required to displace the drug binding from the binding sites. Thus, in vitro studies designed to assess the possibility of in vivo binding displacement must use undiluted plasma and clinically relevant drug concentrations.

The use of supratherapeutic drug concentrations or unusually low protein concentrations may produce binding displacement in vitro, but not in vivo. Zini et al. (1979) showed that indomethacin markedly decreased warfarin binding to human serum albumin in vitro at an indomethacin concentration of 100 $\mu$M. However, Vesell et al. (1975) found no clinically significant displacement interaction between indomethacin and warfarin in vivo where the indomethacin concentration ranged from 0.08 to 1.0 $\mu$M. Bupivacaine caused a 109% increase in the free fraction of mepivacaine in a solution of $\alpha_1$-acid glycoprotein, but only a 9% increase in the free fraction of mepivacaine in plasma containing the same $\alpha_1$-acid glycoprotein concentration (Hartrick et al., 1984). Both bupivacaine and mepivacaine are highly bound to high-affinity and low-capacity $\alpha_1$-acid glycoprotein and low-affinity and high-capacity albumin in plasma.

Similar to metabolism-based drug interaction, the interpretation and extrapolation of in vitro displacement interaction data requires a good understanding of pharmacokinetic principles. Rowland and Aarons (Rowland, 1980; Aarons and Rowland, 1981) have reviewed the theoretical and clinically relevant issues regarding drug displacement interactions. Depending on whether it is a low- or high-clearance drug, displacement interaction will cause different alterations in pharmacokinetics. As shown in equation [10], changes in the free fraction ($f_p$) in plasma caused by displacement binding will affect drug distribution. As seen in equations [6] and [10], an increase in the $f_p$ of high-clearance drugs caused by binding displacement interaction will have little change in the clearance (cL), but will lead to an increase in the volume of distribution ($V_d$); hence, the elimination $t_{½}$ will increase. The $t_{½}$ is related to both the cL and $V_d$ as follows:

$$t_{½} = \frac{0.693 \times V_d}{cL}. \qquad [12]$$

For low-clearance drugs, both cL and $V_d$ will increase with an increase in $f_p$ as shown in equations [5] and [10]. Although the changes in cL and $V_d$ may not exactly balance, the $t_{½}$ will be affected to a much smaller degree compared with that of highly cleared drugs.

Because only unbound drug is responsible for pharmacological effect, it is important to make a clear distinction of the effects of displacement interaction on unbound and total drug concentrations in plasma. The simplest way of considering the effect of protein binding on the unbound and total drug concentration profiles is to examine the AUC. For low-clearance drugs, the AUC of unbound and total drug after intravenous dosing can be expressed as:

$$AUC_{total} = \frac{dose}{cL} = \frac{dose}{f_p \cdot cL_{int}} \qquad [13]$$

and

$$AUC_{unbound} = AUC_{total} \cdot f_p = \frac{dose}{cL_{int}}. \qquad [14]$$

On the other hand, the AUC of unbound and total drug of high-clearance drugs after intravenous administration can be expressed as:

$$AUC_{total} = \frac{dose}{cL} = \frac{dose}{Q_h} \qquad [15]$$

and

$$AUC_{unbound} = AUC_{total} \cdot f_p = \frac{dose \cdot f_p}{Q_h}. \qquad [16]$$

From equations [13] and [14], it is evident that the AUC of unbound drug for low-clearance drugs is independent of any change in $f_p$ if $cL_{int}$ is unaffected by displacement interaction, whereas an increase in the $f_p$ caused by binding displacement interactions will result in a decrease in the AUC of total drug. On the other hand, exactly the opposite situation occurs with a high-clearance drug in which the clearance and, hence, total drug concentration is unaffected by changes in plasma protein binding, whereas the unbound drug concentration increases as a result of increased $f_p$ as shown in equations [15] and [16]. Figure 7 depicts the effects of displacement from protein binding sites on the steady-state unbound and total drug concentrations of low- and high-clearance drugs during intravenous infusion (Aarons, 1986).

After oral administration, the AUC of unbound and total drug, regardless of whether it is a high- or low-clearance drug, can be expressed as equation [17], which

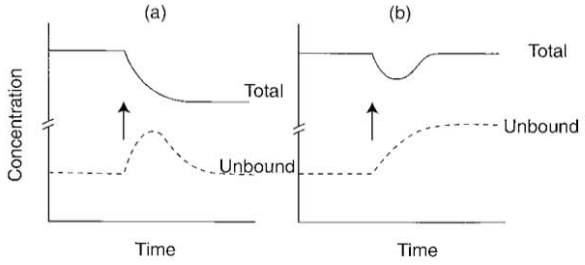


FIG. 7. The effect of displacing a low-clearance drug (a) or high-clearance drug (b), given chronically, from plasma protein binding sites. Displacement is produced by infusing a drug that displaces the first drug, starting from the arrowed point. Reproduced with permission from Aarons (1986).

is similar to equation [8]:

$$AUC_{total} = \frac{F \cdot dose}{cL} = \frac{dose}{f_p \cdot cL_{int}} \quad [17]$$

and

$$AUC_{unbound} = AUC_{total} \cdot f_p = \frac{dose}{cL_{int}}. \quad [18]$$

From equations [17] and [18], the AUC of unbound drug after oral dosing is insensitive to the changes in the $f_p$, whereas the AUC of total drug will decrease when the $f_p$ increases as a result of displacement interactions.

Because a significant change in the unbound AUC of drugs after oral dosing is not expected, and because most drugs are given orally, the displacement interactions rarely have significant clinical effects (Mackichan, 1984,1989; Sellers, 1979). When changes in binding are associated with clinical effects, it has almost always been found that this is the result of a change in the $cL_{int}$ caused by a mechanism quite independent of plasma protein binding as indicated in equation [18]. Warfarin-phenylbutazone interaction is a good example. When concomitantly administered with warfarin, phenylbutazone caused profound potentiation of a hypoprothrombinemic response (Sellers, 1986). Although phenylbutazone is known to displace warfarin from plasma proteins, it is clear from equation [18] that the hypoprothrombinemic effect was not caused by binding displacement of phenylbutazone, because the unbound concentration of warfarin should not be changed. Later, it was found that phenylbutazone stereoselectively inhibited the metabolism of *S*-warfarin (Lewis et al., 1974; O'Reilly et al., 1980). Thus, the metabolism inhibition, rather than binding displacement, causes the serious hemorrhagic complications of warfarin-phenylbutazone interaction. Similarly, although sulfaphenazole is known to displace tolbutamide from plasma proteins, the inhibitory effect of sulfaphenazole on the metabolism of tolbutamide is responsible for the serious hypoglycemic reactions (Christensen et al., 1963).

Whereas the unbound concentration after oral dosing is unaffected by displacement interaction, the transient increase in the unbound drug concentration occurring immediately after introduction of the displacing drug sometimes may be of clinical significance (Levy, 1976). Øie and Levy (1979a,b) reported that rapid intravenous infusion of salicylic acid or sulfisoxazole resulted in a transitory increase of unbound bilirubin concentration in rats. This suggests that the fatal kernicterus seen in the newborn after administration of sulfonamides may be due to a transitory increase in unbound bilirubin in the brain. In addition, the displacement interactions will be of clinical significance for high-clearance drugs after intravenous dosing. As shown in figure 7, a substantial increase in the unbound concentration may occur.

## V. Interindividual Variability: A Critical Issue in Drug Development

From the market point of view, it is desirable that the dosage can be generalized to provide drugs for the treatment of a large number of patients. In reality, the generalization may work for most patients, but not for all. The standard dosage regimen of a drug may prove to be therapeutically effective in most patients, ineffective in some patients, and toxic in others. Variability in drug response becomes an important problem in drug therapy for drugs that have a narrow therapeutic window. Warfarin is a good example. There is a wide range of daily dose requirements (<2 mg–>11 mg) of warfarin needed to produce a similar prothrombin time (Koch-Weser, 1975). Variability in drug response can be broadly divided into pharmacokinetic and pharmacodynamic bases. Sources of pharmacokinetic variability include genetics, disease, age, and environmental factors (Breimer, 1983).

### *A. Pharmacokinetic Variability*

The patient's exposure to drug is a crucial determinant of the drug's actions, and therefore its efficacy and safety. The term "drug exposure" is defined as the time course of the concentration of the drug and its active metabolites in plasma. The time course of drug concentration is governed by absorption, distribution, metabolism, and excretion. All these processes can contribute to pharmacokinetic variability.

*1. Variability in absorption.* Variation in absorption is one of the major sources of pharmacokinetic variability. An impression prevails that the degree of variability in the amount of drug reaching the systemic blood circulation is minimized if a drug has high bioavailability, whereas the risk of greater variation in the amount taken up is increased if a drug has low bioavailability. However, all too often, the degree of variability in absorption is similar for drugs of high and low bioavailability. The causes of absorption variability include pharmaceutical formulation, gastrointestinal physiology, and first-pass metabolism.

Being absorbed primarily from the upper part of the small intestine, oral absorption of drugs is often affected by the gastric emptying time and small intestinal motility, which vary considerably between individuals (Meyer, 1987; Weisbrodt, 1987). Usually, rapid gastric emptying results in rapid drug absorption. Changes in gastric emptying normally affect the rate of absorption but do not affect the amount of drug absorbed unless the drug is chemically unstable in the stomach or associated with saturable first-pass metabolism (Nimmo, 1976).

Dietary factors are also important sources of absorption variability that can be accounted for. The influence of food on the absorption of drugs is largely unpredictable. Food may enhance or reduce the absorption of some drugs while having no effect on others, depending not

only on the composition and volume of the meal or the drink, but also on the physicochemical properties of drugs. For example, absorption of the lipophilic drugs griseofulvin and sulfamethoxydiazine increased considerably when given with a high-fat meal (Crouse, 1961; Kaumeier, 1979). Amoxicillin, a poorly soluble antibiotic, was absorbed to a greater extent when swallowed with 250 mL water (Welling et al., 1977). In addition, dietary factors have been shown to alter drug-metabolizing enzyme activity, leading to changes in first-pass metabolism and bioavailability. Both charcoal-broiled beef and a high-protein, low-carbohydrate diet cause an increase in theophylline and antipyrine metabolism (Kappas et al., 1978, 1976). Certain vegetables, including brussel sprouts, cabbage, broccoli, and cauliflower, contain chemicals that induce drug-metabolizing enzyme activities (Pantuck, 1979). Because the diet is so different among patients, it is conceivable that the effects of food account for a substantial part of the absorption variability. Ironically, most clinical studies designed to address the question as to whether food intake affects drug absorption were conducted in healthy volunteers with or without a more or less standardized meal. Thus, such information may not be meaningful, sometimes even misleading.

The problem of absorption variability is complicated further by diseases. Hepatic disease may influence the oral bioavailability of drugs highly metabolized by the liver. The bioavailability of propranolol was increased significantly from 35% in normal subjects to 54% in cirrhotic patients, and the steady-state unbound propranolol concentration increased from 7.5 ng/mL to 22 ng/mL (Wood et al., 1978). The increased bioavailability was due mainly to a decrease in hepatic first-pass metabolism.

*2. Variability in binding.* As discussed earlier, plasma protein binding is an important determinant of the drug's disposition and actions. The $f_p$ varies widely among drugs, and often (for highly bound drugs) among individuals. Differences in binding among drugs arise primarily from differences in their affinities for binding proteins, whereas differences in binding among individuals are due mainly to qualitative or quantitative differences in binding proteins. Nevertheless, interindividual variability in drug binding is generally less as compared with that in other pharmacokinetic processes such as absorption and metabolism (Yacobi and Levy, 1977; Barth et al., 1976).

$\alpha_1$-Acid glycoprotein is a major determinant for the binding of basic drugs in plasma (Piafsky and Borgå, 1977; Piafsky et al., 1978). Several inflammatory states (infections, rheumatic disorders, and surgical injury) and pathological conditions (myocardial infarction, malignancies, and nephritis) elevate the plasma concentration of $\alpha_1$-acid glycoprotein (Abramson, 1982; Freilich and Giardini, 1984). Furthermore, $\alpha_1$-acid glycoprotein is known to be inducible. Treatment with phenobarbital resulted in a substantial increase in plasma concentration of $\alpha_1$-acid glycoprotein (Abramson, 1991). Because there is a strong correlation between the binding of basic drugs and the plasma levels of $\alpha_1$-acid glycoprotein (Lunde et al., 1986; Sjöqvist and Koike, 1986), an elevation of this protein will increase the binding of basic drugs.

In contrast to the elevation of $\alpha_1$-acid glycoprotein, hypoalbuminemia is always associated with a large variety of pathological conditions, including liver cirrhosis, renal failure, nephrotic syndrome, chronic inflammation, malignancies, and sepsis (Gugler and Jensen, 1986). In hypoalbuminemia, the binding of acidic drugs is reduced, and the decrease is related to a decrease in the plasma albumin concentration. Although normal subjects have a plasma albumin concentration of at least 35 mg/mL, plasma albumin concentrations can be as low as 10 mg/mL in patients with nephrotic syndrome.

In addition to the quantitative changes in plasma protein concentrations, qualitative structural changes of plasma proteins also alter the binding of drugs. High doses of acetylsalicylic acid can acetylate serum albumin and modify its binding sites (Hawkins et al., 1968). Cyanate, spontaneously formed from urea, carbamylates lysine residues on the albumin molecules and decreases the binding of acidic drugs in uremic patients (Erill et al., 1980). Furthermore, in uremic patients, retained endogenous acids that are highly protein bound can displace the binding of drugs from proteins. Collier et al. (1986) have identified one of these acids, 3-carboxy-4-methyl-5-propyl-2-furanpropanic acid, as a potent displacer of drug binding. From these data, it is clear that disease states also are the main sources of binding variability.

Genetically determined variations in amino acid sequences of serum albumin and $\alpha_1$-acid glycoprotein also can contribute to binding variability. To date, more than 30 apparently different genetic variants of human serum albumin have been identified. Only approximately half of these variants have been absolutely characterized by peptide mapping and sequence determination (Eap and Baumann, 1991). Kragh-Hansen et al. (1990) have compared the binding affinities (association constants) of warfarin, salicylate, and diazepam to five variants of human serum albumin with known mutations. The association constants of all three drugs to albumin Canterbury (313 Lys→Asn) and to albumin Parkland (365 Asp→His) decreased substantially by a factor of 4- to 10-fold, whereas the binding affinity to albumin Verona (570 Glu→Lys) was unchanged. These results suggest that the region 313–365 seems to exert important effects on the binding of drugs, whereas the mutation 570 near the C-terminus does not affect drug binding.

Three main variants of $\alpha_1$-acid glycoprotein, namely ORM1 F1, ORM1 S, and ORM2 A, have been fully characterized (Eap and Baumann, 1991). Among the three variants, ORM2 A is the most important variant associ-

ated with the binding of basic drugs. Eap et al. (1990) have determined the in vitro binding of *d*-methadone, *L*-methadone and *dl*-methadone in plasma samples from 45 healthy subjects. The concentrations of $\alpha_1$-acid glycoprotein variants also were measured. Using multiple stepwise regression analysis, significant correlations were obtained between the binding of methadone and the total $\alpha_1$-acid glycoprotein or ORM2 A concentrations, but only a weak correlation between the binding and ORM1 S concentrations, and no correlation between the binding and ORM1 F1 concentrations were found. The frequencies for the three phenotypes, i.e., ORM1 F1/ORM2 A, ORM1 F1/ORM1 S/ORM2 A, and ORM1 S/ORM2 A were found to be 33.7, 50.5, and 15.2%, respectively, in a Swiss population (Eap et al., 1988). These results suggest genetically determined variations in $\alpha_1$-acid glycoprotein could be a major source of variability in the binding of basic drugs.

*3. Variability in excretion.* Although metabolism is the major route of elimination for most drugs, some drugs are excreted mainly as unchanged drug via the kidneys and liver. Both biliary and renal excretion correlate to their function. Ceftazidime, a cephalosporin antibiotic, is excreted mainly by the kidneys. The total clearance of ceftazidime correlated linearly with creatinine renal clearance in patients with varying degrees of renal function (Van Dalen et al., 1986). Similarly, a strong correlation should exist between the clearance and hepatic function if a drug is excreted mainly by the liver. The biliary excretion of indocyanine green correlated well with hepatic function in cirrhotic patients (Kawasaki et al., 1985).

Many endogenous organic acids are accumulated in the plasma of patients with renal dysfunction. These endogenous organic acids may inhibit the transport of certain drugs in the liver. The hepatic uptake and biliary excretion of bromosulfophthalein and dibromosulfophthalein are decreased in rats with acute renal failure (Silberstein et al., 1988). These data demonstrate that variations in hepatic and renal function, particularly in patients with hepatic and renal disorders, contribute significantly to pharmacokinetic variability.

Reabsorption is one of the important factors governing renal clearance of drugs. Lipophilic drugs tend to be extensively reabsorbed, whereas hydrophilic drugs do not. Urine flow and pH have a substantial effect on the renal clearance of a drug that is mostly reabsorbed. An increase in the urine flow will result in a decrease in reabsorption, leading to an increase in renal clearance. The renal clearance of theophylline increases with increasing urine flow rate (Tan-Liu et al., 1982). Similarly, the renal clearance of phenobarbital is also dependent on the urine flow rate (Linton et al., 1967).

Unlike plasma that has a narrow pH range of 7.3 to 7.5, urine pH ranges from 4.5 to 8.5. Thus, the urine pH is an additional factor that influences the reabsorption of drugs that are weak acids and bases. The renal excretion of salicylic acid is markedly pH-dependent. Renal excretion of salicylate increases more than ten-fold as the urinary pH increases from 5 to 8 (Macpherson et al., 1955). In contrast, the renal clearance of quinidine has been shown to diminish with increasing urinary pH (Gerhardt et al., 1969). Drugs that show pH-sensitive reabsorption also generally show flow-rate dependence. Clearly, variations in urine flow and pH also contribute significantly to excretion variability.

### *B. Pharmacogenetics of Drug Metabolism*

All enzymes involved in the metabolism of drugs are regulated by genes and gene products. Because of evolutionary and environmental factors, there is a remarkable degree of genetic variability built into the population. Thus, the genetic factor represents an important source of interindividual variation in drug metabolism. Mutations in the gene for a drug-metabolizing enzyme result in enzyme variants with higher, lower, or no activity or may lead to a total absence of the enzyme. Therefore, it is not unusual to find a ten-fold or as much as a 50-fold difference in the rate of drug metabolism among patients.

With the technological breakthroughs in molecular biology, significant progress has been made in understanding the role of genetic polymorphisms in drug metabolism. The major polymorphisms that have clinical implications are those related to the oxidation of drugs by CYP2D6 and CYP2C19 (Meyer et al., 1990b, 1992; Meyer, 1994; Wilkinson et al., 1989; Broly and Meyer, 1993; Alvan et al., 1990), acetylation by *N*-acetyltransferase (Evans, 1992), and *S*-methylation by thiopurine methyltransferase (Weinshiboum, 1992; Creveling and Thakker, 1994). Individuals who inherit an impaired ability to catalyze one or more of these enzymatic reactions may be at an increased risk of concentration-related adverse effects and toxicity.

*1. Polymorphism in drug oxidation.* CYP2D6 polymorphism is perhaps the most studied genetic polymorphism in drug metabolism. Since its discovery in 1977 (Mahgoub et al., 1977), hundreds of studies have been carried out to investigate the nature of CYP2D6 polymorphism, the mode of inheritance, and the consequences of the deficient trait on drug disposition and pharmacological effects. This polymorphism divides the populations into two phenotypes: EM and PM. Approximately 5 to 10% of individuals in Caucasian populations are the PM phenotype, compared with only 1 to 2% of individuals in Asian populations. To date, more than 50 drugs, including antidepressants, antipsychotics, and cardiovascular drugs, are known to be catalyzed primarily by CYP2D6 (Parkinson, 1996).

Clinical studies have demonstrated that the PMs of CYP2D6-mediated drugs represent a high-risk group with a propensity to develop adverse effects. The disposition of haloperidol, a potent neuroleptic, was studied in a panel of six EMs and six PMs of debrisoquine (Llerena

et al., 1992). The PMs that received 4 mg of haloperidol developed neurological side effects, whereas at the same dose, the EMs experienced only mild side effects, such as tiredness, difficulty concentrating, and some restlessness. The PMs eliminated haloperidol significantly slower than the EMs, and the high plasma concentrations of haloperidol might, therefore, be associated with the side effects observed in the PMs. Similarly, an increased risk of side effects also was observed in the PMs of debrisoquine when taking other neuroleptics, such as perphenazine (Dahl-Puustinen et al., 1989) and thioridazine (Meyer et al., 1990a). Both drugs also are metabolized by CYP2D6.

Similarly, propafenone, a class I antiarrhythmic agent, is metabolized by CYP2D6. The relationship between debrisoquine phenotype and pharmacokinetics and pharmacodynamics of propafenone was studied in 28 patients (22 EMs and 6 PMs) with chronic ventricular arrhythmias (Siddoway et al., 1987). Steady-state concentrations of propafenone in plasma were found to be significantly higher in PMs than EMs. These higher concentrations were associated with a greater incidence of CNS side effects in the PMs (67%), relative to the EMs (14%).

The effects of CYP2D6 polymorphism on pharmacological responses can be quite complex, depending on whether the parent drug or metabolites, or both, are pharmacologically active. Encanide, a class I antiarrhythmic, is a good example. CYP2D6 *O*-demethylates encanide to a metabolite that is 6 to 10 times more potent than the parent drug in blocking sodium channels. In both PMs and EMs, standard doses of this drug tend to produce similar therapeutic responses, because relatively high parent drug concentrations in the former are matched by relatively high active metabolite concentrations in the latter (Buchert and Woosley, 1992). Similarly, both propafenone and its 5-hydroxy propafenone metabolite are pharmacologically active. The metabolism of propafenone to 5-hydroxy propafenone is grossly impaired in the PMs, resulting in very low or no levels of this active metabolite. However, as with encanide, there were no significant differences between EMs and PMs in an effective propafenone dosage or frequency of antiarrhythmic response (Siddoway et al., 1987). This again can be explained by the compensatory effect of the active metabolite of 5-hydroxy propafenone, present in the plasma of EMs but not in that of PMs.

Codeine is metabolized extensively by glucuronidation; the *O*-demethylation of codeine to morphine is a minor pathway that is mediated by CYP2D6 (Chen et al., 1988). As only a small fraction of the drug is metabolized by the *O*-demethylated pathway, PMs are not expected to have an altered disposition of codeine relative to EMs. As anticipated, plasma concentrations of codeine were similar in PMs and EMs, but measurable concentrations of morphine, its more analgesic *O*-demethylation product, were only detected in EMs (Sindrup et al., 1991). Consequently, codeine increased the pain thresholds to copper vapor laser stimuli in EMs, but not in PMs, affirming the functional importance of the codeine-morphine biotransformation for codeine analgesia.

CYP2C19 also exhibits genetic polymorphism in drug metabolism. The incidence of the PM phenotype in populations of different racial origin varies; approximately 2 to 6% of individuals in the Caucasian populations are the PM phenotype, as are 14 to 22% in the Asian populations (Wilkinson et al., 1992; Kalow and Bertilsson, 1994). Although it is expected that PMs will have higher plasma concentrations of drugs metabolized by CYP2C19 than EMs and experience an increase in adverse effects, the clinical implications of CYP2C19 polymorphism have not been thoroughly characterized. Contrary to CYP2D6, CYP2C19 has been studied far less, which is reflected by the much shorter list of known drugs characterized by CYP2C19 than by CYP2D6 (Parkinson, 1996).

Diazepam is demethylated by CYP2C19 in humans (Anderson et al., 1990). The disposition of diazepam has been studied in 13 Caucasians of the EM phenotype and 3 Caucasians of the PM phenotype (Bertilsson et al., 1989). The plasma clearance of diazepam in the EMs was more than 2 times that in the PMs (11.0 and 5.0 mL/min, respectively), whereas the $t_{1/2}$ in the EMs was shorter than that in the PMs (59 and 128 h, respectively). The difference in the plasma clearance appeared to be related to formation of the desmethyl metabolite.

Omeprazole, a proton pump inhibitor, is metabolized (by CYP2C19) by hydroxylation and oxidation of the sulfoxide group to a sulfone (Anderson et al., 1990). The metabolism of omeprazole has been studied in the EMs and PMs of *S*-mephenytoin selected from phenotyped healthy Swedes and Chinese (Andersson et al., 1992). The plasma concentrations of omeprazole and its metabolites were determined after a single oral dose (20 mg). The AUC of omeprazole was substantially higher in PMs than in EMs in both Swedes (11.1 and 0.94 $\mu$M·h) and Chinese (13.3 and 2.6 $\mu$M·h). Although the AUC was not different between Swedish and Chinese PMs, there was a significant interethnic difference in EMs. The fact that the AUCs in Chinese EMs were 3 times higher than those of the Swedish EMs might be due to the higher proportion of heterozygotes in the Chinese.

From a genetic point of view, the different enzyme polymorphisms in drug metabolism are inherited independently. However, an inherited deficiency of different drug-metabolizing enzymes could occur simultaneously on the basis of probability. A population study of mephenytoin hydroxylation and debrisoquine hydroxylation was carried out in 221 unrelated normal volunteers (Küpfer and Preisig, 1984). Twelve (5%) of them exhibited defective hydroxylation of mephenytoin, and 23 (10%) could be identified as PMs of debrisoquine. Among these 35 subjects, 3 (1 female and 2 males) displayed

simultaneously both defects of mephenytoin and debrisoquine hydroxylation.

Propranolol is hydroxylated by CYP2D6 and *N*-dealkylated by CYP2C19. The relative contributions of these two isoforms to propranolol metabolism have been studied in a panel of phenotyped normal volunteers (Ward et al., 1989). Six subjects were EMs of both mephenytoin and debrisoquine. Four subjects were PMs of debrisoquine but rapid metabolizers of mephenytoin. Five subjects were PMs of mephenytoin but rapid metabolizers of debrisoquine, and one subject had a deficiency for both debrisoquine and mephenytoin. PMs of either mephenytoin or debrisoquine had a similar disposition of propranolol to that of EMs, whereas the subject with both mutations had a $t_{1/2}$ 2 times longer than the other subjects'.

In view of the examples presented above, it is clear that genetic polymorphism in drug metabolism could lead to clinically significant differences in pharmacokinetics and pharmacological responses of some patients and therefore might result in adverse effects or therapeutic failure. Thus, drugs metabolized by enzymes exhibiting genetic polymorphism are considered to be undesirable. However, the development of a drug sometimes is prematurely terminated based solely on the fact that its metabolism is polymorphic. To avoid premature termination, the clinical relevance of genetic polymorphism must be assessed carefully. Pharmacokinetic differences between phenotypes are most relevant for drugs with narrow therapeutic indices. For compounds with a variability of plasma concentrations outside the therapeutic range that is not associated with adverse effects, polymorphic metabolism will be of less or little concern. Propranolol is a typical example. Despite the critical involvement of CYP2D6 and CYP2C19 polymorphism in the metabolism of propranolol, this drug is quite safe clinically. Another important factor in determining the go/no-go decision is the overall benefit-to-risk ratio. If the benefit of a drug is significantly greater than its risk, and dosage can be titrated by direct clinical monitoring, then polymorphic metabolism is of less consequence.

*2.* N-*Acetylation polymorphism.* Acetylation is an important route of elimination for a large number of hydrazine and arylamine drugs (Weber et al., 1990). The *N*-acetyltransferase (NAT) polymorphism in humans was discovered as a result of studying the rate of isoniazid elimination in tuberculous patients in 1960 (Evans et al., 1960). The patients could be classified as slow and rapid acetylators based on their plasma concentrations of isoniazid. In addition to isoniazid, sulfamethazine, hydralazine, procainamide, dapsone, and nitrazepam also are polymorphically acetylated (Evans, 1992, 1989). The proportions of rapid and slow acetylators vary considerably between ethnic groups. For example, the percentage of slow acetylators in Egyptians and Mideasterners is 80 to 90%, whereas in Asian populations, it is only 10 to 20%, with European and North American Caucasians having an intermediate value of 40 to 70% (Evans, 1989). On the other hand, other *N*-acetylated compounds, such as p-aminobenzoic acid and p-aminosalicylic acid, were unable to distinguish rapid and slow acetylators in vivo and in vitro (Evans, 1989). These compounds are, therefore, classified as monomorphic substrates.

Although the acetylation polymorphism was suspected for nearly 40 years, the molecular mechanics underlying this polymorphism were not known until recently. Meyer and his colleagues (Blum et al., 1990; Grant et al., 1991) have successfully cloned three human genes: NAT1, NAT2, and a related pseudogene, NATP. The discovery of two separate genes encoding NAT1 and NAT2 resolved the old question on monomorphic and polymorphic substrates. NAT2 has a high affinity for polymorphic substrates, whereas NAT1 has a high affinity for monomorphic substrates. Mutations of the NAT2 gene result in slow acetylation. The most common acetylator allele in Caucasians clearly is that with three mutations at positions 341, 481, and 803 (NAT2-B), followed by that with two mutations at positions 282 and 590 (NAT2-C) and that with two mutations at positions 282 and 287 (NAT2-D). These three alleles account for >95% of mutant alleles in Caucasian slow acetylators (Meyer et al., 1993; Lin et al., 1993a).

In general, slow acetylators are more susceptible to adverse effects than are rapid acetylators, because the *N*-acetylated drugs are not cleared from the body as well in slow acetylators. On the contrary, therapeutic effects may be suboptimal in rapid acetylators because of the rapid elimination of drugs. In a study of 744 pulmonary tuberculosis patients, there was a tendency for cavity closure and sputum conversion to occur significantly earlier in slow acetylators (Harris, 1961). However, the slow acetylators were more susceptible to hepatotoxicity (Mitchell et al., 1976). Furthermore, slow acetylators are more prone to develop systemic lupus erythematosus and rheumatoid arthritis (Lawson et al., 1979; Reindenberg and Martin, 1974).

Recently, the association of the acetylation morphism with an increased risk to develop certain cancers, e.g. bladder cancer or colorectal, has received much attention (Evans, 1992; Bock, 1992). It has been shown that the relative risk of developing bladder cancer in slow acetylators is 2 to 3 times that in rapid acetylators (Hassen et al., 1985). Consistent with this, the incidence of bladder cancer is low (6.3/100,000) in Japan, which has a low frequency of slow acetylator phenotype, approximately 11%, compared with the situation in the United States, where the incidence and frequency are 25.8/100,000 and 58%, respectively (Schultz, 1988). Similarly, the Japanese population exhibits a very low incidence of colorectal cancer (Connor et al., 1986). These data suggest that the *N*-acetylation phenotype is prob-

ably an important factor contributing to the multifactorial etiology of certain cancers.

Unlike the polymorphism of drug oxidation, neither slow nor rapid acetylation phenotype is rare in all ethnic groups. For example, most populations in Europe and North America have 40 to 70% slow acetylators and 30 to 60% rapid acetylators. Therefore, an important point to consider is the impact of polymorphic acetylation on the development of new drugs. In clinical trials, sufficient numbers of people should be studied to ensure that both the slow and rapid acetylation phenotypes are adequately represented. In some instances, it might be of value to phenotype patients to adjust dose regimens.

*3.* S-*Methylation polymorphism. S*-Methylation is an important metabolic pathway of many sulfhydryl drugs. Two enzymes, thio methyltransferase (TMT) and thiopurine methyltransferase (TPMT), are involved in the *S*-methylation. TPMT is a cytoplasmic enzyme that preferentially catalyzes the *S*-methylation of aromatic and heterocyclic sulfhydryl drugs, such as 6-mercaptopurine and azathioprine, whereas TMT is a membrane-bound enzyme and preferentially catalyzes the *S*-methylation of aliphatic sulfhydryl drugs, such as captopril and *D*-penicillamine (Weinshiboum, 1992; Creveling and Thakker, 1994).

Both TPMT and TMT are genetically polymorphic. In a study of 298 subjects, 88.6% had high erythrocyte TPMT activities, 11.1% had intermediate activities, and 0.3% had undetectable activity (Weinshiboum and Sladek, 1980). Although the TPMT activities in the red blood cells do not play a significant role in the *S*-methylation, the regulation of TPMT activity in the red blood cells reflects those in other tissues such as the kidney and liver (Woodson et al., 1982; Szumlanski et al., 1988). A significant correlation was found between myelosuppression in patients who were being treated with 6-mercaptopurine and azathioprine and low TPMT activities in their erythrocytes (Lennard et al., 1987, 1989). The patients with low TPMT activities had high blood levels of 6-thioguanine nucleotide (6-TGN) that may be incorporated into DNA. Both 6-mercaptopurine and its prodrug azathioprine are catalyzed competitively by *S*-methylation and the metabolic pathway, leading to the formation of 6-TGN. Because of compensatory effects, the patients with low TPMT activities will have higher 6-TGN levels and be more susceptible to the risk of developing thiopurine-induced bone marrow suppression.

TMT also exhibits genetic polymorphism. The genetic frequencies for low and high activities were estimated to be approximately 60 and 40%, respectively (Price et al., 1989). It is believed that the genetic variability is related to interindividual differences in the *S*-methylation of aliphatic sulfhydryl drugs, such as captopril and *D*-penicillamine. Unlike TPMT, the clinical implications of TMT polymorphism have not been thoroughly characterized yet.

*4. Atypical butyrylcholinesterase.* Patients with genetic variants of butyrylcholinesterase exhibit prolonged paralysis after standard doses of neuromuscle blockers, such as succinylcholine, suxamethonium, and mivacurium, as a result of impaired ester hydrolysis (Lockridge, 1992; Bevan, 1993; Goudsouzian et al., 1993). The genetic variant most frequently found in patients who responded abnormally to the neuromuscular blockers is atypical butyrylcholinesterase, which occurs in homozygous form in 1 of 3500 Caucasians (Lockridge, 1992). By definition, the genetic allele that regulates the butyrylcholinesterase activities is not a common polymorphism but is a rare genetic variant. Several human enzymes may be involved in hydrolysis of ester drugs, including arylesterase and acetylcholinesterase. Genetic variants are known not only for butyrylcholinesterase, but also for arylesterase (La Du, 1992). No genetic variants are known for human acetylcholinesterase.

Although problems with the neuromuscular blockers are rare (<1% of patients), the prolonged muscle paralysis can be serious. The patients may be unable to breathe and have to be maintained on mechanical ventilators. Because butyrylcholinesterase is present in plasma and because the in vitro test procedures using dibucaine are relatively simple (Kalow and Genest, 1957), patients should be screened for their butyrylcholinesterase activity before being given the muscle relaxants. So far, no drug-induced toxicity was found to be related to the genetic variants of arylesterase.

As described above, genetic polymorphism in drug metabolism is undesirable and can at times be problematic. However, it should be emphasized that even if a large proportion of the metabolism of a compound is subject to genetic polymorphism, this should not influence its development as a drug. Careful evaluation of clinical relevance of the polymorphic metabolism has to be taken into consideration in making the go/no-go decisions.

## VI. Conclusions

Drug research is an extremely complicated endeavor. It encompasses several diverse disciplines united by a common goal, namely the development of novel therapeutical agents. As described in this paper, pharmacokinetics and drug metabolism play an important role as determinants of in vivo drug action. Ideally, the process of rational drug design should provide a delicate balance between the chemistry, pharmacology, and pharmacokinetics of the drug. The discoveries of HIV protease inhibitors, indinavir and ritonavir, and the antifungal agent fluconazole are good examples of successfully incorporating pharmacokinetic and metabolic information into drug design.

Due to ethical constraints, relevant pharmacokinetic and metabolism studies must be carried out extensively in laboratory animals or in vitro systems before first drug administration in humans. Although these studies

provide useful information about absorption, distribution, metabolism, and excretion of the drug, extrapolation from in vitro and animal data to humans must be done cautiously. Marked species differences occur in the enzymatic systems involved in drug metabolism, whereas greater similarities are seen in physiological characteristics among different species. Therefore, it is of great importance that the underlying mechanisms responsible for these similarities and differences be examined carefully and weighted appropriately to ensure a reliable prediction from animal data to humans.

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