients are being monitored for compliance and intended outcomes.

Determining a patient's current and prior drug profile is another challenge. Many elderly persons have several diseases and take numerous medications, and they frequently see several health care professionals and obtain their medications in a variety of locations. All of these factors make it difficult to individualize drug information and to track prescriptions. The disparate nature of the health care system and the inadequacies of medical records place the information burden on patients by requiring them to remember each of their numerous medications. Additionally, it is important for information dissemination to flow in two directions—i.e., health care professionals need to educate patients on appropriate medication use and drug interactions, and they also need to receive information from their patients regarding their medication use, adverse effects, and other negative and positive outcomes.

Patients

The elderly population varies with regard to their knowledge and understanding of drug-related information. At one end of the spectrum are elderly patients who are extremely knowledgeable about their health and their medica

¹² This section is based on the workshop presentations by Dr. Stephen Pauker and Dr. Jeffrey Halter.

tions. Pharmaceutical advertisements, direct mail information, and the growth of consumer health information and the Internet all assist patients who want to be well informed and want to discuss this information with their health care professional. Addressing the questions of well-informed patients raises a number of issues including the need for high-quality data and an increased length of time for patient-health professional interaction.

Toward the other end of the spectrum are those older persons who may have decreased cognitive function primarily related to the speed with which they process information (Park and Halter, In press). Older patients may have less working memory capacity, may experience visual and hearing limitations, and may have problems sorting out critical information. Although they generally have more experience with the medical system, they tend to seek out less information when making medical decisions than do younger persons. Drug-related information is often presented using complex terminology, and older patients can get overloaded with the extensive amounts of information that are not provided in an accessible or coherent way. Thus, the challenge is to present drug-related information and that will assist them in making informed decisions about their medical treatment. In addition, attempts to overcome challenges in the elderly population such as impaired vision, poor manual manipulation skills, and memory lapses may be assisted by devising new methods for distributing medications, such as by automating pillboxes or other medication delivery systems.

Cultural differences and disparate ethnic backgrounds between health care providers and elderly patients from minority populations may interfere with the effective transfer of information about drug use and potential side effects. Further, health care providers may not be aware of the community groups and service resources that are available to provide information to patients of different ethnic backgrounds regarding their medication use.

INVESTIGATORS¹³

There are serious shortfalls in the number of primary care physicians and internists trained in geriatrics, the number of physicians trained in geriatrics, and the number of geriatricians involved in research and education, including geriatric pharmacology research. As with many other fields of medical research, funding is increasingly scarce and more time-consuming to secure, and the economic realities resulting from changes in the health care system are diverting funds away from research training. Moreover, the applied nature of much of

¹³ This section is based on the workshop presentations by Drs. Jesse Roth and John Ruffin.

geriatric pharmacotherapy research puts it outside the mandate of funding agencies such as NIH. In addition, geriatric medicine fellowships have been shortened from 2 or 3 years to 1 year which has resulted in inadequate time for research and an almost exclusive focus on clinical training. Another problem in attracting geriatricians to research endeavors is the need for clinical geriatricians to treat the increasing numbers of elderly patients.

Thus, there is a need to develop mechanisms for attracting and retaining researchers in geriatrics. There are many decision points along a typical career path that may be addressed to reach this goal. First, it is important to attract young people who are in college or recently graduated. New approaches suggested by the workshop speakers included a 1- or 2-year postbaccalaureate program that would provide research assistant positions in geriatric medicine programs linked to pharmacology and clinical therapeutics. Such a postbaccalaureate program offered by schools of medicine or pharmacy could provide exposure to research and clinical activities and to a series of role models including geriatric physicians, clinical pharmacists, and investigators evaluating drugs used with the elderly. The predoctoral Intramural Research Training Award fellowship at NIH was suggested as a model for a postbaccalaureate program in geriatric pharmacology and clinical therapeutics. The latter program would include schools of pharmacy and pharmacy clinicians. The post-baccalaureate program, in addition to providing inspiration and role models for nascent researchers, would also provide much needed assistance to their mentors, young investigators in the field.

The beginning years of the research track are often difficult due to an increasing gap between the availability of initial funding and the assurance of long-term funding. As originally conceived, there was continuing support from fellowship training to first awards to independent grant support. However, the gap has widened between fellowship training and independent support. This issue needs to be addressed in order to assure continuity of support for young investigators. Loan-forgiveness programs could be developed modeled on the NIH loan-forgiveness program for researchers in AIDS. Stipends that are competitive with salaries for people with similar experience are needed. Potential sources for such stipends include the FDA, the Department of Veterans Affairs, the Department of Defense, pharmaceutical companies (models include the programs sponsored by Merck in partnership with the American Federation for Aging Research or the program sponsored by Pfizer in partnership with the American Geriatrics Society), foundations (e.g., the Hartford and Brookdale Foundation programs), or insurance companies. Another potential mechanism is the NIH R03 grant, a one-time research award available to young investigators so they can garner the preliminary data needed to apply for more definitive funding such as an NIH First Independent Research Support and Transition Award (R29) or an NIH Independent Investigator Award (R01). It is equally important to retain midcareer professionals in this field. Mechanisms for support

at this stage of the career include merit awards at the midcareer level and research sabbaticals to retrain midcareer geriatricians in research methodologies.

Recruiting minority students into the field of geriatrics, and specifically geriatric pharmacology and clinical therapeutics, is of importance. Collaborations and true partnerships are needed between minority institutions (e.g., historically black colleges and universities) and academic health sciences centers to provide minority students with extensive research training in this field. The National Institute of General Medical Sciences and the NIH Office of Research on Minority Health have initiated model programs to build these partnerships through an M.S.–Ph.D. program. Students at minority institutions who are accepted into a master's program at the minority institution are simultaneously accepted into the Ph.D. program at the affiliated academic health sciences center. The student can choose his or her research subject from either institution and have research mentors at both. Programs that are truly collaborative will benefit the entire community and will increase the number and diversity of motivated, well-trained investigators.

SUMMARY OF THE WORKSHOP¹⁴

The topics presented in this workshop fall into two main categories: approaches to research issues and the resources needed to carry out research. The research issues that need to be addressed in this field are numerous and can overwhelm the resources available for investigator-initiated research. It is crucial to overcome the traditional linear way of thinking about sciences moving exclusively from the laboratory bench to the bedside and instead recognize that research ideas need to be exchanged between the laboratory, clinical, and social sciences. Future research should emphasize interdisciplinary efforts and should not overlook the role of the social sciences in studying pharmacotherapy in elderly populations. The broad scope of important research questions will have to be addressed by encompassing a range of methodologies including observational as well as traditional experimental studies.

Ensuring adequate, sustained research funding is of critical importance—without that, it will be impossible to pursue answers to the research questions identified for this field. As discussed throughout the workshop, there are a number of innovative methods that could be implemented to increase recruitment of minority elderly populations in clinical trials. In addition, the maintenance of professional career paths will require new and expanded approaches and funding mechanisms. Finally, the changes taking place in the health care system will continue to present challenges and will require a reassessment of the optimal

¹⁴ This section is based on the summary presentation by Dr. Marcus Reidenberg.

way to answer the numerous questions on pharmacokinetics and drug interactions in elderly populations.

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3

Conclusions and Future Research Directions

The ongoing study of pharmacokinetics, pharmacodynamics, and drug interactions in elderly persons is critical for the development of safe and effective therapies and for the prevention of drug toxicities and adverse drug reactions. Aging is associated with an increase in chronic illness and anatomical and physiological changes that affect drug distribution, metabolism, and excretion. Thus, as the number of older Americans increases, it can be expected that polypharmacy in this population will have significant health, social, and economic consequences. Additionally, research should focus on alleviating the disease burden in elderly minority populations.

Box 3.1 summarizes the committee's conclusions regarding future directions for research in this field. The remainder of this chapter provides a more detailed discussion of the committee's conclusions.

RESEARCH NEEDS AND OPPORTUNITIES

Expanding the Scientific Knowledge Base

Although progress has been made in understanding the aging process, there is still a paucity of data at the intracellular, organ, system, and population levels. The impact of aging on cells and organ systems has commonly been studied in isolation; however, a more integrated approach is needed that will examine the effects of aging on the body. Pharmacokinetic and pharmacodynamic models need to be developed that encompass the entire range of changes occurring at multiple levels throughout the body.

BOX 3.1: MAJOR CONCLUSIONS AND FUTURE DIRECTIONS

Research

- Develop an integrated approach to researching the effects of aging on multiple organ systems
- Develop more sophisticated pharmacokinetic and pharmacodynamic models of multiple drug regimens and multiple drug interactions
- Examine the social and psychological aspects of medication use in the elderly
- Implement longitudinal studies of chronic use of medications by older persons
- Develop research databases that link health outcomes and prescription medication information, explore the feasibility of a national data resource
- Develop mechanisms for effectively disseminating drug-related information to health professionals and to elderly patients
 Recruitment into Clinical Trials
- Include the older and frailer segments of the elderly population in clinical trials
- Expand recruitment of elderly minority populations into clinical trials Capacity Building
- Recruit young health professionals into geriatric pharmacology and clinical therapeutics research
- · Provide continuity of funding for young investigators
- · Implement incentives to retain mid-career professionals
- Develop programs to retrain mid-career professionals in research methodologies and geriatrics

The following list highlights specific areas of research that would add to the body of knowledge and clarify our understanding of the aging process especially with regard to improving pharmacotherapy. This list is by no means comprehensive, as numerous research avenues could yield important information on the impact of pharmacotherapy and drug interactions in the elderly. Areas for future research include the impact of aging, gender, genetics, and ethnicity on physiology and metabolic processes. Specifically,

- age-related changes in cellular transport mechanisms and extrahepatic metabolism and transport including the activity of different enzyme isoforms;
- biomarkers of drug exposure;
- mechanisms that cause variable responses to medications in aging racial and ethnic populations;

- age-related hormonal changes affecting drug metabolism or drug sensitivity;
- the impact of nutrition on the aging process;
- mechanisms underlying diseases prevalent in the elderly (e.g., hypertension, diabetes, osteoporosis, and Parkinson's and Alzheimer's disease);
- in vitro models for multiple drug regimens and multiple drug interactions that may be predictive of and correlated with in vivo research;
- models for drug interaction related to altered reflex activity and changing homeostatic mechanisms;
- the potential beneficial and adverse health effects of nutraceuticals; and
- social and psychological aspects of medication use in the elderly (e.g., access to medications, adherence to prescription regimens), with a special emphasis on minority populations.

Addressing Issues in Minority Populations

Many diseases are disproportionately prevalent in elderly African-American and other minority populations. The causes and implications of this excess burden need to be more completely understood and addressed. For example, hypertension and the impact of antihypertensive medications in elderly African Americans have not been fully studied even though the morbidity and mortality is higher in this population than in other segments of the aging population.

Research is needed on multiple levels (molecular, cellular, system, population) to clarify the effect of race and ethnicity on disease prevalence and on variations in the effectiveness of pharmacotherapeutic and other treatment interventions. Such research would be a valuable tool in increasing our understanding of the physiology of aging for all populations and may have implications for pharmacotherapies aimed at various elderly groups. Research on diseases and health conditions that primarily affect minority elderly populations needs to be a priority to alleviate the disease burden experienced by these populations.

Recruitment of Elderly Patients into Clinical Trials

In 1989, the FDA published a guideline for the inclusion of elderly persons in clinical trials (FDA, 1989). However, a number of characteristics of the elderly population may present barriers to conducting clinical trials that are representative of this population. Studies need to include the oldest segment of the population (see Chapter 2). In addition, subgroups of the elderly population should be stratified based primarily on their functional status and disease burden and less on their chronological age.

Recruiting minorities for inclusion in studies should be a priority, although it is important to recognize the trends toward multiracial backgrounds and the complexities associated with categorizing race or ethnicity. The workshop speakers presented many innovative ideas about increasing the recruitment of minority populations. The committee supports a number of approaches, including providing transportation, involving the minority community, providing extensive patient education, and decentralizing clinical trials (i.e.., going to patients' homes or to community centers to provide and assess treatment). In addition, collaborative efforts and consortia need to be strengthened between historically minority and other academic institutions. These partnerships will be vital to recruiting minority investigators and to attracting and sustaining minority students in research programs. Further, patient recruitment efforts can draw on the populations available to both institutions.

Obtaining informed consent in elderly populations involves complex issues that need to be addressed including the extent of dementia or cognitive impairment in some elderly patients and their vulnerability to coercion. Informed consent forms have evolved into highly technical legal documents, and a reevaluation of how to best meet their original purpose is needed. Other ethical issues that need to be addressed include studies on vulnerable populations (e.g., nursing home residents) and the confidentiality of patient information.

Research Methodologies and Tools

Trials of acute drug use are well funded; however, there are few long-term studies that examine chronic effects and drug interactions. Inasmuch as elderly persons are living longer and may take the same medications for many years, increased postmarketing surveillance is needed to examine the effects of long-term use of drugs. Incentives to strengthen postmarketing surveillance should be considered. Some of these drugs (e.g., hormone replacement therapy, antidepressants, and lipid-lowering medications) may be used as preventive measures (e.g., treating high cholesterol levels in the absence of cardiovascular disease or prescribing hormone replacement therapy to prevent hip fractures); however, their long-term health effects are not fully known. Further, the pharmacodynamics of many of these medications are only beginning to be investigated.

Research Methodologies

Studying the impact of pharmacotherapy on the elderly population is often difficult from a methodological standpoint. Cross-sectional studies are problematic because confounding variables abound among the elderly, and it is difficult to distinguish the effects of aging from those of disease. Randomized clini cal trials often recruit study subjects who represent the younger segments of the elderly population, and who have fewer comorbid conditions, use fewer medications, and may be more compliant in terms of following prescription medication regimens. In addition, many studies use small numbers of patients, frequently with homogenous geographic and ethnic backgrounds. Longitudinal studies are needed that involve large numbers of patients who reflect the diversity of "real world" populations. Furthermore, studies of elderly populations should include observational studies, case-control studies, and cohort studies to take advantage of the realm of methodological approaches that are available. Studies of optimal pharmacotherapies need to consider their cost-effectiveness and delivery. Outcome measures must also be reexamined, and quality-of-life outcomes need to be considered. One workshop speaker recalled the adage that, "adding life to years is at least as important as adding years to life."

Databases Available for Research

There is a notable lack of adequate databases to research the prevalence and health impact of adverse drug reactions in elderly populations. Prescription information on elderly persons is not currently linked to diagnostic information or health outcomes data. For example, state Medicaid databases are used to reimburse pharmacies for prescriptions, therefore, the data on medication utilization are quite complete and accurate. However, diagnostic information for outpatient care is often incomplete or unavailable, and is not linked to pharmacy utilization databases.

Current changes underway in the health care delivery system may provide opportunities for new databases to be developed, although there are concerns that these changes may instead result in the loss of publicly available data. Trends of interest include the purchase of pharmacy benefit companies by pharmaceutical manufacturers and the increased use of managed care through proprietary health plans paid for by Medicaid and Medicare. Increased use of managed care to provide health care for the elderly offers opportunities for databases to be implemented that would link health outcomes (particularly adverse drug reactions) and prescription information, while paying close attention to patient confidentiality issues. However, these changes may instead be implemented to restructure datasets and require new levels of approval for data use or publishing. It is crucial that the larger issues involving potential censoring or loss of publicly available data on prescription drug use and health outcomes be addressed. The increased privatization of health care services for the elderly may lead to barriers to accessing datasets due to proprietary and competitive interests.

An area of interest to the committee is exploring the feasibility of developing a cooperative national data resource that would expand the researcher's

ability to examine population-based data rather than utilizing a piecemeal approach to data collection. This data resource could include information on diagnosis, medications prescribed, clinical interventions, health outcomes, and other relevant data. Of utmost importance would be maintaining patient confidentiality. This resource could be utilized as a repository to which individual researchers could submit peer-reviewed and approved research questions. Examining the feasibility of developing such a data resource would require the input of patients, health care providers, researchers, ethicists, and other interested persons and groups.

Dissemination of Information

Drug-related information can be complex, and information overload is a common phenomenon among health professionals and patients. Because information regarding drug use and interactions changes rapidly, information systems should be available to health care professionals that can provide up-to-date information that is unbiased, case specific, interactive, and readily accessible. In addition, it is important to develop diverse information dissemination strategies to effectively meet the needs of the heterogeneous elderly population. The information provided should be presented in a manner that can be understood by patients who cannot necessarily process complex information, yet need to make informed decisions and understand their options for treatment. Private- and public-sector initiatives are required to address this critical challenge. Health sciences centers that focus on training medical, nursing, and pharmacy students should be used to conduct independent, unbiased research and continuing education programs for practicing physicians, pharmacists, nurses, and the interested public (Woosley, 1994).

Capacity Building: Researchers and Clinicians

One of the major factors limiting the expansion of research in the area of geriatrics, and particularly geriatric pharmacology and clinical therapeutics, is the small number of health professionals entering this field. This is an area in which, as demographers can attest, the patient base is expanding and will continue to grow. Quality geriatric care depends on the development of multidisciplinary teams (including nursing, physical and occupational therapy, social work) to assess the concomitant problems and implement multiple interventions. However, reimbursements do not adequately cover the time required to handle the complexity of geriatric care. A recent report by the Alliance for Aging Research (1996) found that the United States has less than one fourth the number

of academic physician-scientists needed in geriatrics to teach and conduct research.

There is a pressing need to develop innovative approaches for recruiting and retaining researchers and clinicians. Programs are needed at many points along the career path, beginning early in the college and postbaccalaureate years to kindle an interest in the field of geriatrics and continuing throughout the professional years to retain the best investigators and clinicians available. Recruitment of minority investigators should be included within broader programs supporting young and mid-career investigators. The options available for approaching this issue include

- 1- to 2-year postbaccalaureate programs to provide research and clinical experience to young people considering a career in this field;
- opportunities for medical, nursing, pharmacy, and other health professional students to have additional exposure to geriatric treatment and research during their education;
- collaborative efforts between minority academic institutions and academic health sciences centers to encourage minority students to pursue a research program in this field;
- loan-forgiveness programs to assist young researchers with high debt loads from health professional or graduate schools;
- new sources of fellowships (e.g., through FDA, pharmaceutical companies, or insurance companies);
- increased commitment to funding from fellowship training to first awards to independent grant support;
- merit awards at the midcareer level and specialized sabbaticals to retrain midcareer professionals; and
- retraining in research methodologies during sabbaticals for midcareer level geriatricians.

SUMMARY

Currently there is only a limited understanding of the impact of aging on pharmacokinetics, pharmacodynamics, and drug interactions. Research is needed at the molecular, cellular, organ, system, and population levels for safer and more effective medications to be developed, delivered, and utilized by elderly persons. In addition, attention must be given to understanding and alleviating the disproportionate disease burden in elderly African-American and other minority populations.

The committee's major conclusions are summarized in Box 3.1 at the beginning of this chapter. The committee discussed and reflected only on the workshop presentations and acknowledges that there are numerous research

opportunities in geriatric pharmacology that need to be explored. Research in geriatric pharmacology and clinical therapeutics will require a commitment to fund studies that can further elucidate the relationship between pharmacokinetics and adverse drug interactions in the elderly and the complex individual variability of the aging process. Increasing the knowledge base will enable more effective therapeutic interventions and improved quality of life for the growing population of elderly persons.

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Appendix

Workshop Agenda, Speakers, and Participants

Pharmacokinetics and Drug Interactions in the Elderly and Special Issues in Elderly African-American Populations

Institute of Medicine

National Academy of Sciences

Committee on Pharmacokinetics and Drug Interactions in the Elderly

April 9, 1997

Xavier University of Louisiana

College of Pharmacy

New Orleans, LA

AGENDA

8:30–9:15 a.m.	Welcome
	Marcellus Grace
	Dean
	College of Pharmacy
	Xavier University of Louisiana
	John Ruffin
	Director
	NIH Office of Research on Minority Health
	J. Taylor Harden
	Assistant to the Director for Special Populations
	National Institute on Aging
	Leslie Z. Benet, Committee Chair
	University of California, San Francisco

Janice Schwartz

Definition of the Elderly Population Northwestern University Medical School

MORNING SESSION

State of the Science and Future Opportunities

9:15–10:00 a.m.	Physiology of Aging
	What are the age, gender, race, disease, and environment
	related factors influencing physiology as they impact
	pharmacotherapy?
	Overview
	Fran E. Kaiser
	St. Louis University
	Hypertension in Elderly African Americans
	Keith Ferdinand
	Xavier University of Louisiana
10:00-11:00 a.m.	Intracellular Function
	What are the age, gender, race, disease, and environment
	related factors influencing intracellular function as they
	impact pharmacotherapy?
	Kinetics—Enzymes and Transport Proteins
	Grant Wilkinson
	Vanderbilt University
	Receptors
	Physiologic
	Darrell R. Abernethy
	Georgetown University Medical Center
	Neurologic
	Kurt Rasmussen
	Eli Lilly and Company, Inc.
11:00–11:30 a.m.	DISCUSSION

11:30 a.m12:15 p.m.	Response and Outcomes
	What are the age, gender, race, disease, and environment
	related factors influencing response and outcomes?
	Response
	Jeffrey Halter
	University of Michigan
	Outcomes—Pharmacoepidemiology
	Jane Cauley
	University of Pittsburgh
	Economics of Pharmacotherapy
	Andy Stergachis
	University of Washington
12:15–12:45 p.m.	DISCUSSION
12:45–1:30 p.m.	LUNCH

AFTERNOON SESSION

Resources and Opportunities

What are the barriers and opportunities related to age, gender, race, disease, and the environment in pharmacotherapy research?

1:30–2:30 p.m.	Recruitment of Study Participants
_	Defining the Study Population
	Nanette Wenger
	Emory University
	Greg Sachs
	University of Chicago
	Issues in Recruiting and Retaining African
	Americans in Clinical Trials
	Techniques in Recruitment
	Jackson Wright
	Case Western University
	Compliance and Other Issues
	Richard Corriveau
	Xavier University of Louisiana

2:30-3:30 p.m.	Chronic Medication Use
	Pharmaceuticals
	Bruce Pollock
	University of Pittsburgh
	Nutraceuticals
	Louis Lasagna
	Tufts University
	Methodology
	Wayne Ray
	Vanderbilt University
3:30–3:45 p.m.	BREAK
3:45–4:00 p.m.	Dissemination of Information to Prescribers, Pharmacists,
-	Patients
	Stephen Pauker
	New England Medical Center
4:00–4:20 p.m.	Investigators/Funding
-	Jesse Roth
	Johns Hopkins University School of Medicine
4:20–5:10 p.m.	DISCUSSION
5:10–5:30 p.m.	Summary
-	Marcus Reidenberg
	Cornell University Medical Center
5:30 p.m.	Adjourn

SPEAKERS

Darrell R. Abernethy Francis Cabell Brown Professor of Medicine and Pharmacology Director Division of Clinical Pharmacology Georgetown University Medical Center Washington, DC Leslie Z. Benet Professor and Chairman of **Biopharmaceutical** Department Sciences University of California, San Francisco San Francisco, CA Jane Cauley Associate Professor Graduate School of Public Health University of Pittsburgh Pittsburgh, PA **Richard Corriveau** Director, Clinical Trials Unit College of Pharmacy Xavier University of Louisiana New Orleans, LA Keith Ferdinand Professor. Clinical Associate Pharmacology Medical Director, Heartbeats Life Center College of Pharmacy Xavier University of Louisiana

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47

Bruce Pollock Professor of Psychiatry and Pharmacology University of Pittsburgh School of Medicine Pittsburgh, PA Kurt Rasmussen Neuroscience Research Therapeutic Area Discovery Research and Clinical Investigation Eli Lilly & Company, Inc. Indianapolis, IN Wayne Ray Professor Department of Preventive Medicine and Public Health Vanderbilt University School of Medicine Nashville, TN Marcus M. Reidenberg Clinical Pharmacology and Therapeutics Cornell University Medical Center New York, NY Jesse Roth Raymond and Anna Lublin Professor of Medicine Division Director, of Geriatric Medicine Johns Hopkins University School of Medicine Baltimore, MD John Ruffin Director Office of Research on Minority Health National Institutes of Health

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