SPECIAL ARTICLE

PHARMACOKINETICS WITHOUT EQUATIONS : FACTORS MODIFYING DRUG EFFECTS IN INDIVIDUALS

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The majority of people respond to most drugs in a similar enough fashion to permit the calculation of a standard therapeutic dose of a drug. This statistically derived "average" dose, however, only represents the starting point from which to estimate the dose appropriate for a given subject. The many variables contributing to the individuality of a complex living organism, or associated with the conditions present at the time of drug administration must be considered as potentially capable of modifying the anticipated drug effect (Figure 1).

We shall be concerned here only with those factors that modify the pharmacokinetics of a drug, i.e.: the absorption, distribution, biotransformation and excretion. Factors that can alter genetically controlled rates of drug disposition in normal subjects include: age; sex; diurnal rhythms ; diet; exposure to inducing or inhibiting compounds, such as ethanol and cigarette smoking; stress; concomitant administration of other drugs, and even the simple factor of body position, e.g.; the influence on absorption of lying on the right

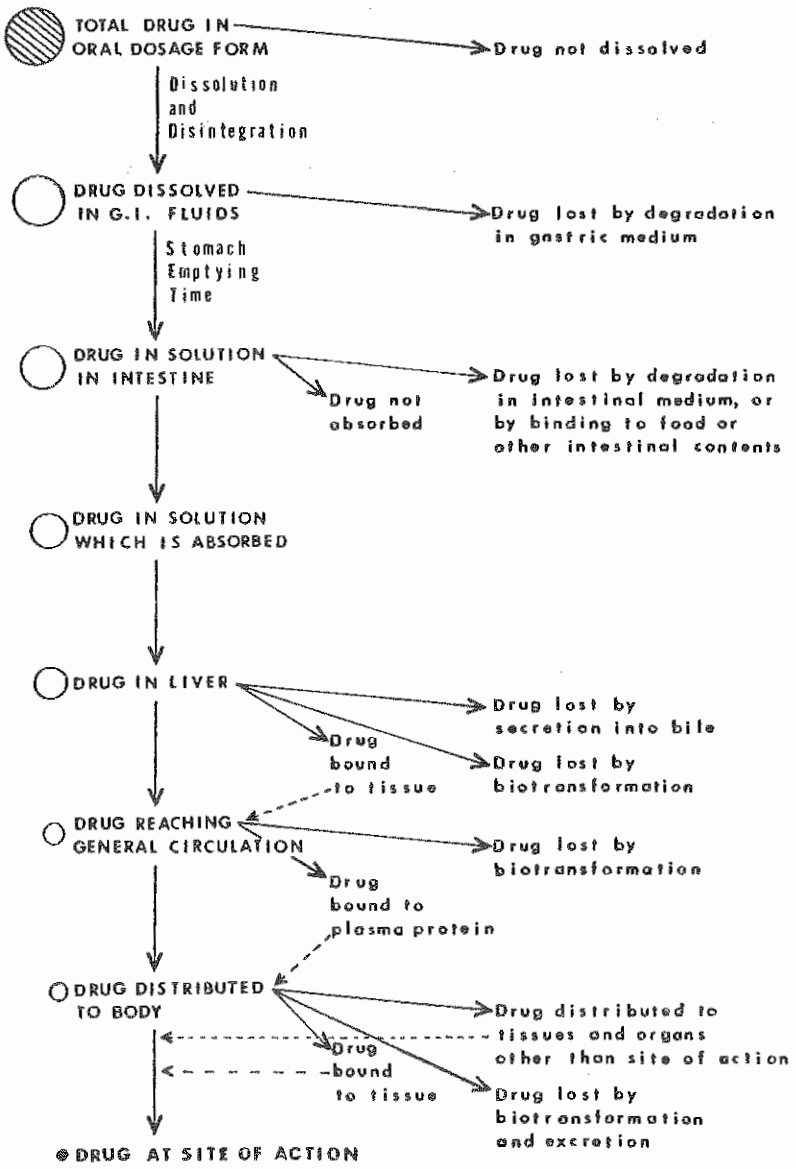

Fig. 1 Factors modifying the quantity of drug reaching a site of action after a single oral dose.

(From R.R. Levine, Pharmacology: Drug Actions and Reactions, 2nd ed., 1978, p.206. Courtesy of Little-Brown and Co., Publisher, Boston, MA.)

side versus the left side. Disease states not only introduce new factors that can modify drug response but also can change the nature and extent of the impact of the factors affecting normal subjects. In general, however, all of these factors produce quantitative, rather than qualitative change in drug response, since they affect the quantity of drug reaching a site of action and not the site of action itself.

Let us now look at the ways in which these factors affect the separate processes of absorption, distribution, biotransformation and excretion. To put the influence of these factors on drug disposition into proper perspective, we shall stress their clinical and biological significance rather than their statistical significance.

ABSORPTION

Differences in the rate and extent of absorption account in large part for the quantitative differences in response to drugs after different routes of administration. It is very likely that differences in absorption, particularly after oral administration, also account for much of the commonly observed biologic variation in responsiveness to drugs.

The rate of stomach-emptying is one of the principal factors which influence rate of absorption, since the largest portion of the oral dose of most drugs is absorbed in the upper small intestine. This is well illustrated by some of our work on the absorption of methadone (Walsh et al, 1975). Studies carried out in the intact rat show that absorption from the ligated stomach is extremely slow-the half-time of absorption of methadone being about 10 hours. This contrasts sharply with the rate of methadone absorption from the small intestine where the half-time is about 15 minutes.

That the stomach is not an important site of absorption for this basic drug, is to be anticipated from the pH partition hypothesis. But what is frequently overlooked and is contrary to established teaching, is that both the pH partition hypothesis and the stomach do not play a major role in absorption from the gastrointestinal tract regardless of the basic, acidic, or neutral nature of the drug.

For example, if we increase the pH of the gastric contents to correspond to that in the upper small intestine, we do indeed increase the rate of methadone absorption (Table 1). However,

Table 1 Effect of pH on the Gastric Absorption of Methadone

A 100 mg dose of methadone in water or Milk of Magnesia was administered into the rat stomach occluded at the pylorus. After a 1-hr absorption period, pH and stomach methadone content were determined. The range of pH values is given. Absorption data are given as the mean ± SD.

Vehicle	pH of Stomach contents	Percent Absorbed from Stomach in 1 Hr.
Water	3.0	9.2 ± 4.9
Milk of Magnesia	6.5-9.5	29.2 ± 9.7

this rate is still markedly lower than that made possible by the relatively huge absorbing surface of the duodenum. Therefore, the rate-limiting step in absorption of most drugs given by the oral route is the gastric emptying time.

Under ordinary conditions, the rate of stomach emptying follows first-order kinetics and is relatively slow with a $t_{1/2}$ in excess of 2 hours. In addition, gastric emptying is influenced by many factors only some of which are shown in Table 2 .

Table 2 Factors Influencing the Rate of Gastric Emptying

Decreased Emptying Rate		Increased Emptying Rate
	PHYSIOLOGIC	
Solids		Liquids
Acids		Gastric Distention
Fat		Posture (Lying on Right Side)
	PATHOLOGIC	
Trauma and Pain		Gastroenterostomy
Gastric Ulcer		
Myocardial Infarction		
Migraine		
	PHARMACOLOGIC	
Anticholinergics		Metoclopramide
Ganglionic Blockers		Reserpine
Narcotic Analgesics		Anticholinesterases
Isoniazid		Sodium Bicarbonate
Aluminium Hydroxide		

Alterations in rate of gastric emptying ordinarily only affect the rate of drug absorption and not the total amount of drug absorbed from the gut. This is certainly the case for drugs that are slowly absorbed such as the digitalis glycosides. However, a decrease in the rate of absorption as a result of slower gastric emptying may produce a decrease in the intensity of drug effect, and in some cases, even a complete absence of drug effect, i.e.: effective blood concentrations may never be reached, when the absorption rate is made so slow that drug entering the body cannot offset drug being lost by elimination. This becomes clinically

significant for drugs such as propranolol which are rapidly degraded on their "first-pass" through the liver (Heagerty et al, 1981). In contrast, increasing gastric emptying rate usually increase the rate of drug absorption and the intensity of drug effect of those drugs rapidly absorbed from the gut. Increased gastric emptying rate can, however, lead to decreased bioavailability of those drug formulations requiring gastric acidity for dissolution (Romankiewicz, 1976). This problem has been noted with various digoxin preparations and tetracycline formulations. Recent studies indicate that the bioavailability of the oral formulation of chloramphenicol may be superior to the I.V. preparation-but this bioavailability is dependent on the hydrolysis of chloramphenicol palmitate to the active free drug in the acid medium of the stomach (Kauffman et al, 1981). Of course, a drug such as cimetidine which reduces the acidity of the gastric fluid can and has been shown to decrease the amount of poorly water soluble drugs that depend on an acid medium for dissolution (Somogyi and Gugler, 1982).

Given the fact that: 1) Gastric absorption accounts for little of total amount of drug absorbed; 2) Gastric emptying is sporadic and easily influenced by a host of different factors; 3) The greatest absorptive capacity resides in the small intestine; 4) Absorptive capacity of the gut resides in all sections of the small intestine; 5) Transit time through the intestine is apparently not markedly altered in the presence of food, one may legitimately ask "Why aren't all drugs, except those that are dependent on the existence of an acid medium for dissolution, given as enteric-coated preparations that would disintegrate on entering the duodenum where they would be immediately exposed to the surface with the greatest absorptive capacity and at the highest attainable concentration gradient?"

In contrast to the influence of gastric motility on drug absorption, changes in intestinal motility produce little effect on the rate

and extent of absorption until transit time through the intestine is markedly shortened by the use of laxatives or the presence of diarrhea (Table 3). For example, the use of laxatives, particularly their chronic use by the elderly, has been shown to produce clinically significant decreases in the bioavailability of digoxin and increased toxicity of other digitalis preparations as a result of excessive loss of K^+ in the stool (Cooke, 1977)

Chemically inert powders used in the treatment of diarrhea, such as kaopectate or bismuth subsalicylate, or even other drugs used as adsorbants, such as cholestyramine, can adsorb not only bacteria and toxins but also nutrients, enzymes and drugs. Such drug interactions become clinically significant when the bioavailability of antibiotics, or essential medications, such as the digitalis glycosides and the oral

Table 3 Interactions Affecting Drug Asborption

Drug Affected:	Affected By:	Mechanism	Effect on Absorption
Thyroxine	Cholestyramine		↓
Acetylsalicylic Acid	" "		↓
Warfarin	" "	Removal	↓
Chlorothiazide	" "	From	↓
Cardiac Glycosides	" "	Solution	↓
$FeSO_4$	" "		↓
Vitamins B_{12} and K	" "		↓
Tetracycline	Mg^{++} and Al^{+++} Antacids	Chelation	↓
Dicoumarol	$Mg(OH)_2$	Chelation	↑
Tetracycline	$NaHCO_3$	↓ Dissolution	↓
Digoxin	Laxatives	↑ Intestinal Motility	↓
Digitalis Glycosides	Laxatives	↓ Absorption of K^+	(Digitalis Toxicity)

anticoagulants or essential vitamins,is decreased. For example, the administration of a kaolin-pectin suspension 2 hours before digoxin resulted in a 20% reduction and coadministration of the two agents produced a 62% decrease in digoxin absorption. In other studies the bioavailability of tetracycline and deoxycycline was reduced about 35% by the administration of 60 ml of a bismuth subsalicylate mixture (Feldman and Pickering, 1981). The adverse effect of these adsorbants on drug absorption can be averted, however, by selecting an appropriate time interval between doses of the antidiarrheal preparation and other medications. This is extremely important, since the physiologic changes that occur during an episode of diarrhea are so profound that they potentially could have greater effect on the gastrointestinal absorption of drugs than antidiarrheal drugs. For example, the bioavailability of digoxin tablets given to patients with diarrhea was 16% compared to 84% when given under normal conditions (Kolibash et al, 1971). It is interesting to note here, that diarrhea could be an important consideration in the therapeutics of drugs administered by routes other than oral when enterohepatic circulation plays an important role in the pharmacokinetics of the drug. For example, the plasma clearance and the fraction of the total dose lost from the G.I. tract of parenterally administered methotrexate was markedly increased in a patient with severe vomiting and diarrhea as compared to other patients (Van Den Berg, et al, 1980).

Another critical factor that affects intestinal absorption is intestinal blood perfusion, since the rate at which a drug diffuses across a biologic barrier is a function of the concentration gradient- and the rate at which blood flow removes the transferred material is important to the maintenance of the gradient.

Different foods affect blood flow differently. For example, splanchnic blood flow decreases after a liquid glucose meal and

increase after a high protein meal (Romankiewicz and Reidenberg, 1978). In elderly subjects intestinal blood flow has been demonstrated to decrease by 40 to 50 per cent from that in young adults. This reduction would be expected to slow drug absorption in the gut for both passively diffused and actively transported drugs. Despite these theoretical considerations suggesting reduced rates of gastrointestinal drug absorption with age, age by itself appears to exert no significant effect on either rate or extent of drug absorption. It appears that rate of blood flow through the intestine, must be reduced more than 50% before reduction in drug absorption is notable.

The gut is a particularly important site for drug biotranformation which can take place within the intestinal lumen as a result of the exocrine secretions or the enzymic activity of the microflora, or within the gut wall itself. Drugs likely to be affected by exocrine secretions are generally not given by mouth, but until recently little attention has been directed to the metabolic changes that can influence drug absorption as a result of degradation by the gastrointestinal mucosa or the intestinal microflora (Table 4). Both phase I and phase II reactions of the gastrointestinal mucosa have been described (George, 1981). However, phase I reactions, with the exception of oxidative deamination, appear to be quantitatively unimportant in contrast to the synthetic reactions. Sulfate conjugation, in particular, limits the bioavailability of orally administered β-adrenergic agents and probably accounts for the great individual variability in absorption of the agents. Glucuronide conjugation is also an important factor in the poor availability of ethinyl estradiol.

In the case of the reactions carried out by the microflora, it would appear that both hydrolysis and some special synthetic processes play significant roles in drug absorption as noted in

Table 4 Biotransformation Occurring in the Gut Wall

Reaction	Substrate
Phase 1	
Oxidation - Microsomal	Flurazepam
Oxidation - Non-Microsomal	Ethyl Alcohol Tyramine
Hydrolysis	Acetylsalicylic Acid Pivampicillin
Phase II	
Acetylation	Hydrazaline Isoniazid PAS
Sulfate Conjugation	Isoproterenol Isoetharine Terbutaline
Methylation	Isoproterenol
Glucuronidation	Estriol Estrone

their decreased bioavailability or increased toxicity when the activity of the microflora are inhibited by antibacterial agents. For example, a decrease in the entero-hepatic cycling of methotrexate can be brought about by inhibiting the drug metabolizing activity of the microflora, and a clinically significant increase in the toxicity of anticoagulants can occur as a result of a decrease in the production of vitamin K by microflora that are inhibited by drugs such as sulfonamides and broad spectrum antibiotics (Forick et al, 1967).

BIOTRANSFORMATION

We are, of course, all aware that changes in the rate of drug biotransformation play a major role in variability in drug response, and that the activity as well as the quantity of enzymes that participate in the chemical reactions can be influenced by many factors including age, genetic abnormalities, pathologic conditions and the presence of more than one drug. The very young infant, for example, may be significantly more sensitive than older individuals to low doses of drugs because of the immaturity of enzyme systems for drug inactivations. In the elderly, it is a general impaired ability to carry out enzymic reactions effectively that may lead to enhanced drug effect. However, because so many factors can influence drug disposition concomitantly in elderly people, it is often difficult to determine just what is responsible for altered pharmacokinetics in a particular geriatric patient. The mechanisms are frequently complex and involve more than depressed rates of biotransformation. But the fact remains that the physician needs to exercise special care to avoid toxicity when drugs are administered singly or in combination to geriatric patients-and especially when the drugs have narrow margins of safety or are essential medication.

The important role that enzyme induction may play in drug therapy has also been well recognized. Physicians are alert today to the need for monitoring and adjusting dosage in chronic drug therapy with single or multiple drugs when therapy is associated with stimulation of the microsomal enzymes involved in drug biotransformation. What has not received as much attention and is, therefore, not as well understood is the same need for caution in the use of multiple drug therapy when one of the agents inhibits an enzyme system-particularly a microsomal system (Table 5). The widespread and often uncritical use of cimetidine, a potent inhibitor of various microsomal

drug-metabolyzing enzymes, affords an excellent illustration of the considerable potential for the occurrence of serious interactions in multiple drug therapy with a microsomal enzyme inhibitor (Somogyi and Gugler, 1982).

Table 5 Interactions Inhibiting Drug Biotransformation

Drug Affected:	Affected By:	Effect Produced:
Tyramine (from various foods)	MAO Inhibitors	
Sympathomimetic Amines (Appetite-depressing drugs; cough, cold, sinus remedies; nasal decongestants)	" "	Hypertensive Crisis
Coumarin Anticoagulants	Allopurinol	↑ Anticoagulation
	Cimetidine	
Phenytoin	Isoniazid Cimetidine	↑ Toxicity of Phenytoin

Cimetidine inhibits the biotransformation of warfarin, various benzodiazepines, phenytoin, theophylline and some β-blocking agents such as propranolol. After chronic dosing with cimetidine, for example, warfarin clearance was reduced by about 25% and prothrombin times significantly increased; diazepam, desmethyldiazepam and chlordiazepoxide plasma clearance values were reduced 43, 28 and 63%, respectively. Whereas a decrease in elimination of benzodiazepines during cimetidine dosing may not necessitate dosage changes in most patients, since benzodiazepines have a wide therapeutic concentration range, cimetidine-induced inhibition of metabolism of warfarin

can have very serious consequences. It is to be expected that a number of other drugs with narrow margins of safety which are eliminated primarily by microsomal enzyme activity, will also be adversely affected by interactions with cimetidine. Patients with already impaired liver function would be at even greater risk, since the degree of inhibition of metabolism by cimetidine is more pronounced in such patients.

It is also well-known that many drugs are rapidly biotransformed after leaving the intestinal lumen during their first passage through the intestinal mucosa and liver. For some drugs, such as morphine, this first-pass effect precludes their effectiveness by the oral route (Walsh and Levine, 1975). Although propranolol is orally effective, it also undergoes extensive first-pass hepatic metabolism after oral administration. Until recently, however, little attention was paid to the effect of enzyme inhibitors on the bioavailability of drugs such as propranolol that are cleared on first-pass through the liver after absorption from the G.I. tract. The recent demonstration that cimetidine can produce a 2 to 3-fold increase in the bioavailability of orally administered propranolol (Heagerty et al, 1981) has indicated the need for extreme care in patients on such multiple drug therapy - for what is true for propranolol may also be true for other drugs that undergo first-pass extraction. To repeat-the clinical consequences of inhibition of drug biotransformation by cimetidine as well as by other drugs will be predominantly manifested in the cases of those drugs which have a narrow therapeutic index - phenytoin, warfarin, theophylline. The interaction will lead to higher steady-state blood concentration associated with toxicity.

DISTRIBUTION

Changes in the response to drugs attributable to modifications in drug distribution are usually brought about by differences in 1) the ratio of total body water or fat to body mass, or 2) the binding capacity of non-receptor proteins. One would anticipate that obesity, for example, would profoundly alter drug distribution, since total body water and muscle mass are a smaller percentage of the total body weight in the obese compared to lean or ideal weight individuals. Extremely lipophilic substances would be disproportionately distributed into bodyweight in excess of ideal bodyweight, whereas non-lipophilic drugs would have distribution limited mainly to lean body mass. Adjustment of drug dosage in the obese individual, however, depends on the relationship between total metabolic clearance and total bodyweight. At present there is need to exert caution in prescribing doses of drugs that have narrow safety margins for the obese individual but there is no predictable framework upon which such dosage adjustments can be formulated.

In the very young infant and in the very lean individual, where body water content is a larger percentage of bodyweight, one would anticipate modifications of drug distribution quite different from those in obese individuals. Again, however, no hard rules can be set down for drug dosage adjustments, since we must remember that hepatic and renal clearance are so markedly affected by volume of distribution.

Binding of drugs to plasma proteins is commonly believed to play an important role in drug interactions, especially those involving tightly bound substances. A great deal of emphasis has been placed on the possibility of adverse drug reactions arising from competition for plasma protein binding sites. Let us see just how much of a problem such interactions pose.

It is fairly apparent that the amount of drug in the tissue compartments will depend strongly on the proportion of free drug in the plasma compartment-on the amount of drug that is available for exchange with tissues. Particularly in the case of highly bound drugs, small changes in binding would be expected to cause relatively large changes in concentration of free drug. The increase in amount of free drug, in turn, resulting in more rapid elimination and a rise in drug concentration in tissues. A decrease in the proportion of bound drug from 90 to 80%, for example, doubles the plasma concentration of free drug-but it does not double the tissue concentration. The increase in tissue concentration depends on the volume into which the newly freed drug is distributed. The greater the volume of distribution-the smaller the change in tissue concentration produced by the freed drug. Adverse drug reactions arising from competitive displacement from plasma protein binding sites are likely to occur only with those drugs with a narrow margin of safety and with a volume of distribution greater than the extracellular fluid compartment as indicated in Table 6.

Table 6 Interactions Affecting Drug Distribution by Competition for Protein Binding Sites

Drug Affected:	Affected By:	Effect Produced:
Sulfonylureas	Aspirin	↑ Hypoglycemia
	Sulfonamides	↑ Hypoglycemia
Coumarin Drugs	Aspirin	↑ Anticoagulation
	Indomethicin	↑ Anticoagulation
	Clofibrate	↑ Anticoagulation
Methotrexate	Salicylates	↑ Toxicity

EXCRETION

Modifications which influence the excretion of a drug or its metabolites produce only quantitative changes in the effects of drugs, since it is only the rate of removal from the body which is affected. The kidney, as the principal organ for drug excretion, is also the site where most of these changes in rate of drug removal take place. And almost all the factors which modify the rate of urinary excretion produce a decrease in rate which, in turn, leads to an increased duration of drug action. Only when drugs are given by a route of slow-absorption, will a decrease in rate of elimination result in highter blood levels of drug and, thus, in a greater intensity of drug effect. In all instances, the persistence of effective blood levels of drug for longer periods of time, indicates the necessity of adjusting dosage schedules to avert drug accumulation and resultant toxicity.

Alterations in the rate of urinary excretion of drug may be the result of changes in the rate of either glomerular filtration, tubular reabsorption, or tubular secretion. In infants the decrease in rates of both glomerular filtration and tubular secretion is primarily responsible for their impaired ability to excrete drugs. In infants, the filtration rate is decreased because less drug is presented to the glomerulus. Not only is there less blood flowing through the immature kidney, but also the volume of distribution of drug is greater in the infant (total body water is 70% of body mass) than in the adult. Incomplete development of active transport process accounts for the decrease in rate of tubular secretion in the infant.

In the healthy subject, the traditional normal range for creatinine clearance values, which reflect the glomerular filtration

rate, changes dramatically with age; i.e., as a normal person progresses from middle to old age, the creatinine clearance declines (Rowe et al, 1976). Thus in the elderly even without overt renal disease, glomerular filtration rate declines to approximately half the value observed in normal young adults.

The influence that decreased glomerular filtration rate exerts on the overall elimination rate of a drug depends on the drug and the extent to which renal mechanisms control the drug's elimination from the body (Table 7).

Table 7 Plasma Half-Life in Altered Renal Function

	Normal Hrs.	Anuria Hrs.
Penicillin	0.5	8
Streptomycin	2.5	50-100
Chloramphenicol	2 to 3	3 to 4
Chloramphenicol Glucuronide	4	100

For drugs such as penicillin, streptomycin and digoxin whose elimination depends mainly on renal function, impairment of renal function can greatly prolong their sojourn in the body. For a drug such as chloramphenicol, which is eliminated primarily by biotransformation, impaired renal function has little effect on its duration of action. Estimates of the degree of renal dysfunction as judged by reductions in creatinine clearance form the basis for published nomographs that permit selection of appropriately lowered doses of drugs with relatively small therapeutic indices such as streptomycin and digoxin (Dettli,1976).

Changes in the pH of the tubular urine will affect the rate of reabsorption of ionizable drugs. Changes in urinary pH may be brought about by disease, by drugs which influence the normal formation of urine, as well as by the intake of larger quantities of acids or bases, or foods which give rise to acidic or basic excretory products.

Alterations in the rate of the renal tubular secretory mechanisms affect the excretion of only those organic acids or bases, either normal metabolic products or drugs, which are transported by these processes. Decreased tubular secretion may be the consequence of interaction of drugs competing for the same secretory mechanism, or of pathologic conditions which decrease renal blood flow or impair the function of the secretory processes themselves.

In summary then, from the practical point of view, each patient is unique and this individuality is determined by factors that are both genetic and environmental. Factors may be operative simultaneously and have a variable effect on the net rate of drug disposition. Thus it may be impossible for a physician to anticipate just how a given patient will respond. Yet there is urgent need to select both the appropriate drug and dose for each patient. To achieve this goal, the physician must rely on his knowledge of the practical aspects of pharmacokinetics and on quantitative assessment of individual drug response.

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