RACIAL AND ETHNIC DIFFERENCES IN RESPONSE TO MEDICINES: TOWARDS INDIVIDUALIZED PHARMACEUTICAL TREATMENT

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It is now well documented that substantial disparities exist in the quality and quantity of medical care received by minority Americans, especially those of African, Asian and Hispanic heritage. In addition, the special needs and responses to pharmaceutical treatment of these groups have been undervalued or ignored. This article reviews the genetic factors that underlie varying responses to medicines observed among different ethnic and racial groups. Pharmaco-genetic research in the past few decades has uncovered significant differences among racial and ethnic groups in the metabolism, clinical effectiveness, and side-effect profiles of many clinically important drugs. These differences must be taken into account in the design of cost management policies such as formulary implementation, therapeutic substitution and step-care protocols. These programs should be broad and flexible enough to enable rational choices and individualized treatment for all patients, regardless of race or ethnic origin. (*J Natl Med Assoc.* 2002; 94:1–26.)

Key words: race ◆ ethnicity ◆ pharmaceuticals ◆ pharmacogenomics

The recent report of the Institute of Medicine (IOM), "Unequal Treatment: Confronting Racial and Ethnic Disparities in Healthcare," illustrates in eloquent scientific detail that racial and ethnic disparities in health care do exist and are prevalent in both the treatment of medical illness and in the delivery of health

care services to minorities in the United States.[1] Of greater significance is the finding that these disparities still exist even after adjustment for differences in socioeconomic status, insurance coverage, income, age, comorbid conditions, expression of symptoms, and access-related factors. These disparities are not confined to any one aspect of the health care setting, and can even be found in the delivery of pharmaceutical services, which are under increasing cost control measures.

Implicit in this transaction is the ultimate outcome of increased morbidity and mortality for African Americans and other minorities. This is mostly due to a diminished quality of medical care and health services, but also due to a predilection to avoid using better quality

but higher costing pharmaceuticals in the treatment of African American and other minorities by practitioners and health care institutions.

The conscious or unconscious decision by health care providers to withhold needed pharmaceuticals and services from minorities is most notable in several key diseases. Studies in cancer patients demonstrate that chemotherapy[2] and analgesic therapy[3] are more likely to be given to nonminorities. African Americans with HIV disease are less likely to receive antiretroviral agents,[4] prophylaxis for *Pneumocystis* pneumonia and protease inhibitors compared with nonminorities.[5] In the area of cardiovascular care, there are clear differences in treatment regimens after coronary angiography, not related to clinical factors.[6] As reported elsewhere in this publication, studies have shown that African Americans and Hispanics receive fewer antidepressants for clinical depression, and are relatively under-treated with analgesics for pain from fractures or postoperative pain.[7] African American and Hispanic patients with severe pain of any cause are less likely than White patients to be able to obtain commonly prescribed pain medicine because pharmacies in predominately non-White communities do not normally carry adequate stocks of opiates.[8]

In assessing potential sources of disparities in health care, the 2002 IOM report identified patient-level, provider-level and health care system-level factors that might play a role beyond access-related causes of disparities. Patient-level and provider-level attributes were felt to be largely based on racial attitudes, discrimination, bias, stereotypes, and clinical uncertainties that exist in the United States. This is reflected in their conclusion "that much of American social and economic life remains ordered by race and ethnicity, with minorities disadvantaged relative to Whites."

Health care system-level factors, however, can be influenced and modified by government through appropriate public policy. The current evolution in the organization, financing and delivery of health care services, including pharmaceutical services, toward managed care models bent on cost containment has adversely affected African Americans and minorities.[9]

Publicly funded managed care plans, especially Medicaid HMOs, may paradoxically reduce access to health care services for minorities.[9] A distressing outgrowth of these efforts to contain costs in public insurance plans is the emergence of new state laws requiring generic drug substitutions for Medicaid recipients. Effective October 1, 2002, in New York and other states, Medicaid patients will have to use generic drugs in lieu of brand name drugs as a matter of law, if such drugs have been determined to be "therapeutically equivalent." Exemptions can be sought by persons or entities providing a valid study showing that the generic is less effective than the brand, has untoward outcomes or adverse side effects, or a potential negative impact on a recipient within a special population. This will impose barriers that busy health care providers can seldom overcome. It also imposes an additional duty and obligation upon health care institutions that serve these patients to monitor outcomes in using generic drugs on "all comers."

There is good evidence to show that therapeutic substitution of drugs within the same class places minority patients at greater risk. This is because effectiveness and toxicity can vary among racial and ethnic groups. Physicians and managed care plans must be more alert under these new "formulary laws" for atypical drug responses or unexpected untoward side effects when treating patients from racial and ethnic minority groups. Dosage adjustments might be necessary in using generic drugs as therapeutic substitutions in untested racial and ethnic groups. There is a distinct possibility of a toxic accumulation of such drugs from slower metabolism, or the need for medical service substitutions to supplement the ineffective generic drugs in some racial and ethnic and minority groups. Either outcome will demand a greater use of health system resources and thus obviate the original purpose of cost containment.

The high concentration of minorities within the Medicaid population and with "bare bones" health plans sets the stage for health care disparities in the statutory use of "therapeutically equivalent," but untested, generic drugs within this group. This typifies what is referred to in the 2002 IOM report as the socioeconomic fragmentation of health plans. It has been suggested that such fragmentation leads to the development of "different clinical cultures, with different practice norms, tied to varying per capita resource constraints." None of this favorably impacts outcomes in health care for racial and ethnic minorities.

A greater effort must be undertaken by policy makers to hold publicly funded health plans accountable for providing beneficiaries with products and services equal in quality to those of privately funded health plans.[10]

Consideration must also be given for patient protections as more beneficiaries are enrolled in Medicaid managed care HMOs. As with private managed care organizations, a number of issues should be addressed, including full pharmacy benefits. A clear mechanism must be in place to appeal denied services and the availability of nonformulary medications. The latter becomes particularly important in assessing the provision of needed brand name, nongeneric medications in states where the statutory use of "therapeutically equivalent" generic drugs is mandated. The physician's duty is to prescribe the most efficacious and safe drug for patients even if a lengthy appeals process before a formulary committee or institutional board is the price to pay to best serve the patient's interest.

The goal of individualized pharmaceutical therapy is to provide the right drug to the right patient for the right illness in the right dose at the right time. The recent confirmation of the large gaps in health care equality between minorities and whites in America should provide a further incentive and a redoubling of the efforts of all responsible health care providers to rapidly close this gap.

EXECUTIVE SUMMARY

This monograph reviews the genetic, environmental, and cultural factors that underlie variations in drug response among different racial and ethnic groups. (While the meanings of the terms 'racial' and 'ethnic' continue to evolve, here 'racial' refers to genetically defined differences—most obviously, for example, skin pigmentation—while 'ethnic' refers to cultural differences. Thus, 'Hispanic' defines an ethnic group that includes several different races.) Racial and ethnic groups comprise important subpopulations whose special needs and drug responses have traditionally been undervalued or ignored. The article focuses on drug classes in which differences in drug response because of racial and ethnic variation may directly affect institutional policies such as formulary management, therapeutic drug substitution, and step-care protocols. Available information suggests that patients in particular racial and ethnic groups may be subject to greater risks than those in other groups if they are prescribed or switched to an "equivalent" drug because: (1) the agent may not be as effective; or (2) substantial dosage adjustments may be necessary to avoid overdosing or underdosing.

The factors determining racial variations in response to medications are complex and interdependent. Environmental factors (climate, smoking, alcohol consumption, etc.) may have a profound effect on drug metabolism and disposition. Cultural or psychosocial factors may affect the efficacy of or adherence to a particular drug therapy. Genetic factors, however, are the major determinants of the normal variability in drug effects. The study of genetically determined variations in drug response resulting from inherited differences in drug metabolism or drug targets is called pharmacogenetics, when referring to the study of individual genes, or pharmacogenomics, when referring to the study of all of the genes, i.e., genome.

Pharmacogenetic research in the past few decades has uncovered significant differences

among racial and ethnic groups in the metabolism, clinical effectiveness, and side effect profiles of therapeutically important drugs. Most studies have concentrated on cardiovascular agents (beta-blockers, diuretics, calcium channel blockers, and angiotensin-converting-enzyme inhibitors) or central nervous system agents (antidepressants and antipsychotics). Analgesics (acetaminophen, codeine), antihistamines, and alcohol are other pharmacologic compounds with varying effects among different racial and ethnic populations. Most of the research applies to African Americans, Asians, and Whites. Fewer studies have specifically targeted Hispanics who, according to the 2000 US Census, are now the largest racial or ethnic group after Whites.

Genetic Polymorphisms

Polymorphisms are naturally occurring variants in the structures of genes and the products they encode. The relevant gene products here are drug metabolism enzymes, receptor proteins, and other proteins involved in drug response or disease progression. Polymorphisms occur in all human genes, but only some of them alter the functioning of the gene product, and only some of these vary significantly in frequency among different populations. Polymorphisms in drug metabolism enzymes have been intensively studied because they affect many drugs across different drug classes. The two most important polymorphisms for this discussion affect the metabolism of antiarrhythmics, antidepressants, beta-blockers, neuroleptics, opioids, barbiturates, and benzodiazepines. A third polymorphism affects metabolism of caffeine and isoniazid. This polymorphism was first studied when isoniazid was introduced for the treatment of tuberculosis. Patients were classified as fast or slow eliminators of isoniazid on the basis of a genetically determined defect in their ability to metabolize the drug. The proportions of rapid acetylators and slow acetylators vary considerably in different populations: 52 to 62% of Whites are slow acetylators compared to 7 to 34% of Chinese and Japanese.

Polymorphisms in drug targets and proteins involved in disease progression can be major determinants of drug efficacy. Polymorphisms in the gene encoding the serotonin receptor alter response to clozapine and antipsychotics. Polymorphisms in apolipoprotein E (Apo E), a protein involved in cholesterol homeostasis, alter the risk of developing Alzheimer's disease and the response to tacrine treatment. Tacrine is less effective in individuals carrying a particular Apo E polymorphism that is more prevalent in African Americans and Africans (20% to 30%) than among Asian populations (5% to 10%).

Implications

Polymorphisms may influence a drug's action by altering its pharmacokinetic (absorption, distribution, metabolism, excretion) or pharmacodynamic (effect on the body) properties. Clinically, there may be an increase or decrease in the intensity and duration of the expected drug effect and substantial dosage adjustments may be necessary for individuals from different populations. Importantly, because different agents of the same drug class are often cleared by different metabolic pathways, drugs of a class may differ in their susceptibility to genetic differences in metabolism. In addition, the pathophysiology of disease may differ among racial groups (e.g., hypertension) and some agents will be more effective than others in a given racial group.

Recommendations

Attention should be paid to the need to individualize drug therapy for specific population groups by health care policy makers and providers. The following recommendations can have positive benefits on the quality of care for racial and ethnic subpopulations and may also help to control health care costs.

1) Health care institutions should limit the practice of therapeutic substitution,

i.e., the interchange of agents of the same pharmacologic or therapeutic class. Patients of certain racial and ethnic groups are subject to greater risks if they are prescribed an "equivalent" drug. In some cases, substantial downward dosage adjustments may be necessary, since individuals in these groups may not be able to tolerate standard dosage levels. Alternatively, standard doses of some agents of a class may not be effective in certain racial and ethnic groups. Other cost management programs that restrict access to pharmaceuticals, such as formularies, step-care protocols, and tiered copayments, should be broad and flexible enough to enable rational choices of drugs and dosages for all patients, regardless of race or ethnic origin.

2) Physicians should give individualized treatment to each patient and resist the temptation to apply "cook-book" drug therapy that does not take into account racial or ethnic origin. Physicians should also be alert to atypical drug responses or unexpected side effects (especially with cardiovascular or psychotropic agents) when they treat patients from diverse racial and ethnic backgrounds. Dosage adjustments may be required in some patients, if supported by pharmacological evidence.

3) Pharmaceutical companies should continue to include significant numbers of patients representing varied racial and ethnic groups in drug metabolism studies and clinical trials. Most companies test and evaluate new pharmacological compounds on numerous population subgroups. Inclusion of different racial and ethnic populations in clinical trials is likely to reveal drug actions and side effects specific to these groups, and may also to lead to the discovery of therapies of specific advantage to patients of varied racial and ethnic backgrounds.

Toward Individualized Therapy

Race or ethnicity is a risk factor that changes the probability that an individual will respond in the expected way to a given drug therapy. However, "race" is an imprecise label for genetic variations that an individual person might or might not possess. Technological advances in the wake of the Human Genome Project will eventually enable us to move beyond race and to tailor drug therapy precisely to each patient. It is now possible to take a genetic 'fingerprint' of an individual and determine precisely the presence of polymorphisms in the genes known to be involved in drug interaction. Instead of a person's race or ethnicity being a risk factor for the possession of polymorphisms involved in drug response, a genotypic profile can determine with certainty whether or not the individual possesses these polymorphisms.

In the future, drug treatment will be individually tailored rather than race-based. Genetic fingerprinting using DNA arrays is already practical, but the knowledge base relating genomic variations to drug response and disease progression has not been developed. Studies in which DNA fingerprints are correlated with data present in medical records about medical history and drug response will have a profound impact on the ways in which new drugs are developed and used.

INTRODUCTION
Cost Control and Restricted Access to Pharmaceuticals

Many polices aimed at managing the cost of medications—including restrictive formularies, substitution of alternative drugs of a class, mandating the use of specific agents, step-care protocols specifying the order in which agents are used, tiered copayments, and prior authorization for certain drugs—have been introduced with little consideration of any possibly discriminatory effects on racial and ethnic groups.

Prior authorization by Medicaid programs is widespread. Prior authorization is sometimes used to limit access to newer generation pharmaceuticals and represents an administrative burden on physicians and their staff who must obtain clearance from Medicaid before prescribing certain medications. In addition, for certain subpopulations that have a different response to medication or who have different symptoms, such limitations may produce suboptimal, adverse, or unexpected responses. Health care plans have turned to formularies in an attempt to manage their drug costs but often with unintended consequences. Studies show that restrictive formularies can result in service substitution—that is, the replacement of medications with medical services at a much higher cost. Because of the strong association with increased use of health care services, the policy of restricting formularies should be reexamined. The practice of tiered copayments—i.e., the policy of escalating copayments for nonformulary drugs of substitution of brand name for generic drugs—is formulary restriction in another guise.

Disease management is an alternative strategy to prior authorization and other policies that limit access to pharmaceuticals, which ensures access to state-of-the-art pharmaceuticals while controlling overall costs. Disease management benefits chronically ill patients, ensures more appropriate use of medications, and lowers unnecessary spending.

Effects of Restrictive Policies on Patients from Varied Racial and Ethnic Backgrounds[†]

Disparities in the quality of medical care provided to patients of different racial and ethnic groups have been extensively documented.[10] Most studies have focused on African Americans, but other studies have shown that Hispanic and Asian Americans are similarly af-

fected. Patients in these groups receive less intensive medical treatment than the nation as a whole, including fewer vaccinations, less drug therapy for pain, fewer antiretroviral drugs for HIV/AIDS, and fewer antidepressants. African American and Hispanic patients with severe pain are less likely than White patients to be able to obtain commonly prescribed pain medicines, because pharmacies in predominantly non-White communities do not carry adequate stocks of opiates. Other studies have revealed under-treatment of Hispanics and African Americans for pain from fractures, inadequate management of postoperative pain in non-White patients, and a lower likelihood of curative surgery for cancer in African Americans than in Whites of equivalent socioeconomic status.[7]

The demographic changes anticipated over the next decade magnify the importance of these disparities. According to the 2000 census, racial groups other than 'White' make up 33% of the U.S. population (Fig. 1).[‡] African Americans and Hispanics represent a growing percentage of the urban population in the United States. These groups constitute the new urban majority in American cities such as Washington, Detroit, and Los Angeles. Moreover, a disproportionate percentage of these Americans in urban areas depend on Medicare and Medicaid as their sole health care providers. Consequently, these programs should not adopt policies that ignore the special needs of a growing percentage of the patient groups they are intended to serve. Inappropriate policies regarding the impact of race and ethnicity on pharmaceuticals can have wide-ranging and potentially damaging implications.

[†]While the meanings of the terms 'racial' and 'ethnic' continue to evolve, here 'racial' refers to genetically defined differences, while 'ethnic' refers to cultural differences. Thus, 'Hispanic' defines an ethnic group that includes several different races.

[‡]The classifications of race and ethnicity were different in the 2000 census than in earlier censuses. In 2000, almost seven million individuals reported belonging to two or more racial categories. Ethnic origin was considered to be a separate concept from race, so that people of Hispanic origin could belong to any racial category. Hispanics made up 12.5% of the total 2000 population. Of the 87.5% that were not Hispanic, 79.0% were White.
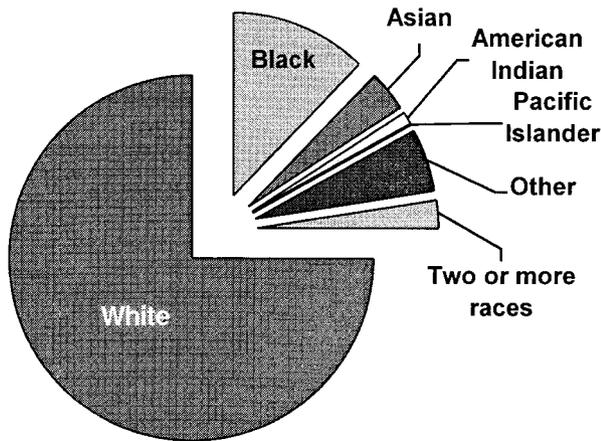
Figure 1. Racial composition of the US population. Source: Bureau of Census data for 2000.

Purpose of this Report

This report has several purposes: (1) to review the interrelated causes of variability in response to medicines among racial and ethnic groups (focusing on the pharmacogenetics of drug metabolism as the factor most intensively researched); (2) to discuss the genetic polymorphisms known to be relevant to the effects of drugs; (3) to discuss the variation of these polymorphisms among different racial groups; (4) to discuss examples of drugs to which racial and ethnic groups respond differently; (5) to discuss the implication for formulary decisions and other institutional policies such as therapeutic substitution and step-care protocols; and (6) to make recommendations for health care providers and policy makers who are responsible for clinical decisions affecting patient care.

ORIGINS OF GENETIC DIFFERENCES AMONG PEOPLES

Human Migration

The 'Out of Africa' theory of human evolution is based on the distribution of genetic polymorphisms,[§] the archeological record, and (for the most recent events) linguistics. In bare outline, it reads as follows:

[§]Polymorphisms are naturally occurring variants in the structures of genes and the products they encode.

Anatomically modern humans evolved in Africa by about 100,000 years ago.[11] Some of these people migrated from East Africa into Eurasia and subpopulations spread east into southern Asia. Australia was inhabited around 50,000 years ago (and subsequently remained completely isolated from the rest of the world until the late 18th century). Modern humans first inhabited Western Europe by about 40,000 years ago. The northern latitudes were penetrated quite late. After the inhabitation of Siberia 15,000 to 35,000 years ago, humans spilled into Alaska and rapidly occupied the whole of the North and South American continents. The Pacific islands were colonized by peoples originating in South China beginning about 5,500 years ago and continuing into the historic period.[12]

Two factors led to genetic differences among peoples and hence potential differences in drug response. First, genetic mutations continued to arise spontaneously in populations that were geographically isolated form one another. These mutations were subject to environmental selection. Second, because these population movements were initiated by subgroups of people, they tended to represent only a particular subset of the genetic polymorphisms that were present in the entire human population. The smaller the migrant subgroup, the more genetically distinct it would be from other subgroups—a phenomenon called the 'founder effect'—leading to distinct patterns of polymorphisms in the descendent populations. Human populations continued to migrate throughout prehistoric and historic times, displacing, coexisting, or intermixing with indigenous peoples. The result is that there are no distinct geographic boundaries between genetic variations; rather, there are gradations in the prevalence of polymorphisms across geographical distance.

Environmental Selection

Stereotypic features of the different 'races,' skin color in particular, but also hair color and texture, body shape, and facial details, are su-

perficial and are thought to be adaptations to climate and geography involving relatively few genetic changes. The loss of skin pigmentation among peoples living at high latitudes (the 'White race') is hypothesized to have been selected for by the requirement for exposure to sunlight for the biosynthesis of vitamin D and hence the prevention of rickets. Skin color is determined by melanins whose production is hormonally regulated via the *MC1R* (melanocortin-stimulating hormone receptor) gene. Multiple polymorphisms in *MC1R* that have evolved relatively recently may explain much of the variation in skin color.[13]

Genetic Variation within and between Populations

Most human genetic variation antedates the migration of modern humans out of Africa. Put differently, most genetic variation occurs within any given population rather than between populations. An average population from anywhere in the world includes 85% of all the variation in autosomal genes (genes on chromosomes other than the sex chromosomes). Differences among populations from the same continent contribute 6% of genetic variation, and differences among populations from different continents contribute 9% to 13%.[14]

The Uses of Racial Categorization in Medicine

Individual genetic polymorphisms change gradually in prevalence across continents and do not separate populations into clearly demarcated groups that correspond to the popular idea of race. Physical traits commonly associated with 'racial' groups—skin and hair color, facial features, etc.—are superficial characteristics that have little relevance to the response to drugs or to the progression of complex diseases such as diabetes mellitus, coronary heart disease, and so forth.[14,15] What, then, is the scientific rationale for race continuing to occupy such an important place in the medical consciousness? Genetically determined differences in the response to drugs do exist among individuals, and

there are differences in the prevalence of these determinants among different populations. Research in the last 35 years has uncovered significant differences among racial and ethnic groups in their rates of drug metabolism, in clinical responses to drugs, and in drug side effects. African American and White patients differ significantly in their responses to beta-blockers, ACE inhibitors, and diuretics used either alone or in combination for the treatment of hypertension. Chinese are considerably more sensitive than Whites to the effects of the beta-blocker propranolol on heart rate and blood pressure. Asians are more likely to require lower dosages than Whites of a variety of different psychotropic drugs, including lithium, antidepressants, and antipsychotics.

Race is an imprecise substitute measure of these genetic differences. When relevant to a particular drug, race and ethnicity should be considered along with other factors such as age, gender, diet, smoking status, and other factors that modify, often only slightly, the risk of disease or drug response. Practicing physicians treating individual patients and, equally importantly, institutional policy makers should be sensitive to the implications of racial and ethnic differences in drug therapy. Restrictive policies may pose greater degrees of risk for patients of different racial and ethnic backgrounds. A clear message of the recent findings in this field is that racial and ethnic differences must be factored into formulary selection and prescribing decisions on an individual basis. Otherwise, these groups may be disadvantaged by institutional pharmaceutical policies that restrict individualized drug therapy.

INTERPLAY OF GENETIC, ENVIRONMENTAL, AND CULTURAL FACTORS

The factors contributing to variability in drug response are complex and interrelated (Fig. 2). Differences in drug response among racial and ethnic groups are determined by
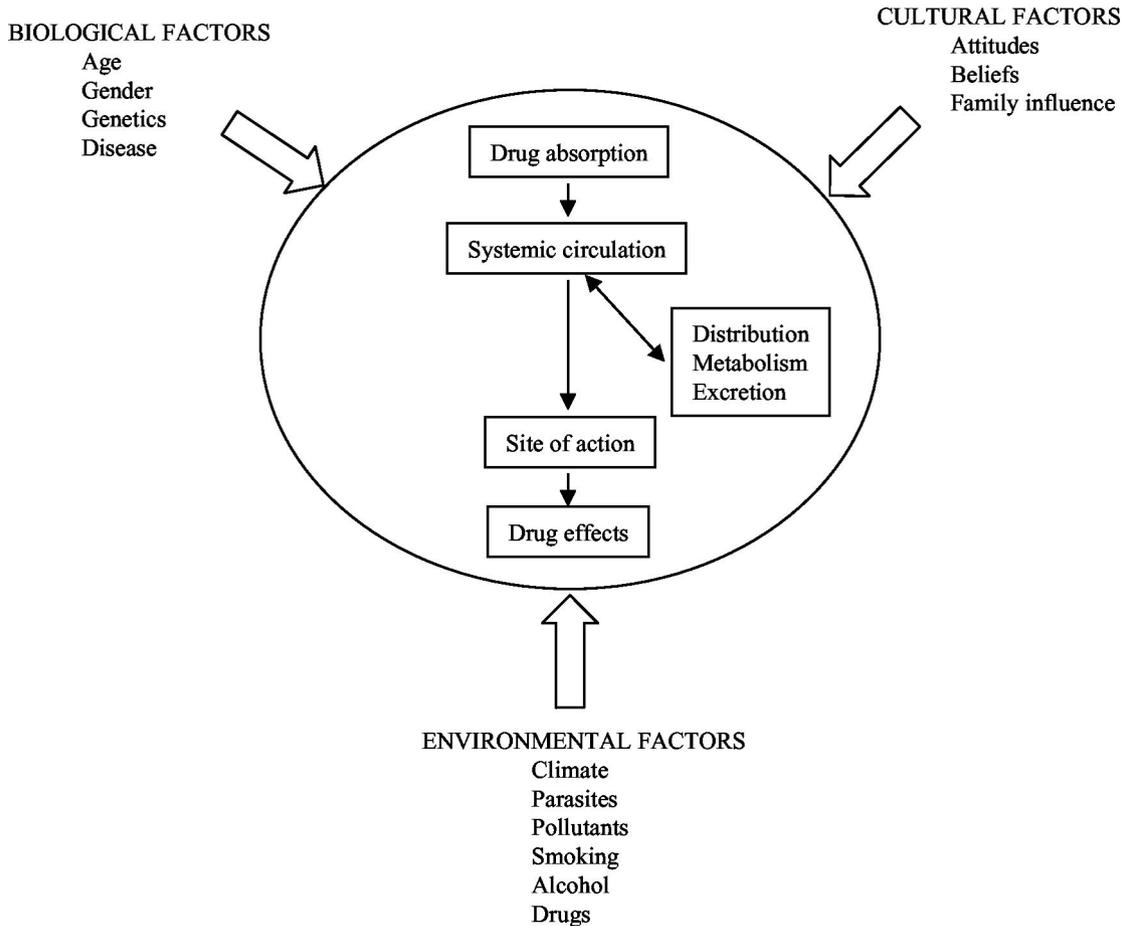
Figure 2. Factors contributing to variability in drug response. Adapted from Poolsup et al. (2000).[16]

genetic, environmental, and cultural (meaning, in this context, psychosocial) factors. These factors may operate independently of one another, or they may interact dynamically and synergistically.

Biological Factors

Age and sex, of course, affect drug response, but the primary biological factor we are concerned with is genetics. Studies of twins and blood relatives have shown that genetic factors are the major biological determinants of the normal variability of drug effects and are responsible for many differences in pharmacologic activity among normal subjects studied under carefully controlled environmental conditions. Over 100 examples have been documented in which inherited individual traits were implicated in atypical, exaggerated responses to drugs, novel drug effects, or lack of effectiveness of drugs.[17]

The genetic makeup of an individual may change the action of a drug in a number of ways as it moves through the body. Genetic factors may influence a drug's action by altering its pharmacokinetic properties (absorption, distribution, metabolism, excretion) or pharmacodynamic properties (effect on the body). Clinically, there may be an increase or decrease in the intensity and duration of the expected typical effect of the drug.

The study of genetically determined variations in drug response is called pharmacogenetics. Variations in drug response are caused

by gene polymorphisms. Genes are considered to be functionally polymorphic when variants of the gene exist stable in the population, one or more of which alters the activity of the gene product (which is typically a protein such as a drug metabolizing enzyme or a drug receptor). Pharmacogenetics has traditionally meant the study of polymorphisms in individual genes. This field has now broadened into pharmacogenomics, which examines the effects of the entire genome, i.e., all of the genes, on drug response. In pharmacogenomics, large arrays of genes are studied in parallel, so that the entire spectrum of genes that determine the response to a particular drug can be examined at one time.

Environmental Factors

Environmental factors—diet, climate, smoking, alcohol, drugs, pollutants[16]—may cause wide variations in drug response within an individual and even wider variations between groups of individuals. Several of these factors can operate simultaneously in the same individual, thus affecting the processes of drug absorption, distribution, biotransformation, excretion, and receptor interaction in different ways and to different degrees.[18]

Differences in diet may significantly alter the metabolism rate or drug blood levels among different ethnic populations. Studies comparing the metabolism of antipyrine between Asian Indians in rural Indian villages and Indian immigrants in England demonstrated that as immigrants adopted the lifestyle and dietary habits of the British, their drug metabolism accelerated. Similar findings have been observed among Sudanese and Western Africans.[19]

A striking example of the interplay of environmental and genetic factors is found in the relationship between malaria and expression of the gene *G6PD* in red blood cells. *G6PD* encodes an enzyme (glucose-6-phospate dehydrogenase), a deficiency of which leads to anemia if the person is exposed to certain foods (e.g., fava beans) or drugs (e.g., primaquine).[20] Evi-

dence has accumulated that a *G6PD* deficiency protects against infection with *P. falciparum,* the parasite that causes a fatal form of malaria. Variants in *G6PD* that lead to reduced enzyme activity occur much more frequently in countries in which malaria is or was endemic (see Fig. 3). There are more than 30 polymorphisms that result in *G6PD* deficiency and hence protection against *P. falciparum.* These polymorphic variants, and the ancestral strain of *P. falciparum,* arose between about 3,000 and 10,000 years ago, coincident it is believed with the spread of farming, which provided conditions conducive to the spread of malaria.[21]

Skin pigmentation is also the result of an interaction between genetic and environmental factors. Light-skinned individuals are subject to drug-induced phototoxicity after ingesting certain drugs.[22–24]

Cultural Factors

Cultural or psychosocial factors, such as the attitudes and beliefs of an ethnic group, may affect the effectiveness of, or adherence to, a particular drug therapy. Cross-disciplinary fields—pharmacoanthropology, medical anthropology, and cultural psychiatry—have emerged to study these issues. Pharmacoanthropology studies interethnic differences in drug responses by examining population characteristics in social and genetic terms and using methods suitable for pharmacological investigation of large numbers of subjects.[25] Medical anthropologists study the effects of a patient's perception of illness and disease in a cross-cultural context to determine the role that ethnic and cultural perceptions and beliefs play in the patient's adherence to or understanding of medical therapy or drug treatment. For example, the physician's ability to treat a patient effectively may be impeded by the patient's culturally determined perception of the meaning of his or her illness.[26] Cultural psychiatry focuses on the interaction of culture and psychiatric disorders, and includes cross-cultural differences in symptoms and diagnoses, and
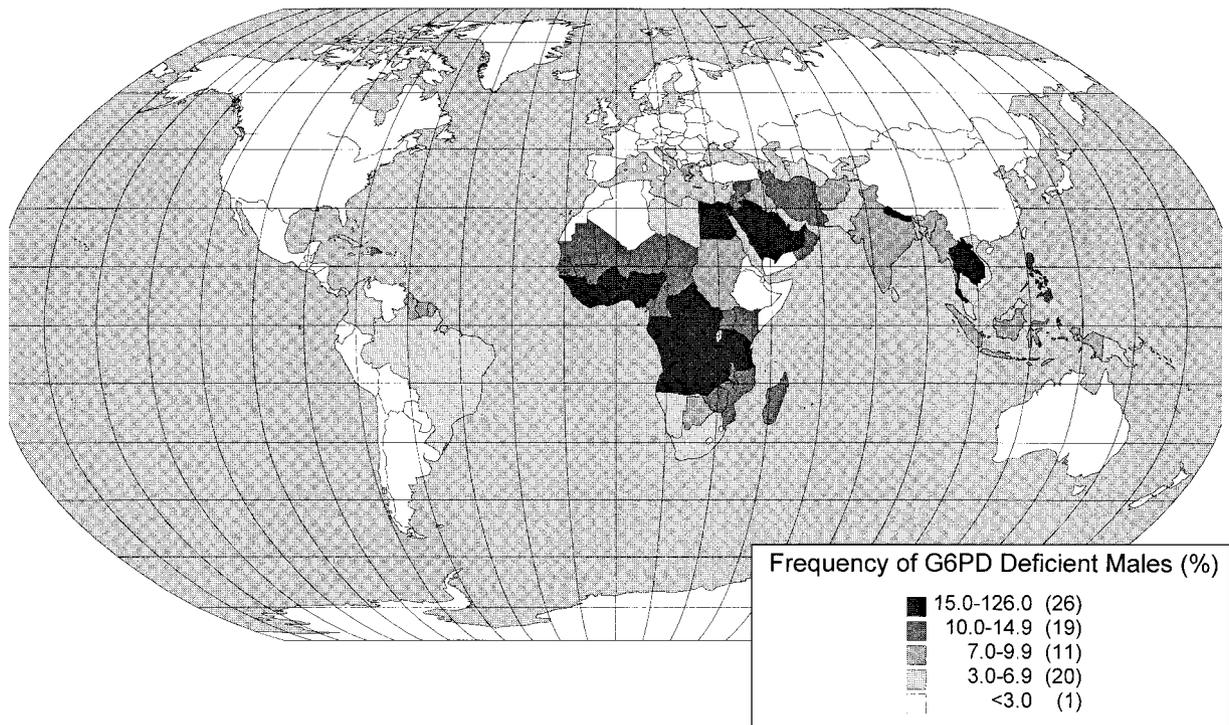
Figure 3. Interplay of environmental and genetic factors: the global distribution of *G6PD* deficiency. The colored areas in the map indicate the prevalence of the *G6PD* deficiency. A deficiency in *G6PD* appears to protect against infection with a parasite (*P. falciparum*) that causes a fatal form of malaria. The countries in which *G6PD* deficiency is most common correspond to those in which malaria is (or was) endemic (regions endemic for malaria not indicated on map). Adapted from Luzzatto & Notaro (2001).[21]

variations in dose response to psychotropics among different ethnic groups.

Studies have consistently shown that African-American patients are more likely to be overdiagnosed as having a psychotic illness and are more likely to be treated with neuroleptics regardless of diagnosis.[19,27] African Americans are also more likely to be placed on implanted or periodically injected rather than oral medications, reflecting physicians' concern about adherence. There is also evidence from large-scale drug trials that the placebo response is greater among non-Whites. Other studies have shown that the perception and report of adverse effects of drugs are influenced by patients' culturally determined beliefs.[19]

Investigators who study the effects of cultural or psychosocial factors on differing drug re-sponses agree that these effects are real and can be documented through case studies or epidemiological surveys. However, it is difficult to design large, controlled clinical trials to isolate any of these factors and determine its effect as an independent variable on drug response in a particular ethnic group. The complex interrelationships of environmental and cultural factors make them less readily amenable to reproducible results, so that research in this field so far has concentrated on identifying genetic factors.

GENETIC POLYMORPHISMS IN DRUG METABOLISM, DRUG TARGETS, AND DISEASE PATHWAYS
Overview
Polymorphisms are naturally occurring variants in the structures of genes and the products they

Table 1. Mechanisms and Examples of Clinically Relevant Genetic Polymorphisms Influencing Drug Metabolism and Effects

Mechanism	Example	Pharmacogenetic effect
Drug metabolism	Cytochrome P450 Enzyme *CYP2D6*	"Poor metabolizer" phenotype in ~25% of all drugs
Drug target	Serotonin (5-HT$_{2A}$) receptor	Altered binding of the atypical antipsychotic clozapine
Disease pathway	Cholesterol esterase transport protein *(CETP)*	Atherosclerosis progression and response to the HMG-CoA inhibitor pravastatin

Source: Kleyn & Vesell (1998).[29]

encode. The gene products are usually proteins that interact in some way with drugs. Polymorphisms affecting the response to drugs can occur in genes involved in one of three processes or mechanisms—drug metabolism, drug targets, and the disease pathway. An example of each of these three mechanisms is shown in Table 1. Of the three mechanisms, polymorphisms in drug metabolism genes are considered most important because they act across classes of drugs, whereas a mutation in the gene encoding a drug target (such as a receptor protein) will only affect the class of drugs that interacts with that target.

Although there are polymorphisms in all genes controlling drug effects, they do not necessarily alter drug response and do not necessarily show significant variation among populations. In this discussion, we shall focus on those polymorphisms known to have clinically important roles and to vary among populations.

Polymorphisms of Drug Metabolism

Most drugs are chemically modified (biotransformed) and thus inactivated in the liver before their clearance from the bloodstream and elimination from the body. Biotransformation is most commonly a process of oxidation or of acetylation or methylation (Table 2). Most oxidation is performed by one of several oxidative enzyme systems associated with cytochrome P450. These enzymes are now referred to by their genetic names (*CYP2C9*, *CYP2C19*, *CYP2D6*, etc.), although they were originally referred to by the test drugs (or 'probe' drugs) whose metabolism they controlled: debrisoquine or sparteine for *CYP2D6*, mephenytoin for *CYP2C19*, and phenytoin for *CYP2C9*. Other important drug metabolism genes are the acetylation gene *NAT2* (encoding *N*-acetyltransferase 2) and the methylation gene *TPMT* (encoding thiopurine methyltransferase).

Common polymorphisms in drug metabolism genes have received the most attention because they affect the metabolism of many clinical important drugs and large numbers of patients. Polymorphic variants in these genes alter the activity of the encoded enzyme most often by reducing it, sometimes by eliminating

Table 2. Polymorphic Genes Influencing Drug Metabolism

Mechanism	Enzyme	Gene	Common probe drugs
Oxidation	Cytochrome P450 enzymes	*CYP2C9*	Warfarin, phenytoin
		CYP2C19	Mephenytoin
		CYP2D6	Debrisoquine, sparteine, dextromethorphan
	Alcohol dehydrogenase	*ADH3*	Ethanol
Acetylation	N-Acetyltransferase 2	*NAT2*	Caffeine, sulphamethazine, isoniazid
Methylation	Thiopurine methyltransferase	*TPMT*	Mercaptopurine, thioguanine, azathioprine

Source: Poolsup et al. (2000),[16] Evans & Relling (1999).[29]

Table 3. Drugs Metabolized by *CYP2D6*

Drug class	Drugs
Psychotropic	
Antipsychotics	Haloperidol, perphenazine, thioridazine, fluphenazine, clozapine, risperidone, chlorpromazine
Antidepressants	Amitriptyline, clomipramine, desipramine, fluoxetine, imipramine, maprotiline, nortriptyline, paroxetine
Cardiovascular	
Anti-arrhythmics	Propafenone, flecainide, sparteine, quinidine
Beta-blockers	Propranolol, timolol, metoprolol, labetalol
Antihypertensives	Debrisoquine, clonidine
Miscellaneous	Codeine, nicotine, methoxyamphetamine

Source: Poolsup et al. (2000).[16]

it, and occasionally by enhancing it. This leads to differential rates of metabolic clearance of the drug metabolized. Those individuals who do not metabolize a certain drug efficiently are called "poor metabolizers" (PM), as opposed to normal or "extensive metabolizers" (EM).

The effect of the poor metabolizer phenotype is to increase the exposure to the active drug by increasing the peak concentration in the blood and the time to clearance. This is the equivalent of an overdose of the drug. The efficacy is not enhanced because dosages are normally targeted to have optimum efficacy, i.e., further increasing the dose does not further increase the effect. Adverse effects are increased, however, because dosages are normally targeted to be close to the bottom of the threshold where adverse effects begin to appear. In sum, the poor metabolizer phenotype effectively decreases the therapeutic ratio (efficacy:toxicity) of the drug.[29]

Polymorphisms in *CYP2D6* are among the clinically most important because so many drugs are metabolized by this pathway, including antiarrhythmic, antidepressant, beta-blocker, neuroleptic, and opioid agents (Table 3). The implications of the *CYP2D6* poor me-

tabolizer phenotype are listed in Table 4. Differences in the frequency of the *CYP2D6* poor metabolizer phenotype have been demonstrated among different racial and ethnic groups and among subpopulations of the same racial group.

Polymorphisms in *CYP2C19* affect the metabolism of mephenytoin, hexobarbital, diazepam, omeprazol, and many other drugs (Table 5). Some drugs, e.g., amitriptyline, clomipramine, propranolol, can be substrates for both *CYP2C19* and *CYP2D6*, indicating that there is redundancy and overlap between these two systems.

Polymorphisms in *NAT2*, the gene encoding N-acetyltransferase 2, affect metabolism of caffeine and other drugs, including isoniazid (Table 2). *NAT2* polymorphisms were first studied when isoniazid therapy was introduced for the treatment of tuberculosis. Patients were classified as fast or slow eliminators of isoniazid on the basis of a metabolic defect in their ability to metabolize the drug. This polymorphism is especially important in the study of racial and ethnic drug responses because the proportions of rapid acetylators (RA) and slow acetylators (SA) vary considerably in different ethnic and/or geographic populations.[17]

Polymorphisms of Drug Targets

Drug targets include hormone or neurotransmitter receptors, specific enzymes, and ion channels (Table 6). Many of the genes encoding drug targets exhibit polymorphisms that alter their sensitivity to particular medications. Examples include: polymorphisms in beta-adrenergic receptors and their sensitivity to beta-agonists in asthmatics; angiotensin-converting enzyme (ACE) and its sensitivity to ACE inhibitors; angiotensin II T1 receptor and vascular reactivity to phenylephrine or response to ACE inhibitors; sufonylurea receptor and responsiveness to sufonylurea hypoglycemic agents; and 5-hydroxytryptamine receptor and response to antipsychotics such as clozapine.[29]

The effect of a drug receptor mutant that reduces binding of the target drug is to reduce

Table 4. Implications of CYP2D6 Poor Metabolizer Phenotype

Decreased elimination resulting in accumulation of parent compound and toxicity	Anti-arrhythmics (sparteine, mexiletine, flecainide)
	Beta-blockers (metoprolol, timolol)
	Neuroleptics (perphenazine)
	Tricyclic antidepressants (nortriptyline, clomipramine)
Decreased prodrug activation	Codeine
Decreased elimination of active metabolite	Imipramine
Decreased elimination of parent compound and active metabolite	Amitriptyline

Source: Wolf & Smith (1999).[30]

the efficacy of the drug and, hence, the therapeutic ratio. Unlike the poor metabolizer phenotype of drug metabolizing genes, there is no direct effect on the incidence of adverse effects.

Polymorphisms of Disease Pathways

Genetic polymorphisms that underlie disease pathogenesis can be major determinants of drug efficacy (Table 7).

Apolipoprotein E is an example of protein that affects disease progression and the action of drugs, and that exists in several polymorphic variants. Apolipoprotein E is a circulating and tissue protein involved in cholesterol homoeostasis and other functions. Common genetic polymorphisms affect both the lipid and receptor associations of apolipoprotein E, altering lipid profiles and correlating with diseases linked to lipid metabolism—particularly cardiovascular disease, but also Alzheimer's disease. The distribution of apolipoprotein E polymorphisms varies among populations. The frequency of the $\epsilon 4$ polymorphism is about 5% to

Table 5. Drugs Metabolized by CYP2C19

Carisoprodol	Amitriptyline
Citalopram	Clomipramine
Diazepam	Hexobarbital
Mephenytoin	Imipramine
Omeprazole	Mephobarbital
	Propranolol

Source: Poolsup et al. (2000).[16]

7% in Chinese populations, 10% in other Asian and American Indian groups, and 20% to 30% in African Americans and Africans.[31] Tacrine, the cholinomimetic drug used to treat Alzheimer's disease, is more effective in individuals who do not carry the $\epsilon 4$ polymorphism. Furthermore, lorazepam-induced memory impairment is greater in elderly individuals carrying $\epsilon 4$.[31] These polymorphisms also appear to affect response to lipid-lowering drugs, including fibrates and statins, but the data are complex and a clear interpretation has not yet emerged.

RACIAL AND ETHNIC VARIATION IN POLYMORPHISMS IN DRUG METABOLISM
How Genetic Polymorphisms Are Expressed in the Population

Polymorphisms are alterations in the genes that potentially alter the activity of the gene product—in this instance, an enzyme involved in drug metabolism. If the gene product retains some activity, the genetic polymorphism is referred to as an active allele ('allele' is the genetic term for a mutant form of a gene; the native form of a gene is called the wild type). There are also inactive alleles that produce no enzyme at all or a completely inactive enzyme. Less often, multiple copies of the wild type gene or an active allele may occur, which results in greater than normal enzyme activity (referred to as the ultra extensive metabolizer phenotype). Thus, many different polymorphisms can produce the same few end results:

Table 6. Clinically Relevant Polymorphisms of Drug Targets

Mechanism/target	Drug	Drug effect linked to polymorphism
Receptors		
β_2 adrenergic receptor	Albuterol	Response in asthmatics
Serotonin (5-HT$_{2A}$) receptor	Clozapine	Altered binding
Enzymes		
5-Lipoxygenase	Zileuton	Response in asthmatics
Angiotensin-converting enzyme	Enalapril, lisinopril, captopril	Renoprotective effects, cardiac indices, blood pressure, immunoglobulin A nephropathy
Potassium Channels		
HERG	Quinidine	Drug-induced long QT syndrome

Source: Evans & Relling (1999).[29]

an enzyme with normal activity, reduced activity, or no activity. Since humans have two copies of every autosomal gene, i.e., one from each parent, either or both of the copies might be a wild type copy or any one of the polymorphic variants. The resulting phenotype, whether extensive metabolizer or poor metabolizer, depends on which combination of two gene copies is present.

This is illustrated in Table 8 for *CYP2D6* polymorphisms. Combinations of the wild type gene and any of the several common active or inactive alleles still produce the EM phenotype because sufficient wild type enzyme is produced from the wild type gene copy. Thus, in total 81.9% of the White population has the EM phenotype, although this is the result of a variety of genotypes. Combinations of the various active and inactive alleles produce the poor metabolizer phenotype. The prevalence of the PM phenotype in the White subjects studied in Table 8 is 11.4%, due in most part to combinations of two inactive alleles with each other or with an active allele.

Racial Variations in *CYP2D6* and *CYP2D19* Polymorphisms

The prevalence of the PM phenotype of both the *CYP2D6* and *CYP2C19* drug metabolism systems in different populations is shown in Table 9—i.e., Table 9 shows phenotypic frequencies and not gene frequencies. The prevalence of the *CYP2D6* poor metabolizer phenotype is in the range of 0 to 2.1% in Asian populations and in populations indigenous to the Asian subcontinent, Egypt, Saudi Arabia, and Panama (Table 9).

The *CYP2D6* poor metabolizer phenotype is more common in White populations (median prevalence 7.2%). The prevalence in Sub-Saharan Africa is greater than in Asian populations but varies greatly, reaching 18.8% in the San bushmen. The prevalence in African Americans is 1.9%.

Table 7. Polymorphisms of Disease Pathways

Protein (Gene)	Drug	Pharmacogenetic effect
Apolipoprotein E	Tacrine	Apo ε4 polymorphism is associated with risk of developing Alzheimer's disease and response to tacrine treatment
Cholesteryl ester transport protein (*CETP*), lipoprotein lipase (LDL), -fibrinogen	Pravastatin	Atherosclerosis progression and response to pravastatin

Source: Kleyn & Vesell (1998),[28] Evans & Relling (1999).[29]

In contrast, the prevalence of the *CYP2C19* slow metabolizer phenotype is high in Asian populations (median 15.7%) and in the Asian subcontinent (17.6%) and low in Whites (median 2.9%—Table 9). The prevalence in African Americans (18.5%) is higher than among Tanzanians (3.6%) and Zimbabweans (4.0%). The prevalence in Chinese populations refer to the majority ethnic Chinese group (Han). However, China is a multinational country with 55 ethnic minorities in addition to the Han majority. The prevalence of the *CYP2C19* poor metabolizer phenotype is significantly lower in some of these groups than in the Han Chinese.[33]

Racial Variations in Acetylation

The prevalence of the slow acetylator phenotype in various populations is shown in Table 10. It is roughly 50% in both the African American and White populations (median 51% and 58%, respectively). The prevalence in Asian populations is considerably lower (median 22% in Chinese and 10% in Japanese).

CLINICAL RELEVANCE OF GENETIC POLYMORPHISMS

It is important to determine whether a given polymorphism has clinical relevance in drug therapy. Meyer poses four questions to determine the clinical importance of a genetic polymorphism:[17]

1) Does the polymorphic pathway of the drug result in a major difference between the EM and PM phenotypes in the clearance or elimination of the drug?
2) Does the drug have a narrow therapeutic index?
3) Is the dosage of the drug individually evaluated on the basis of the therapeutic effect?
4) Is the drug widely used by many physicians or only by a clinical specialist?

First, polymorphisms only have clinical importance when they result in large differences be-

Table 8. Many Different Genotypes Produce the Same Few Phenotypes: Prevalence of the Most Common CYP2D6 Polymorphisms among Unrelated Caucasian Subjects

Genotype*	Phenotype	% of Population
wild type / wild type	EM	47.6
wild type / active allele	EM	-
wild type / inactive allele	EM	34.3
wild type / amplified allele	UEM	6.7
active allele / active allele	PM	-
active allele / inactive allele	PM	2.9
inactive allele / inactive allele	PM	8.5

*Each individual has two copies of every gene— one from each parent (with the exception of genes on the Y chromosome). The normal gene is called the wild type, and altered versions are called alleles. An individual may have any combination of wild type genes or mutant alleles. Active alleles are altered versions of the wild type gene that encode mutant *CYP2D6* enzymes that retain partial activity. The common active alleles are *CYP2D6 A* and *CYP2D6 L*. Inactive alleles are versions of the gene that encode *CYP2D6* enzymes with little and sometimes no enzymic activity. The common inactive alleles are *CYP2D6 B* and *CYP2D6 D* (in this allele, the gene is deleted). In the L_2 polymorphism, an active allele is present in amplified form, i.e., there are multiple copies of the allele; this leads to more *CYP2D6* enzyme being produced and hence the UEM phenotype.
EM, extensive metabolism. PM, poor metabolism. UEM, ultra-extensive metabolism.
Adapted from Linder et al. (1997).[32]

tween the poor metabolizer and extensive metabolizer phenotypes—as is the case, for example, with the psychotropic drugs desipramine and perphenazine. Second, pharmacokinetic differences are relevant chiefly if the drug has a small therapeutic index, e.g., isoproterenol, phenytoin, warfarin, clonidine, and quinidine gluconate. Third, if physicians adjust drug dosage based on the therapeutic effect (as is usual with antihypertensive drugs), then phenotypic differences are automatically corrected, although the physician may not be aware of any pharmacokinetic variation. Fourth, widely prescribed drugs such as beta-blockers or tricyclic antidepressants have broader clinical implications because more patients in more population subgroups are affected.

Table 9. Prevalence of CYP2D6 and CYP2C19 Poor Metabolizer Phenotypes in Various Populations

Population	N Populations[a]	Poor metabolizer phenotype (%)	
		Median	Range
CYP2D6			
African (Sub-Saharan)[b]	6	3.4	1.8-18.8
Amerindian[c]	1	0	
Asian[d]	8	0.5	0-2.1
Asian Subcontinent[e]	1	0	
Caucasian[f]	20	7.2	3.2-10.4
Middle East/North Africa[g]	2	1.5	1.4-1.5
Polynesian (S. Pacific)	1	0	
CYP2C19			
African (Sub-Saharan)[h]	3	4.0	3.6-18.5
Amerindian[i]	1	2.0	
Asian[j]	6	15.7	5.1-23.6
Asian Subcontinent[k]	2	17.6	14.4-20.8
Caucasian[l]	12	2.9	1.3-6.1
Middle East/North Africa[m]	1	2.0	
Polynesian (S. Pacific)	1	13.6	

[a]Number of different populations. Where there were two or more studies of the same population (e.g., Chinese), the data were pooled and the median percentage used.
[b]African American, Ethiopian, Ghanaian, Nigerian, San (S. Africa), Tanzanian.
[c]Cuna (Panama).
[d]Chinese (China), Chinese (Singapore), Filipino (Saudi Arabia), Indonesian, Japanese, Korean, Malays, Thai.
[e]Sinhalese.
[f]Australian, Belgian, British, Canadian, Danish, Dutch, Estonian, French, German, Greenlander, Italian, Jordanian, New Zealand, Polish, Russian (Estonia), Spanish, Swedish, Swiss, Turkish, US.
[g]Egyptian, Saudi Arabian.
[h]African American, Tanzanian, Zimbabwean.
[i]Inuit.
[j]Chinese (Canada), Chinese (China), Filipino (Saudi Arabia), Indonesian, Japanese, Korean.
[k]Indian, Sinhalese.
[l]Canadian, Danish, Dutch, Estonian, French, Greenlander, Jordanian, Russian (Estonia), Spanish, Swedish, Swiss, US.
[m]Saudi Arabian.
Adapted from Poolsup et al. (2000).[16]

DRUGS SHOWING VARYING EFFECTS AMONG RACIAL AND ETHNIC GROUPS

Most pharmacogenetic studies have concentrated on several groups of drugs and their activity in certain populations. These drug groups include cardiovascular drugs (Table 11) and central nervous system (CNS) agents (Table 12). Cross-racial variability in the action of drugs in these categories is clinically significant, and results from differences in pharmacokinetic or pharmacodynamic factors, or in the pathophysiology of disease. The clinical and policy implications of this variability are discussed below.

Cross-Racial Differences in Response to Cardiovascular Drugs

Table 11 lists racial and ethnic variation in drug exposure or the clinical response to representatives of several classes of cardiovascular drugs. The term 'drug exposure' refers to the duration and intensity of the body's exposure to a drug, and is expressed in terms of pharmacokinetic parameters (in Table 11 exposure is measured as the area under the time-blood concentration curve). ACE inhibitors have greater effects on hypertension and heart failure in Whites than in African

Americans. Similarly, the response to the beta-blocker isoproterenol is greater in Whites than in African Americans. Conversely, the antihypertensive response to the diuretic hydrochorothiazide is greater in African Americans, while exposure to the calcium channel blocker nifedipine is lower in Whites than in South Asians, Koreans, or Nigerians.

The beta-blocker propranolol is more effective in reducing blood pressure and heart rate in Chinese than in Whites. Patients in China are prescribed much lower doses of propranolol than patients in the United States and Europe because of a perception that Chinese people respond to lower doses. Consistent with this, a study of the pharmacodynamics of propranolol found that, at equivalent blood levels, Chinese men had greater sensitivity than White men to propranolol's effects on heart rate and blood pressure. Paradoxically, the Chinese subjects metabolized propranolol much more rapidly than the White subjects; the total blood clearance for the Chinese was 76% higher, resulting in a substantially lower area under the time-blood concentration curve (AUC). Clearance of propranolol was two times greater in Chinese subjects because of their increased ability to metabolize the drug, resulting in lower blood concentrations at similar doses. Pharmacokinetic properties, therefore, do not explain the increased sensitivity of the Chinese. The mechanism for the increased sensitivity is not clearly determined, but could be because of a greater suppression of renin in the Chinese population.[34]

Antihypertensive Drugs in Black Populations

Hypertension is disproportionately prevalent in the Black population and is associated with higher incidences of cerebrovascular and renal complications and left ventricular hypertrophy. However, the overall risk of coronary artery disease in the Black male population is lower than in White males, particularly in Europe and the Caribbean, and to a lesser extent in the United States.

There are general differences in the pathophysiology of hypertension between the Black

Table 10. Frequency of Poor Acetylator Phenotypes in Various Populations

Population	N Populations[f]	Poor metabolizer phenotype (%)	
		Median	Range
Black[a]	4	51	42-65
Caucasian[b]	4	58	52-62
Chinese[c]	7	22	13-34
Japanese[d]	2	10	7-12
Eskimo[e]	2	6	5-21

[a]Black populations in East Africa, Nigeria, Sudan, and the United States.
[b]Britain, Canada, Germany, and United States.
[c]Chinese populations in Britain, Canada, Hong Kong, Mainland China, Singapore, Taiwan, and Thailand.
[d]Japan and the United States.
[e]Alaska and Canada.
[f]Number of different populations. Where there were two or more studies of the same population, the data were pooled and the median percentage used.
Adapted from Wood & Zhou (1991).[34]

and White populations. Black hypertensives exhibit enhanced sodium retention, a higher incidence of salt-sensitive hypertension, expanded blood volume, more frequent proteinuria, and a higher prevalence of low blood renin activity[40] (although the majority of renin may reside in vascular tissue). The T594M polymorphism in the epithelial sodium channel occurs in about 5% of Blacks and appears to contribute to hypertension in these individuals.[41] These factors may underlie some of the observed differences in the effectiveness of various antihypertensive drugs in Black populations. Ultimately, the choice of therapy must be tailored to the individual patient.

Although there is a long-standing discussion about the best type of antihypertensive drug to use in Black patients,[42] African Americans respond to drugs from all classes.[15,43] There is no specific class of antihypertensive drugs that categorically should not be used based on race. Diuretics are frequently used to counteract increased salt retention among Blacks, and recent findings suggest that the potassium-sparing diuretic amiloride is effective in controlling blood pressure in patients with the T594M

Table 11. Racial and Ethnic Differences in Response to Cardiovascular Drugs

Drug	Comparison groups	Drug exposure*	Clinical response
ACE inhibitors			
Enalapril	Blacks vs. Whites	N/A	Hypertension and hospitalization for heart failure reduced in Whites but not in Blacks with left ventricular dysfunction
Captopril	Blacks vs. Whites	N/A	Antihypertensive effect greater in Whites
Beta-blockers			
Isoproterenol	Black vs. White men	N/A	Vasodilation response to isoproterenol markedly lower in Blacks
Propranolol	Chinese vs. Caucasians	Lower in Chinese	Chinese twice as sensitive to effects on blood pressure and heart rate
	Blacks vs. Whites	N/A	Antihypertensive effect greater in Whites
Calcium channel blockers			
Nifedipine	South Asians vs. Caucasians	Threefold higher in South Asians	N/A
	Koreans vs. Caucasians	Greater in Koreans	N/A
	Nigerians vs. Caucasians	Greater in Nigerians	N/A
Diuretics			
Hydrochlorothizide	Blacks vs. Whites	N/A	71% of Blacks achieved blood pressure goal vs. 55% of Whites in Veterans Administration study

*Statistically significant differences in exposure to drug expressed in terms of a measure of the blood concentration—in these examples, the area under the blood concentration-time curve (AUC).
N/A, not available.
Sources: [35,36,37,34,38,39]

polymorphism.[41] Although some studies find that beta-blockers, ACE inhibitors, and angiotensin receptor blocking agents do not control blood pressure in African Americans with the same degree of effectiveness as in Whites, targeted blood pressure levels can usually be achieved by adding a second antihypertensive agent, such as a low dose diuretic.[44,45,46,47,48]

The Veterans Administration Cooperative Studies showed that the beta-blocker propranolol was less effective among Blacks than Whites, and that this differential effect was eliminated by addition of a diuretic. Nadolol, atenolol, and penbutolol are also less effective in Black than in White hypertensives.[45] There is

evidence that Blacks may respond differently to different beta-blockers. Labetalol (a combined alpha and beta-blocker) is significantly more effective in controlling blood pressure in Black patients than propranol or atenolol,[49,50] and evidence suggests that bisoprolol may have comparable effectiveness in Blacks and Whites.[45] The Veterans studies also demonstrated that White patients responded better to the ACE inhibitor captopril than Black patients.[39,40] When a diuretic was added, this interethnic difference was eliminated.

ACE inhibitors can be as effective in Blacks as calcium channel blockers or diuretics, and in some cases they may be more effective as a first

Table 12. Racial and Ethnic Differences in Response to Central Nervous System Agents

Drug	Comparison groups	Exposure*	Clinical response
Antidepressants			
Clomipramine	Asians, (Indian, Pakistani) vs. Whites (English)	Greater in Asians (AUC)	Higher incidence and severity of side effects in Asians
Nortriptyline	Japanese vs. American	Greater in Japanese (AUC)	N/A
Benzodiazepines			
Alprazolam	Asians vs. Caucasians	Lower for Asians (CL$_s$)	N/A
Antipsychotics			
Clozapine	Korean Americans vs. Caucasians	N/A	Clinically adjusted dose lower in Koreans, and higher rate of anticholinergic side effects
Haloperidol	Orientals (Chinese, Japanese, Filipino, Korean, Vietnamese) vs. Caucasians	No difference	Neuroleptic dose and optimal response threshold lower for Orientals
	Chinese vs. Non-Chinese (Caucasians, Hispanics, Blacks)	Higher mean blood levels in Chinese than in Americans (when given same dose)	Clinically adjusted dose lower for Chinese than for non-Chinese
	Caucasians vs. American-born Asians vs. foreign-born Asians (Chinese, Filipino, Japanese, Koreans)	Higher for Asians than for Caucasians (Cmax). Similar for American-born and foreign-born Asians.	No difference in side effects

*Statistically significant differences in exposure, i.e., a measure of the blood concentration: either the area under the blood concentration-time curve (AUC/, the peak blood concentration (Cmax), or systemic clearance (CL$_s$).
N/A, not available.
Adapted from Poolsup et al. (2000)[16] and Xie et al. (2001).[38]

line treatment. The AASK trial, which studied the progression of hypertensive kidney disease after treatment with an ACE inhibitor, a beta-blocker, and a calcium channel blocker, determined that the ACE inhibitor reduced the decline in renal function to a greater extent than the other drugs or classes.[51,52] In hypertension complicated by diabetic nephropathy and in the presenceof proteinuria, ACE inhibitors are first-line agents in Black as well as White patients.[40] However, since ACE inhibitors in lower doses can be less effective in Black patients, higher doses may be required.[53,54,55]

ACE inhibitors appear to be less effective in Black populations in the prevention and treatment of heart failure in patients with left ventricular dysfunction. In the SOLVD trials, enalapril reduced the rate of hospitalization for heart failure in White but not in Black patients.[36] (Conversely, the beta-blocker carvedilol is an equally effective treatment for heart failure in Black and White patients.[56]) An-

giodema, a potentially life-threatening side effect of ACE inhibitors, occurs 4.5-fold more often in African Americans.

Cross-Racial Differences in Response to Central Nervous System Agents

Tricyclic Antidepressants. Tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline) have a narrow therapeutic index and are metabolized by *CYP2D6*. Poor metabolizers and ultra extensive metabolizers may have clinical problems when these drugs are taken at usually prescribed doses. Poor metabolizers often develop elevated blood concentrations that may result in adverse effects. These side effects are rarely life threatening, but they are sufficiently unpleasant that problems with patient compliance ensue. Ultra-extensive metabolizers, on the other hand, may not respond to recommended doses because drug concentrations are too low to be efficacious.

Clinical and pharmacokinetic studies have evaluated ethnic variations in dose response to clomipramine, desipramine, and nortriptyline. In a study of clomipramine, the blood concentration (AUC) was greater in Asians than in Whites after an equivalent dose, and Asians had a higher incidence and severity of drug-related side effects (Table 12). Similarly, the blood concentration of nortriptyline was found to be greater in Japanese than in American Whites. Pharmacokinetic studies with desipramine in Asians and Whites have not produced consistent results. In studies of depressive patients, dosages of tricyclic antidepressants were lower for Asians than for White, and Asians responded to lower concentrations of desipramine or imipramine.

There are few reliable studies of cross-ethnic differences in drug disposition and response to tricyclic antidepressants in African and Hispanic individuals. Hispanic patients have been reported to require lower doses of antidepressants and to experience more side effects when compared to Whites. The preponderance of the data suggest that, for a given dose of a tricyclic antidepressant, African Americans show higher blood levels and faster therapeutic response, but also more toxic side effects compared with Whites.[57]

Benzodiazepines

The benzodiazepine diazepam is an important drug affected by *CYP2C19* polymorphisms. However, there have been relatively few studies of ethnic differences in response to diazepam or other benzodiazepines. Asian psychiatric patients often require lower doses of diazepam, but this may be because of differences in body fat rather than to genetic differences in drug metabolism.[16] The clearance of alprazolam, which is metabolized by the *CYP3A4* system, is significantly higher in Whites than in Asians.[38]

Antipsychotics

CYP2D6 polymorphisms affect the metabolism of antipsychotic drugs such as haloperidol and clozapine. Most studies of ethnicity and antipsychotic drug response have been conducted in Asian and White populations. These studies have in general found that, compared with Whites, Asians respond to lower doses of antipsychotic drugs and develop toxic side effects at lower doses.[16,34] Although the data are not entirely consistent, these results may be attributable to differences in pharmacokinetics. Blood levels of haloperidol were higher in Chinese or other Asians than in Whites in two studies (although not in a third). In these studies, the clinically adjusted dose of haloperidol was lower for Chinese and other Orientals than for Whites (Table 12). Similarly, the clinically adjusted dose of clozapine was lower in Korean Americans than in Whites. There was no difference between American-born and foreign-born Asians in response to haloperidol (Table 12).

There have been relatively few studies of the mechanisms responsible for the differences in clinical response to antipsychotics in African American patients. In a study of trifluoperazine and fluphenzine, the pharmacokinetic parameters did not differ between African Americans and Whites. However, antipsychotic use (and often misuse) is more frequent in the African American population. African Americans have also tended to receive substantially higher doses of antipsychotics, perhaps because of diagnoses of more severe illness, but also because of the stereotype that African Americans are more difficult to manage and are less compliant.[57] Rigorous studies are needed to delineate biological and cultural mechanisms that might be responsible for these clinical practices and to characterize the pharmacokinetics and pharmacodynamics in African American populations of these potent and potentially toxic substances.

Other ethnic groups, such as Ashkenazi Jews, may also respond differently to antipsychotic agents, especially with regard to the side effects profile. Lieberman et al. found that clozapine, used to treat schizophrenia, was associated with the development of agranulocytosis in 20% of Jewish patients, although this adverse reaction develops in only about 1% of chronic

schizophrenic patients in the general population.[58] Genetic testing revealed that a specific haplotype (a set of closely linked genes that determine different antigens but are inherited as a unit) was found in 83% of patients who developed agranulocytosis. All of the affected Ashkenazi Jewish patients possessed this haplotype, compared with 8% of these who did not develop the reaction. This haplotype is characteristically found in less than 1% of the White population in the United States, but occurs in 10% to 12% of the Jewish population in Israel and the United States. The increased susceptibility of Ashkenazi Jews in this study to the development of clozapine-induced agranulocytosis may be a result of the high incidence of this haplotype in this ethnic population.[59]

Analgesics

CYP2D6 polymorphisms play a role in the metabolism of codeine. Approximately 10% of codeine is metabolized via the *CYP2D6* system to morphine, from which codeine derives its analgesic effect. However, individuals with the *CYP2D6* poor metabolizer phenotype cannot metabolize codeine to morphine and therefore receive no analgesic or therapeutic effect from the drug.[60] This may have important clinical implications for the 5% to10% of White patients with the *CYP2D6* poor metabolizer phenotype, because codeine is often given as a drug of first choice for treatment of chronic severe pain. Most East Asians and Whites possess different combinations of *CYP2D6* polymorphisms that confer the extensive metabolizer phenotype. The distribution of these polymorphisms, however, and the expression of the phenotype differ among these populations, so that East Asians with the extensive metabolizer phenotype have lower levels of *CYP2D6* activity than do Whites with this phenotype. Hence, the production of morphine from codeine—and the analgesic effect—is lower in Chinese than in Whites with the extensive metabolizer phenotype.[38]

Finally, in a study of White and Asian (mostly Indian) immigrants in London, clearance rates of acetaminophen were significantly higher in Whites. Environmental factors, such as use of alcohol, tobacco, and oral contraceptives were associated with increased clearance rates, but did not account for all the interethnic differences.[61]

POLICY IMPLICATIONS

Physicians should be aware of genetic polymorphism as an important source of variation in drug response among individuals and should incorporate genetic factors into dosage considerations. Even if the physician is not aware of the underlying pharmacogenetic principles involved in distinguishing between genetic phenotypes, knowledge of the widely varying responses of different ethnic groups to certain drugs should alert the physician to the need to individualize therapy and to include consideration of the patient's ethnic or racial origin.

Cross-racial differences in response to drugs are relevant to the implementation of pharmaceutical cost control tactics. For example, the design of step-care protocols should include drugs at the first step that enable optimal therapy for patients of all races.

Metabolic differences among drugs of the same class have clear implications for therapeutic exchange programs, in which another drug from the same therapeutic class is substituted for a prescribed drug. Not all individual drugs within a class are metabolized by pathways subject to functional polymorphism, and some drugs are not metabolized at all but are excreted unchanged. Drugs that are metabolized chiefly through oxidation or acetylation in the liver are likely to show genetic differences in metabolism, whereas drugs that are metabolized through other pathways, or are not metabolized at all, are less likely to show cross-racial variability. As a result, drugs in the same class may differ in their susceptibility to racial and ethnic differences in clinical effect. For example, the class of benzodiazepines, which is prescribed for anxiety, sleep disorders, and convulsions, includes drugs that are subject to

differences in metabolism (diazepam, clonazepam, nitrazepam) and drugs that are not (triazolam, midazolam, lorazepam, temazepam, oxazepam). Similarly some beta-blockers are subject to differences in metabolism (metoprolol, propranolol, timolol, labetalol, pindolol, oxprenolol) and some are not (atenolol, nadolol). While the cost containment strategy behind therapeutic substitution programs seems practical, this policy may also be shortsighted, counter-effective, or clinically risky for patients in different racial and ethnic groups. Unfortunately, the pharmacokinetics of specific agents in most drug classes has not yet been studied in different racial and ethnic groups. Therefore, it is important that therapeutic substitution programs for patients of non-White racial and ethnic groups be undertaken with extreme caution.

Substitutions of antihypertensives drugs within the same class may be particularly problematic for African-American patients. The assumption that all beta-blockers are therapeutically equivalent is directly contradicted by the differences in clinical efficacy between propranolol and labetalol for African American and White hypertensive patients. Hence, the policy of substituting within the class of all beta-blockers without consideration for clinical differences in racial and ethnic response might place African-American patients at a higher risk than Whites for receiving suboptimal therapy if propranolol were substituted for labetalol. Interethnic differences between African American and White patients in response to antihypertensive treatment with beta-blockers also affect decisions about the cost-effectiveness of such treatment.

Finally, the lack of research on drug response differences among Hispanics, now the nation's largest racial or ethnic minority group, is of particular concern for the delivery of quality health care.

The Future of Individualized Therapy

Technological advances in the 1990s have changed the nature of pharmacogenetic research and its future impact on medicine. In the early decades of its existence, pharmacogenetics focused on the enzymes responsible drug metabolism. Differences in the genes encoding these enzymes were inferred from differences in the structure and activity of the enzymes themselves, i.e., from phenotypic differences. The frequencies of polymorphisms in drug metabolism enzymes were observed to vary among different populations defined on the basis of race or ethnicity. Race or ethnicity is, thus, a factor that changes the probability that an individual person will respond to a given drug. However, "race" is an inaccurate label for genetic variations that a given individual might or might not possess.

Two features of the genomics revolution, with the Human Genome Project as its centerpiece, have important consequences for the relationship between drug therapy and race or ethnicity. First, genetic variations are now determined by direct analysis of genes themselves by determination of their nucleotide sequences. Gene sequencing is now a rapid and automated process. Second, the entire spectrum of genes that determine drug behavior and sensitivity can now be studied genetically. That is, the effect of the entire genome on drug behavior can now be determined rather than the effect of the individual gene—hence the change from pharmacogenetics to pharmacogenomics. It is now possible to take a genetic 'fingerprint' of an individual and determine precisely the presence of polymorphisms in the genes known to be involved in drug interaction. Instead of a person's race being a marker for the possession of polymorphisms involved in drug response, a genotypic profile can determine with certainty whether or not the individual possesses these polymorphisms.

In the future, drug treatment will be individually tailored rather than race-based; however, the full impact of these changes will take many years to unfold. Genetic fingerprinting using DNA arrays is already practical, but the knowledge base relating genomic variations to drug response and disease progression has not been

developed. Observational studies are under way in which DNA fingerprints are being correlated with data present in medical records about medical history and drug response, and it is expected that the medical records of an entire country (Iceland) will be correlated with genomic data. These developments will surely have a profound impact on the ways in which new drugs are developed and used.

Continuing research in pharmacogenomics is likely to reveal significant and far-ranging information regarding interindividual and cross-racial differences in the actions of new and existing drugs. These developments, along with the increasing prevalence and influence of patients from a variety of races and ethnicities and the continued pressure to manage health care costs, will require programs having the dual objectives of cost control and individualized therapy for a racially and ethnically diverse population of Americans. Balancing these two, potentially opposing objectives will challenge health policy makers in the coming decades.

CONCLUSIONS AND RECOMMENDATIONS

As a result of advances in pharmacogenetics research, as well as political and social changes affecting racial and ethnic groups, more consideration is being given to the need to individualize drug therapy. Although the preceding review is not an exhaustive account of clinical and pharmacological studies involving racial and ethnic variation, it clearly emphasizes the range and scope of the problem. There can be no mistaking the importance of this issue for all health care providers. The following recommendations offer practical suggestions that can have positive benefits not only on the quality of care provided by health care institutions and physicians, but also on the control of health care costs.

1) Health care institutions should monitor, and restrict if necessary, the practice of therapeutic substitution of drugs within the same drug classes. Patients in particular racial and ethnic groups may be sub-

ject to greater risks than those in other groups if they are prescribed an "equivalent" drug because substantial evidence indicates that, even within a class, drug effectiveness and toxicity can vary among racial and ethnic groups. Institutional drug formularies and step-care protocols should be broad enough to allow rational choices of drugs and dosages for all patients, regardless of race or ethnic origin.

2) Pharmaceutical companies should continue to include significant numbers of patients from varied racial and ethnic backgrounds in drug metabolism and clinical trials in instances where genetic polymorphism for that drug class is relevant. The vast majority of drug manufacturers test and evaluate new pharmacological compounds on population subgroups, including racial and ethnic subgroups. This is likely to reveal drug actions and side effects specific to these groups, and may lead to the discovery of therapies of specific advantage to these populations.

3) Health care providers should give individualized treatment to each patient and resist the temptation to apply "cookbook" drug therapy that does not take into account racial or ethnic origin. For the practicing physician, each patient represents a unique and dynamic interaction among determinants that are both genetic and environmental. While it may be impossible for a physician to anticipate how a particular patient will respond in every instance, it is imperative to individualize therapy with respect to the appropriate choice of both drug and dose.

4) Physicians should be alert to atypical drug responses or unexpected side effects when they treat patients from varied racial and ethnic backgrounds. Dosage adjustments should be made for patients from different racial and ethnic groups if pharmacological evidence supports the adjustment.

5) Finally, and perhaps most important, all

who are involved in patient care should be aware of the growing clinical relevance of pharmacogenetics in determining differences in patient responses to drug therapy.

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