12

Pharmacokinetic Variability—Body Weight, Age, Sex, and Genetic Factors

When individuals are given identical doses of a drug, large differences in pharmacologic response may be seen. For example, the sleeping times of 72 rats after intraperitoneal administration of pentobarbital sodium (30 mg/kg) ranged from about 30 to 190 min; the duration of paralysis in 96 rats after intraperitoneal administration of zoxazolamine (110 mg/kg) varied from 100 to 850 min.[1]

The decrease in blood glucose (expressed as percent of control level) 30 min after a 1 g intravenous dose of tolbutamide in 97 human subjects ranged from 10% to more than 50%.[2] The variable effect of 1 drop of an ophthalmic solution containing 30 mg/ml phenylephrine hydrochloride instilled into the conjunctival sac on pupil diameter in 39 subjects is shown in Figure 12–1.[3]

The dose required to produce a certain response may vary widely from individual to individual. For example, the dose of warfarin required to increase prothrombin time to the range of 18 to 21.5 sec in 15 patients with cardiovascular disease varied from 0.04 to 0.20 mg/kg per day.[4] The daily dose of phenindione required to achieve an adequate degree of anticoagulation ranges from 25 to 200 mg.[5]

Two sources of variability are differences in drug levels at the site of action (as inferred by drug concentration in the plasma), and differences in effect produced by a given drug concentration. Although both sources contribute to the variability in response, there is increasing evidence for many drugs that the principal variation is the drug concentration resulting from a given dose. This is called pharmacokinetic variability.

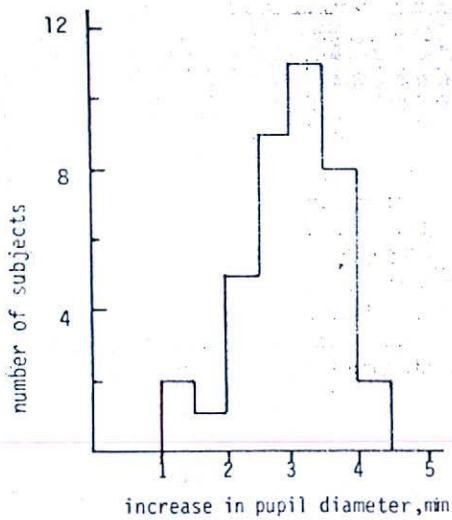

Fig. 12–1. Variable effect of 1 drop of an ophthalmic solution containing 30 mg/ml phenylephrine hydrochloride instilled into the conjunctival sac on pupil diameter in 39 subjects. (Data from Bertler, Å., and Smith, S.E.[3])

The typically large variability in blood levels of drugs is seen in the results of a study in 24 patients with meningitis treated with continuous intravenous infusion of ampicillin, 150 mg/kg per day.[6] On day 5 of treatment, serum levels of ampicillin ranged from 9 to 92 μg/ml. Differences in renal function among the patients partly explain the large range of serum concentrations.

A great deal of variability, both pharmacokinetic and pharmacodynamic, has been seen with midazolam, an intravenous benzodiazepine widely used for sedation before and during surgery. Investigators in The Netherlands studied the pharmacokinetics of midazolam in 17 patients on mechanical ventilation in a general intensive care unit who were receiving a continuous iv infusion of the drug, adjusted according to the level of sedation.[7] The half-life of midazolam was less than 2 hours in 1 patient, ranged from 3.5 to 6 hr in 10 patients, and was greater than 10 hr in 6 patients.

The investigators noted that a "wide range of midazolam serum levels was associated with adequate sedation, and similarly the midazolam levels at the moment of awakening were highly variable." Apparently, it is very difficult to establish a relationship between level of consciousness and midazolam concentration in patients in intensive care because of the variety of drugs that are used and the state of the patient.

Not only is a high degree of variability routinely found between subjects, a wide range of blood levels may also be seen when the same subject takes a drug on different occasions. It is widely believed, however, that intersubject variability is much greater than intrasubject variability. Wagner[8] determined the inter- and intrasubject variation of digoxin renal clearance in normal adult males, using data from 5 different studies. He found that intrasubject coefficients of variation averaged 24% (with a range of 15 to 29%). Depending on the method used to calculate variance, intersubject coefficients of variation averaged 30% (with a range of 18 to 42%) or 42% (with a range of 19 to 50%). Consistent with the prevailing wisdom, intersubject variability in the renal clearance of digoxin was greater than intrasubject variability, but clearly, intrasubject variability is not trivial.

The greatest difference between maximum and minimum renal clearances of digoxin in the five studies averaged 115 ml/min within subjects and 183 ml/min between subjects. The ratio of intra- to intersubject variability ranged from 0.47 to 0.71 with a mean value of 0.64. Physical activity is one factor contributing to intrasubject variability. The renal clearance of digoxin is significantly higher during a period of normal physical activity than during a period of immobilization.

Some drugs show greater variability than others. It is particularly difficult to prescribe the appropriate dose for drugs with nonlinear pharmacokinetics because of interpatient variability in blood levels. The relationship between the concentration of phenytoin in the plasma and the prescribed daily dose is shown in Figure 12–2. More than a 20-fold difference was found in the apparent steady-state phenytoin concentrations in plasma among patients who had been prescribed the same daily dose.[9] The steady-state plasma chlorthalidone concentrations in 10 patients during treatment with a standard dose of 50 mg/day varied 5-fold between individuals, ranging from 211 to 1138 ng/ml.[10]

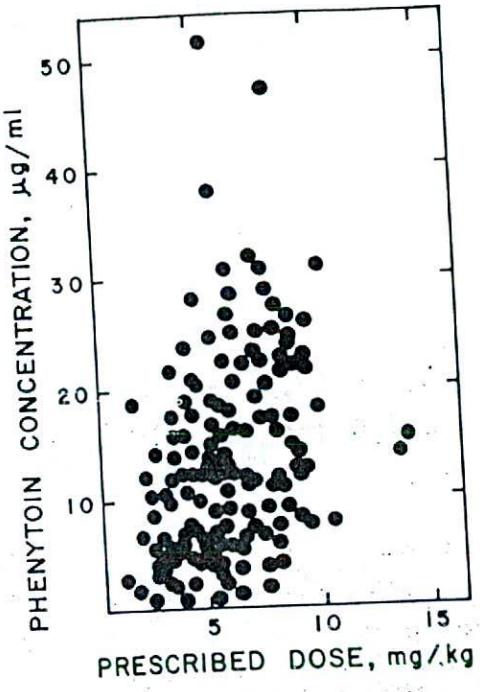

Fig. 12–2. Relationship between the steady-state plasma concentration of phenytoin in epileptic patients and the prescribed daily dose. (Data from Lund, L.[9])

Particularly pronounced pharmacokinetic variability is consistently observed with drugs subject to a high hepatic clearance and substantial presystemic metabolism. An example is shown for the tricyclic antidepressant desipramine in Figure 12–3. The upper and lower curves show the extreme results in 2 patients. The middle curve shows mean values for 9 other patients. All 11 patients were treated with 25 mg of desipramine orally 3 times a day. Plasma levels differed by 30-fold.[11] Steady-state levels of nortriptyline in patients with psychiatric illness receiving 75 mg/day varied from

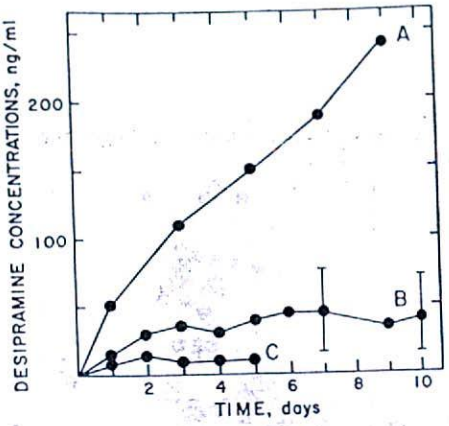

Fig. 12–3. Desipramine concentrations in plasma in patients during repetitive dosing with 25 mg 3 times a day. Curves A and C indicate the levels in 2 patients who showed the highest and lowest degree of drug accumulation, respectively. Curve B reflects the average of 9 other patients. The vertical bars at days 7 and 10 on curve B indicate the range of desipramine concentrations in the individual patients. (Data from Hammer, W., Idestrom, C.M., and Sjöqvist, F.[11])

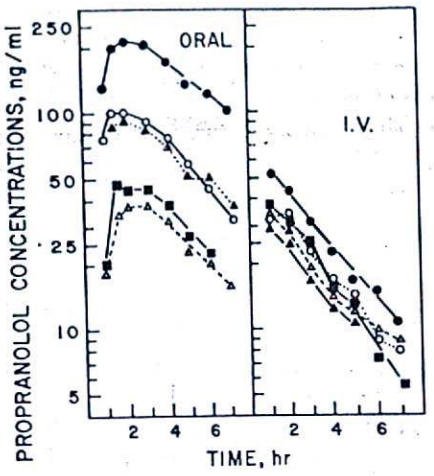

Fig. 12–4. Propranolol concentrations in plasma after a single 80-mg oral or 10-mg intravenous (iv) dose to 5 healthy adults. Less variability is observed after iv administration. (Data from Shand, D.G., Nuckolls, E.M., and Oates, J.A.[14])

about 10 to 260 ng/ml.[12] Steady-state plasma concentrations of alprenolol, a beta-blocking drug, in 30 patients treated for a prolonged period varied 25-fold between individuals receiving identical oral doses.[13]

Theory suggests that a drug subject to substantial presystemic metabolism should show less pharmacokinetic variability after parenteral administration than after oral administration. Figure 12–4 indicates that this is the case after oral and intravenous administration of propranolol.[14]

Many factors contribute to the variability in the relationship between the amount of drug administered or prescribed and the resulting drug concentration in the body. This relationship is influenced by the bioavailability of the drug from the dosage form, a subject discussed in earlier chapters, as well as other factors that may affect the completeness of absorption. It is also influenced by a host of factors that affect drug disposition. Drug absorption, distribution, metabolism, and excretion processes are subject to individual variation from age-related phenomena, genetic and environmental factors, the consequences of disease, and concomitant administration of other drugs. An additional and possibly important source of variability is that certain patients frequently fail to follow directions about taking medicine.

This chapter and the two that follow are concerned with factors that contribute to intersubject differences in drug concentrations in blood and tissues.

BODY WEIGHT AND SIZE

The apparent volume of distribution of a drug is determined by the anatomic space into which it distributes and its relative degree of vascular and extravascular binding. Because the volume of both total body water (TBW) and extracellular fluid (ECF) in adults with normal lean-to-fat ratios is directly proportional to body weight, there is a relationship between apparent volume of distribution and body weight. This relationship is particularly evident for drugs that are poorly bound in the body.

Initial blood levels following a single dose or a loading dose of a drug that is rapidly absorbed are largely dependent on apparent volume of distribution; the larger is the volume of distribution, the lower is the blood level. Whenever peak blood levels are of concern during drug therapy, body weight should be considered in determining the appropriate dose.

Organ size, function, and blood flow are also

related to body weight, but the relationship between drug clearance and body weight is not clear. The correlation between drug clearance and body weight in normal young adults is poor; studies that also include infants, children, and the elderly are confounded by well known age effects on drug clearance. Therefore, there are no general guidelines to relate maintenance doses of drugs to body weight.

Because of pharmacokinetic variability in drug absorption, binding, and elimination and because of pharmacodynamic variability in response, weight adjustments are generally thought unnecessary unless the weight of an individual differs by more than 50% from the average adult weight (70 kg). In practice, adjustments for weight are made only for children and for unusually small, emaciated, or obese adult patients.[15]

Obesity

Obesity, defined as that condition when a patient's total body weight is more than 25% above desirable weight, occurs in almost 20% of the population of the United States and is more prevalent in women than men. Ideal body weight (IBW) is usually defined as follows:

$$\text{IBW (men)} = 50 \text{ kg} \pm 1 \text{ kg/2.5 cm above or below 150 cm in height} \quad (12\text{–}1)$$

$$\text{IBW (women)} = 45 \text{ kg} \pm 1 \text{ kg/2.5 cm above or below 150 cm in height} \quad (12\text{–}2)$$

Drug distribution may change as a result of the changes in body composition in the obese patient. The percentage of fat and lean body mass in an individual may be estimated by measuring height (in inches), weight (in kilograms), and girth (in inches, using the umbilical level at exhalation), and using these data in the following equations:[16]

$$\text{Percent fat} = 90 - 2(\text{Height} - \text{Girth}) \quad (12\text{–}3)$$

$$\text{Lean body mass} = (100 - \text{Percent fat}) \times \text{Weight} \quad (12\text{–}4)$$

The smaller ratio of body water and muscle mass to total body weight, and the greater proportion of body fat in the obese could lead to changes in drug partitioning into the various body compartments. Fat contains less extracellular fluid than other tissues. Therefore, the distribution space for polar drugs, like antibiotics, is relatively less in obese patients and may be a reason for reducing the daily dose, calculated on a mg/kg total body weight basis. On the other hand, the relative distribution space for lipid-soluble drugs may be the same or even larger in obese patients; this may call for the same or even larger daily doses, calculated on a mg/kg total body weight basis. Furthermore, in principle, drug binding, metabolism, and excretion may be affected by obesity. For these reasons, the selection of appropriate dosing regimens for the severely obese patient is a formidable challenge.

Intuitively, one expects an obese patient to need a larger dose than a normal-weight patient. Dosing regimens based on milligrams of drug per kg of total body weight or per square meter of body surface area will indeed deliver a larger dose to the obese patient. But, studies comparing pharmacokinetics in obese and normal-weight subjects suggest that this approach is frequently wrong and may result in drug toxicity.

A dosing regimen that is safe and effective in the average patient may require modification if the apparent volume of distribution, clearance, or half-life of the drug in the patient under consideration is sufficiently different from the average value. The volume of distribution of most drugs is greater, sometimes dramatically greater, in obese subjects than in normal-weight subjects. Largely for this reason, one may find much longer half-lives in obese subjects. On the other hand, differences in drug clearance between significantly overweight and normal-weight patients are often small; in many cases, there is no need to change the total daily dose of a drug when it is given to an obese patient.

Changes in dosing regimen for obese patients might be anticipated if a drug is largely excreted unchanged or eliminated through formation of sulfate or glucuronide conjugates. Creatinine clearance is increased in obese patients and the renal clearance of a drug may be increased to a similar or greater extent. Renal excretion of a drug may be greater in obese patients because of changes in renal blood flow and glomerular filtration rate secondary to increased blood volume and cardiac output. Metabolic clearance reflecting conjugation with sulfate or glucuronic acid also seems to increase as a function of body weight. Oxidative metabolism, on the other hand, does not appear to be affected by weight changes.

If a drug distributes poorly or not at all into the excess body space found in the obese patient, one

would expect the same plasma drug concentrations after administration of the same absolute amount of drug to a patient with normal body weight or to an obese patient, provided their lean body masses were comparable. This is illustrated by the results of studies with digoxin.[17] A single intravenous dose of 0.5 mg of digoxin was given to 5 obese patients before and after an average weight loss of 46 kg. There were no significant differences in the blood concentrations before and after weight reduction.

In another study, the pharmacokinetics of digoxin were determined in 13 obese subjects (average total body weight 100 kg, 162% of IBW) and 16 control subjects (average total body weight 65 kg, 98% of IBW). No important differences were found in absolute volume of distribution (approximately 950 L), clearance (approximately 300 ml/min), or half-life (approximately 35 to 40 hr).[18]

The results of these studies indicate that the obese patient should receive the same average loading and maintenance doses of digoxin as the normal-weight patient. If the drug is dosed on a body weight basis, the obese patient should receive the same mg/kg of IBW dose as the normal-weight patient but a smaller mg/kg total body weight dose of digoxin. Digoxin dosage may be dangerously high if calculated on the basis of total body weight in obese patients.

Several studies have examined the pharmacokinetics of aminoglycoside antibiotics in obese subjects. Schwartz and associates[19] administered 1 mg/kg gentamicin to 6 obese subjects (average body weight 104 kg) and 6 normal-weight subjects (average body weight 55 kg). The apparent volume of distribution was significantly larger in the obese subjects than in the normal-weight subjects (19 L vs 13 L). On the other hand, the apparent volume of distribution corrected for *total* body weight was significantly smaller in the obese subjects than in the normal-weight subjects (0.185 L/kg vs 0.244 L/kg).

These results indicate that gentamicin distributes into the excess body space of obese patients but not as efficiently as it distributes into lean body mass. Korsager confirmed these results and calculated that the uptake of gentamicin into the excess body space in the obese subjects was about 40% of the uptake into lean body mass.[20] Similar findings have been reported for tobramycin[19,21] and amikacin.[22] Dosing these antibiotics on a mg/kg IBW basis produces lower peak blood levels in an obese patient than in a normal-weight patient; dosing on a mg/kg total body weight basis results in higher peak blood levels in obese patients than in patients of normal weight.

Bauer and associates recommend that the loading dose of amikacin in the severely obese patient be based on an apparent volume of distribution (V) calculated as follows:[22]

$$V = 0.26\,[IBW + 0.38\,(FW)] \quad (12\text{–}5)$$

where IBW is ideal body weight, FW is fat weight (total body weight minus IBW), 0.26 L/kg is the apparent volume of distribution in normal-weight individuals, and 0.38 is a factor accounting for the more limited distribution of amikacin in excess body space than in lean body mass.

A patient weighing 150 kg (IBW = 70 kg) is predicted to have an apparent volume of distribution of 26.1 L; a normal-weight patient will have an apparent volume of distribution of 18.2 L. The loading dose of amikacin (in mg or mg/kg IBW) should be about 40% higher for the obese patient than for the normal-weight patient.

Some drugs (e.g., caffeine, lidocaine, lorazepam, and theophylline) distribute about equally between lean body mass and excess body mass (largely adipose tissue). In this case, apparent volume of distribution is larger in obese patients but distribution volume per kg of total body weight is about the same in obese and normal-weight individuals. Other drugs (e.g., phenytoin, thiopental, and diazepam), because they are lipid soluble, distribute disproportionately into excess body weight and volume per kg total body weight is larger in obese subjects. The distribution volume of thiopental per kg total body weight is 1400 ml in normal-weight subjects and 4720 ml in obese subjects. Plots of apparent volume of distribution per kg total body weight vs total body weight tend to be linear, with a negative slope for drugs such as gentamicin, a slope approximating zero for drugs such as caffeine, and a positive slope for drugs such as thiopental.

Blouin and co-workers have studied the pharmacokinetics of vancomycin in obese subjects.[23] The apparent volume of distribution of vancomycin was considerably larger in obese subjects than in normal-weight subjects (50 L vs 33 L). Like the aminoglycosides, however, the apparent volume of distribution of vancomycin normalized for total body weight was smaller in the obese subjects than in the normal-weight subjects, indicating limited distribution into the excess body space. Loading

doses of vancomycin (in mg or mg/kg IBW) should be higher for obese patients than for normal-weight patients.

Another important finding of the vancomycin studies is that the clearance of vancomycin was more than twice as large in obese subjects than in normal-weight subjects (188 ml/min vs 81 ml/min). This result was consistent with the larger creatinine clearance in the obese subjects compared to that observed in normal-weight subjects (180 ml/min vs 138 ml/min). The same mg/kg total body weight daily dose in obese and normal-weight subjects yields comparable average vancomycin concentrations at steady state.[21] Higher drug clearance in obese subjects than in normal-weight subjects has also been reported with aminoglycoside antibiotics.[19-22]

Bauer et al.[24] studied the clearance of cimetidine in normal-weight (62 kg) and obese (140 kg) subjects. In subjects with normal total body weight and renal function, about one-half of an iv dose of cimetidine is excreted unchanged in the urine. The investigators observed that the clearance of cimetidine from serum was much greater in obese subjects than normal-weight subjects (1147 vs 637 ml/min). This difference was almost entirely the result of a substantially higher renal clearance of cimetidine in obese than in control subjects (808 vs 318 ml/min).

Studies with theophylline in obese subjects are of interest because, unlike the aminoglycosides, theophylline is almost completely metabolized via oxidative pathways. The large increase in absolute volume of distribution of theophylline in obese subjects, compared to that observed in normal-weight subjects, indicates that theophylline readily distributes into fat. Loading doses of theophylline should be calculated on the basis of total body weight; however, the absolute clearance of theophylline (in ml/min) is remarkably similar in obese and normal-weight patients.[25] Therefore, maintenance dose calculations for theophylline should be based on IBW; total daily dose (in mg or mg/kg IBW) should be similar in obese and normal weight patients. The clearance of nordiazepam (desmethyldiazepam), the active metabolite of clorazepate, is also similar in obese and normal-weight subjects.[26]

The effects of obesity on the kinetics of three other drugs subject to oxidative metabolism (viz, propranolol, trazodone, and verapamil) have also been reported. Bowman et al.[27] compared the pharmacokinetics of propranolol in obese and control subjects. Clearance, determined after iv dosing, was nearly identical in the two groups. A trend toward decreased first-pass metabolism in the obese group after oral administration was not statistically significant. The half-life of propranolol was longer in the obese group because of a nearly 2-fold change in volume of distribution.

Similar results were observed with trazodone.[28] Clearance was about the same in obese and control subjects but the large difference in apparent volume of distribution (162 vs 67 L) resulted in a prolonged half-life in obese subjects (13 vs 6 hr). The investigators concluded that the dose of trazodone should be based on ideal rather than total body weight; average daily dose should be about the same in normal-weight and obese patients.

Abernethy and Schwartz[29] gave iv verapamil to obese and normal-weight patients with hypertension and found that elimination half-life was prolonged in obese patients (10 vs 4 hr) because of a marked increase in volume of distribution (713 vs 301 L) with no significant change in total verapamil clearance [1340 (obese) vs 1250 ml/min].

Ibuprofen, a widely used NSAID, appears to be an exception to the general rule that obesity has a minimal effect on the clearance of drugs eliminated by oxidative metabolism.[30] A 600 mg oral dose of ibuprofen resulted in a significantly lower peak concentration in obese subjects than in controls (37 vs 48 mg/L) consistent with a larger volume of distribution. Surprisingly, the total area under the ibuprofen concentration in plasma vs time curve was also lower in obese subjects. This difference could be explained by decreased absorption or increased clearance in obese subjects; plasma protein binding was nearly the same in each group.

Ibuprofen undergoes aliphatic hydroxylation and carboxylation rather than ring hydroxylation or oxidative N-demethylation, the more common oxidative pathways. Perhaps the cytochrome P-450(s) concerned with aliphatic hydroxylation and carboxylation is increased selectively in obese subjects. The results suggest that larger doses of ibuprofen are required for obese patients to attain plasma levels similar to those in normal-weight patients.

Relatively few drugs are eliminated by nitroreduction but this pathway applies to one of the most widely used benzodiazepines in Europe: nitrazepam. Investigators have determined that the half-life of nitrazepam is markedly greater in obese

subjects than in controls (33.5 vs 24 hr) due to increased distribution volume (290 vs 137 L), calculated by assuming complete absorption after oral administration.[31]

Plasma levels of nitrazepam after a single dose were appreciably lower in obese subjects, suggesting an increased clearance. Mean oral clearance was 101 ml/min in the obese group compared with a value of 67 ml/min in the control group. A correlation analysis involving all subjects indicated a statistically significant relationship between apparent nitrazepam clearance and percent of ideal body weight.

These investigators observed that "benzodiazepines which undergo hydroxylation or oxidative N-demethylation, including diazepam, desmethyldiazepam, alprazolam, and midazolam have minimal if any change in clearance in obese subjects . . . In contrast, the benzodiazepines lorazepam and oxazepam, which are biotransformed in man by glucuronide conjugation, have increases in clearance in obese man which are well correlated with degree of obesity. The increased clearance of nitrazepam in obese subjects suggests that the nitroreduction pathway for biotransformation of xenobiotics may also be increased in obese individuals."

In addition to the elimination of lorazepam and oxazepam, drugs subject to glucuronide conjugation, the elimination of acetaminophen, which is subject largely to sulfate conjugation, is also enhanced in obese subjects.[32] Another example of the effects of obesity on conjugative metabolism is seen with salicylate.[33] The major elimination pathways for salicylate are glycine and glucuronide conjugation. The clearance of salicylate after administration of aspirin was about 20% greater in obese subjects (113 kg TBW) than in normal-weight subjects (67 kg TBW).

As a rule, an increase in distribution volume results in an increase in half-life, whereas an increase in clearance produces a decrease in half-life. Most drugs have a longer half-life in obese than in normal-weight subjects, reflecting changes in volume of distribution. A most dramatic example of the effect of obesity on half-life has been reported with theophylline in a study involving a patient who weighed 523 kg.[34] Although theophylline clearance in this patient was similar to values observed in normal-weight subjects, a half-life of about 34 hr was determined, about 4 times longer than expected for normal-weight individuals with average clearances.

Neonates, Infants, and Children

Dosing guidelines for children are more complicated than those for adults. Evidence indicates that children require and tolerate larger mg/kg doses of many drugs than do adults. For example, the usual doses of digoxin are 15 to 20 μg/kg per day for children 4 weeks to 2 years of age, 10 to 15 μg/kg per day for children 2 to 12 years of age and 4 to 5 μg/kg per day for adults.[35] These doses result in average digoxin concentrations in plasma of about 1 to 1.5 ng/ml when given to patients of the appropriate age.[36]

Estimates of the dose required for infants and children are often obtained on the basis of the surface area of the young patient relative to the surface area of an adult. Body surface area (SA) can be calculated using the following height-weight formula:[37]

$$SA\ (m^2) = \text{weight}\ (kg)^{0.5378} \times \text{height}\ (cm)^{0.3964} \times 0.024265 \quad (12\text{–}6)$$

A less accurate but still useful estimate of surface area in children can be calculated from the following equation:[38]

$$SA\ (m^2) = \text{weight}\ (kg)^{0.728} \quad (12\text{–}7)$$

The body surface area of the average adult is assumed to be 1.73 m^2.

A still simpler equation to calculate body surface area, one that is easily solved using a calculator with a square root function, has also been proposed.[39] In this relationship, surface area (in m^2) is equal to the square root of the product of height (in cm) and weight (in kg), divided by 60. That is,

$$SA = (\text{height} \times \text{weight})^{1/2}/60 \quad (12\text{–}8)$$

Validation of this equation was based on measurements in adolescent and adult subjects. A 185-cm tall, 80-kg patient is predicted to have a body surface area of 2.03 cm^2. Other investigators tested the accuracy of this simplified equation when applied to children.[40] The body surface area of 168 children between the ages of 1 and 14 years was calculated. The resulting values were then com-

pared to the classic equation of DuBois and DuBois.[41] That is,

$$SA = 0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425} \quad (12\text{–}9)$$

The investigators found a correlation coefficient between the two methods of calculation of greater than 0.99, suggesting that this simplified approach to the estimation of body surface area is reliable in both adults and children.

Calculations based on body surface area indicate that, in general, the average 3-month-old child weighing 6 kg should receive twice the mg/kg dose given to an average adult, whereas the average 5-yr-old child weighing 20 kg should receive 1.5 times the mg/kg dose given to adults.[38] Because of age-related differences in drug metabolism, however, still larger doses are sometimes required.

One study examined the variability in peak serum concentration of gentamicin in patients from different age groups, ranging from 6 months to 42 years of age, who received parenteral doses standardized for body weight (1 mg/kg) or body surface (30 mg/m²).[42] Age-related variability was less after administration of a dose calculated on surface area than after a dose calculated on weight. Children under 10 years of age require a larger mg/kg dose than older patients to achieve comparable serum gentamicin concentrations. The same mg/m² dose of gentamicin results in roughly comparable serum levels in all age groups.

The requirement for larger mg/kg doses in children than in adults is related in part to the fact that TBW and ECF make up a larger percentage of the total body weight in children than in adults. Total body water decreases with age, from 78% of the newborn's body weight to 60% of the adult's weight.[43] Differences in extracellular water (ECW) are even greater. Extracellular water represents about 45% of the body weight in the newborn but only 20% of the adult's body weight.[44] This means that the same mg/kg dose of a drug that is not bound and is distributed only in the ECW produces less than half the blood level in the newborn as in the adult, and about 70% of the blood level in a 2-year-old child as in an adult.[45]

In general, age-related changes in drug distribution tend to decrease the volume of distribution in adults compared with neonates for most water-soluble drugs. Drugs that are lipid soluble may have a lower volume of distribution in neonates because of age-related differences in adipose tissue.

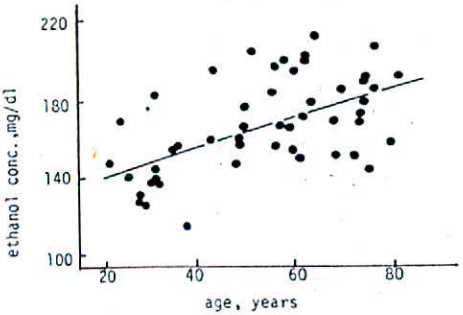

Fig. 12–5. Ethanol concentrations in blood at the end of a constant rate intravenous infusion as a function of age. (Data from Vestal, R.E., et al.[47])

Fisher and his colleagues[46] have studied the pharmacokinetics of vecuronium, a polar nondepolarizing muscle relaxant, in 5 infants (3 to 11 months old) and 5 children (1 to 5 years old). The muscle relaxant was given by iv infusion after anesthesia during elective surgery. The apparent volume of distribution of vecuronium was larger (357 vs 204 ml/kg) and the mean residence time was longer (66 vs 34 min) in infants than in children.

The investigators pointed out that they expected changes in the distribution volume because of several factors. "First, the distribution of muscle relaxants such as vecuronium is limited to extracellular fluid (ECF). ECF volume decreases markedly during the first year of life, starting at approximately 44% of body weight at birth and approaching the adult value of 22% at 1 year of age." Previous studies by these investigators found that the volume of distribution for d-tubocurarine, a related drug, was 514 ml/kg for infants, 405 ml/kg for children, and 309 ml/kg for adults, values that shadow the age-related changes in ECF.

No significant difference was observed in clearance between infants and children. Values of 5.6 and 5.9 ml/kg/min, respectively, were calculated. Therefore, the longer mean residence time of vecuronium in infants is almost strictly related to the larger volume of distribution in these patients.

Elderly Patients

Age-related changes in body composition at the other end of life may also affect drug distribution. On the average, lean body mass decreases and body fat increases in relation to total body weight in the

aging individual. The percentage of total body weight composed of adipose tissue is on the order of 36% in elderly men and 48% in elderly women, much higher than that found in young adults, 18% in men and 33% in women. It follows that the apparent volume of distribution of a relatively water-soluble drug such as antipyrine may remain the same or decrease slightly with age, whereas that of lipid-soluble drugs such as diazepam may be much larger in elderly patients than in younger ones.

Vestal and co-workers have observed a decrease in the lean body mass per unit surface area as a function of age, over an age range of 21 to 81 years, in healthy human subjects.[47] The apparent volume of distribution of ethanol, which is largely unbound and distributed in TBW, also decreased with age. The smaller volume of body water and the decreased lean body mass in elderly subjects probably account for the higher peak ethanol levels in blood after administration of a constant dose of ethanol as compared with young subjects (Fig. 12–5).

AGE

Age itself, rather than body size and composition, also affects the distribution and elimination of many drugs. Drug binding, metabolism, and excretion may change as a function of age. A study that documents changes in pharmacokinetic parameters from newborns to elderly particularly well is that of Sereni et al., who examined the pharmacokinetics of sulfamethoxypyridazine in subjects of different ages.[48] The study panel was divided into 5 groups: newborns (2 to 3 days), infants (1 to 12 months), children (4 to 9 years), adults (16 to 37 years), and elderly subjects (>70 years). The half-lives and apparent volumes of distribution of the sulfonamide in each age group are summarized in Table 12–1.

The half-life of sulfamethoxypyridazine was considerably longer in newborns and elderly subjects than in young adult subjects. On the other hand, infants and children eliminated the drug more rapidly than did adults. The apparent volume of distribution was larger in newborns and infants than in adults, suggesting differences in binding and/or in the relative size of body compartments.

Table 12–1. Half-Lives ($t_{1/2}$) and Apparent Volumes of Distribution (V) of Sulfamethoxypyridazine in Human Subjects of Different Ages*

Age groups	$t_{1/2}$ (hr)	V (L/kg)
Newborns	136	0.47
Infants	54	0.36
Children	51	0.20
Adults	63	0.22
Elderly subjects	98	0.26

*Data from Sereni, F., et al.[48]

Table 12–2. Elimination Half-Lives (hr) of Various Drugs in Neonates and Adults*

Drug	Neonates	Adults
Amobarbital	17 to 60	12 to 27
Carbamazepine	8 to 28	21 to 36
Diazepam	25 to 100	15 to 25
Indomethacin	14 to 20	2 to 11
Meperidine	22	3 to 4
Nortriptyline	56	18 to 22
Phenylbutazone	21 to 34	12 to 30
Phenytoin	21	11 to 29
Theophylline	24 to 36	3 to 9
Tolbutamide	10 to 40	4 to 9

*Data from Rane, A., and Tomson, G.[51]

Another comprehensive examination of the effect of age on drug elimination has been reported for ceftriaxone.[49] Clearance increased from 0.9 to 2.5 ml/min when comparing patients 1 to 8 days old with patients 9 to 30 days old. The mean clearance of ceftriaxone in children ranging in age from 1 to 12 months and from 1 to 6 years was 6.2 ml/min and 9.1 ml/min, respectively. The 18 to 49 year old age group had the highest clearance of ceftriaxone, 17 ml/min. Older groups of patients had progressively lower values of clearance. Very elderly patients, 75 to 92 years of age, had an average clearance of about 8 ml/min.

These findings are generally consistent with results from other studies that compare the pharmacokinetics of drugs in a more limited number of age groups. For example, the clearance of cyclosporine, normalized for either total body weight or surface area, is greatest in bone marrow transplant recipients less than 10 years old (82 ml/min/kg), lowest in patients older than 40 years (20 ml/min/kg), and intermediary in patients ranging in age from 11 to 40 years (43 ml/min/kg).[50]

In general, drug elimination is impaired in newborns, particularly premature newborns; it improves with age and tends to be more efficient in older infants and children. Thereafter, drug elimination declines with age.

Drug Metabolism in Newborns

The most dramatic age-related differences in drug elimination often occur between the newborn

and the adult. Most of the enzymatic microsomal systems required for drug metabolism are present at birth, but their titers are usually lower than adult levels. In general, drugs subject to biotransformation are eliminated more slowly in newborns than in adults (Table 12–2).[51]

Apparent exceptions to this generalization include the anticonvulsant drugs phenytoin and carbamazepine. The similarity of plasma half-lives of these drugs in newborns and adults is in contrast to the other drugs listed in Table 12–2. These data, however, were obtained in newborns who acquired the drug in utero from the mother who was receiving anticonvulsant treatment during pregnancy. Chronic exposure of the fetus to antiepileptic drugs throughout gestation may lead to induction of drug-metabolizing enzymes.

Although drug oxidation in the neonate seems to be almost uniformly impaired, drug conjugation in the newborn presents a mixed picture. Sulfate conjugation seems to be as efficient in newborns as in adults, but conjugation with glucuronic acid is considerably reduced, reaching adult levels only after 3 years of age. This deficiency is responsible for the serious adverse effects observed in newborns after administration of chloramphenicol, a drug that is ordinarily conjugated with glucuronic acid. Blood levels of chloramphenicol are higher and persist considerably longer in 1- and 2-day-old infants than in 4- to 5-year-old children.[52]

Reports of the variable effectiveness of indomethacin in the closure of significant patent ductus arteriosus in preterm infants have prompted an examination of the relationship between gestational age and indomethacin elimination in the newborn. One investigator found that the half-life of indomethacin decreased with gestational age.[35] Improved indomethacin elimination during development may be associated with treatment failures. Infants who did not respond to indomethacin eliminated the drug more rapidly and had lower plasma levels than those infants who did respond to the drug.[54]

Investigators in Seattle studied the pharmacokinetics of morphine in infants less than 10 weeks of age.[55] The clearance of morphine in newborns (1 to 4 days old) was less than half that found in older infants (6 vs 24 ml/min/kg). Differences in volume of distribution between the two groups modulated the effect of clearance on half-life but the half-life of morphine was longer in the newborns (7 vs 4 hr). The investigators suggested that the combination of lower clearance and longer elimination half-life in newborns may explain a prolonged duration of action for morphine in very young infants.

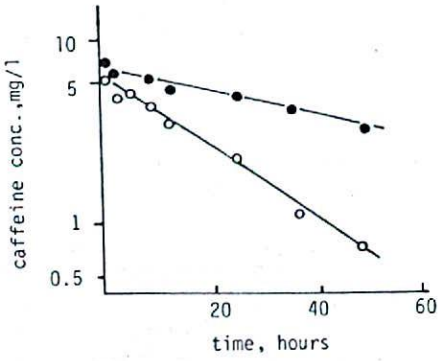

Fig. 12–6. Semilogarithmic plot of caffeine concentrations after a single iv dose to the same infant at ages 1.5 mo (●) and 2.5 mo (○). Half-life decreased from 41 to 16 hr from one administration to the next. (Data from Aranda, J.V., et al.[58])

Theophylline is used frequently in newborns for treatment of apnea associated with immaturity, weaning from mechanical ventilation, and as a bronchodilator in infants with bronchopulmonary dysplasia. Compared with an adult, the preterm infant has a low clearance for theophylline. The amount of unchanged theophylline in urine in premature infants decreases with postnatal age, whereas the excretion of metabolites increases with age. One study found a strong correlation between theophylline half-life and postnatal age in premature infants 12 to 191 days old; half-life decreased from about 50 hr to 5 hr over this age range.[56]

Differences in the elimination of caffeine in newborns and adults are among the most remarkable reported for any drug.[57,58] The half-life of caffeine in the newborn is about 4 days; in adults, it is about 4 hr. Adults eliminate less than 2% of a dose of caffeine unchanged in the urine; the rest of the dose is metabolized to demethylated xanthines and urates. In the newborn, however, unmetabolized caffeine accounts for more than 85% of the urinary excretion products.[57] Caffeine remains the predominant urinary component for the first 3 months of life, but its percentage decreases gradually to the adult level of less than 2% by the age of 7 to 9 months. Figure 12–6 shows plasma levels of caffeine in the same infant at ages 1.5 months and

2.5 months. The long half-life of caffeine in the neonate is the result of slow urinary excretion of unchanged drug, which is the primary route of elimination in the infant because there is little or no metabolism.

Some drugs are metabolized in the gastrointestinal tract by intestinal bacteria in the large bowel. Cardioinactive digoxin reduction products can be detected by radioimmunoassay in the urine of about one-third of adults during treatment, signalling inactivation of digoxin by reduction of the lactone ring, mediated by anaerobic intestinal bacteria. About 10% of adult patients excrete large amounts of reduced metabolites. In these patients, more than 40% of total urinary digoxin and its derivatives is in the form of digoxin reduction products.

Investigators in New York carried out a study to determine whether infants and children metabolize digoxin in this way.[59] Eighty-nine patients on chronic digoxin therapy, younger than 21 years of age, were evaluated. None of the 36 digitalized infants 8 months of age or less excreted reduced digoxin metabolites in the urine; about 12 patients would have been expected in this category if the adult pattern prevailed. Among the 45 children older than 16 months, digoxin reduction products were found in the urine of 20. However, large quantities of digoxin reduction products in the urine, such as are found in 10% of adults, were not found in children less than 9 years of age.

Even though reduced metabolites were not found early in life, stool cultures of 20 of 73 infants younger than 8 months of age contained high concentrations of bacteria that reduced and inactivated digoxin in vitro, in some cases as early as the second week of life. In summary, children were found to be colonized with intestinal bacteria early in life but the capacity to inactivate digoxin developed only gradually. The investigators concluded that "the discrepancy between the time digoxin reduction product-forming organisms appear in the stool and production is detectable in vivo dictate caution in characterizing gut flora metabolic processes based only on in vitro observations."

Plasma Protein Binding in Newborns

Differences in plasma protein binding and tissue binding of drugs have also been reported between newborns and adults. Table 12–3 shows binding data and apparent volumes of distribution for several drugs in neonates and adults.[60] In each case, binding to plasma proteins is less in the newborns than in the adults. Generally consistent with the decrease in plasma protein binding is an increase in apparent volume of distribution in the newborn. Diazepam, despite the fact that the fraction unbound to plasma proteins is 4 times larger in neonates than in adults, is an exception. Apparently, the extravascular (tissue) binding of diazepam is even more impaired in the newborn than is plasma protein binding.

The relatively low plasma protein binding in neonates is often associated with elevated levels of bilirubin, which is avidly bound to albumin and may compete with drug for binding sites. At one time it was thought that competition between drugs and bilirubin for binding sites on albumin could result in displacement of bilirubin leading to its deposition in the central nervous system and kernicterus. Current thinking is that displacement of bilirubin by a drug is unlikely because the affinity of bilirubin for albumin is greater than that of any drug studied to date. Other mechanisms are probably involved in the development of CNS toxicity in neonates with elevated bilirubin and jaundice.

Decreased plasma protein binding of drugs and differences in body composition with respect to TBW and ECW largely explain why larger mg/kg doses are required to produce peak blood levels in neonates comparable to those in adults.

Table 12–3. Plasma Protein Binding (Fraction Free in Plasma), and Apparent Volume of Distribution in Neonates and Adults

Drug	Free fraction		Volume (L/kg)	
	Neonates	Adults	Neonates	Adults
Diazepam	0.16	0.04	1.6	2.4
Digoxin	0.8	0.7	5 to 10	7
Phenobarbital	0.68	0.53	1.0	0.55
Phenytoin	0.2	0.1	1.3	0.63
Sulfamethoxypyrazine	0.43	0.38	0.47	0.24
Sulfisoxazole	0.32	0.16	0.38	0.16

*Data from Morselli, P.L.[60]

Renal Excretion in Newborns

Although the ratio of kidney weight to total body weight in the newborn is twice that in the adult, the organ is anatomically and functionally immature; all aspects of renal function are reduced. Neonatal renal plasma flow and glomerular filtration rates normalized for body surface are still only 30 to 40% those of the adult, as indicated by aminohippurate and inulin studies.[61,62] One would anticipate that drugs subject to renal excretion would be eliminated more slowly in the newborn than in the adult patient.

The different processes of renal excretion mature at different rates. Average glomerular filtration rate is 38.5 ml/min/1.73 sq m and maximal tubular secretory capacity for para-aminohippurate (PAH) is 16 mg/min/1.73 sq m in full-term neonates, compared with adult values of 127 and 80, respectively. At 6 months of age, glomerular filtration rate is nearly 90% that found in the average adult, whereas maximal tubular secretory capacity for PAH is only about 60% of the adult value.[63] Immature renal function affects the elimination of aminoglycosides, indomethacin, digoxin, penicillins, sulfonamides, and many other drugs. The risk of adverse drug effects in newborns is high unless close attention is paid to the size of the dose.

Studies with digoxin are illustrative. Repetitive administration of 12 to 13 μg/kg per day of digoxin to full-term neonates (3 to 30 days), infants (1 to 12 mo), and children (1 to 10 years) results in mean steady-state plasma digoxin levels of 2.1, 1.2, and 1.4 ng/ml, respectively.[64] The elevated digoxin levels in the neonates are related to the low renal clearance of digoxin, which is, on the average, less than half that found in children and adults with normal renal function.

Drug Metabolism in Children

Although drug metabolism is impaired in neonates compared to adults, older infants and children actually metabolize certain drugs more rapidly than adults. Rates of drug metabolism for many drugs reach a maximum somewhere between 6 months and 12 years of age and thereafter decline with age. Accordingly, children often require higher mg/kg doses than do adults.

Drugs showing faster elimination in children than in adults include antipyrine, clindamycin, diazoxide, phenobarbital, carbamazepine, valproic acid, ethosuximide, and theophylline. Theophylline has been the most carefully documented.

In one study the pharmacokinetics of theophylline were determined in asthmatic children (6 to 17 years of age) and in normal adults, after a 4 mg/kg intravenous dose of aminophylline.[65] The average total clearance of theophylline was 87 ml/hr per kg in the children and 57 ml/hr per kg in the adults. The average half-life of theophylline was 3.7 hr in the children and 5.5 hr in the adults.

Wyatt and co-workers determined that the average daily dose of theophylline required to maintain serum levels in the therapeutic range of 10 to 20 μg/ml was 24 mg/kg for children up to 9 years of age, 18 mg/kg for children aged 12 to 16 years, and 13 mg/kg for patients older than 16 years.[66] Administration of the adult dose to the younger children seldom produces therapeutic levels; administration of the dose required for children to adults results in blood levels usually associated with adverse effects.

Body surface area has been found to be a better correlate of dosing requirements in children than body weight, perhaps because it is a better correlate of cardiac output, of hepatic and renal blood flow, and of glomerular filtration rate in children and adults. According to one approach based on body surface area, a child's maintenance dose is calculated as follows:

$$\text{Child's dose} = \frac{\text{SA of child (m}^2\text{)}}{1.73\ \text{m}^2} \times \text{Adult dose (mg/day)} \qquad (12\text{–}10)$$

where 1.73 m^2 is the surface area (SA) of the average 70-kg adult. The SA of the child may be estimated from Equations 12–6 or 12–7. Equation 12–10 leads to higher mg/kg doses for a child than for the adult. The larger mg/kg dose resulting from the use of Equation 12–8, however, is still inadequate to meet the requirements for theophylline in children.

Clinical experience in pediatric patients has suggested that children often require large doses of procainamide for suppression of arrhythmias. In adults, the half-life of procainamide ranges from 2.5 to 5 hr, with rapid acetylators grouped at the lower end of the range; plasma clearance averages about 8 to 9 ml/min/kg. A study in 5 children 7 to 12 years of age found an average half-life of 1.7 hr and a clearance of nearly 20 ml/min/kg.[67] Quinidine is also metabolized more rapidly in children than adults.[68]

Drug Elimination in the Aged

The probability of experiencing adverse effects from a drug in adults appears to increase with age. This is related in part to the decline in organ function that occurs as a result of advancing age. For example, cardiac output decreases by 30 to 40% between the ages of 25 and 65 years.[69] Glomerular filtration rate (GFR) declines progressively with age after the age of 20 yr.[70] Differences in the pharmacokinetics of certain drugs between young and old adults are anticipated, and, indeed, some important differences have been observed.[71,72]

Glomerular filtration falls at a rate of about 1 ml/min per 1.73 m^2 per year between the ages of 20 and 90 years.[70] Parallel declines in tubular secretion and active tubular reabsorption have also been observed. The total clearance of drugs largely eliminated by renal excretion declines approximately in proportion to the reduced GFR. The 50% decline in renal function in the elderly patient relative to the young patient is often of little clinical importance, but must be considered in determining the appropriate dose of certain drugs in the elderly; these drugs include digoxin, cimetidine, lithium, and the aminoglycoside antibiotics.[71,72]

The same amount (0.5 mg) of digoxin administered intravenously to elderly men (73 to 81 years) and young men (20 to 33 years) resulted in higher blood concentrations and longer half-lives in the elderly.[73] This is principally due to diminished urinary excretion of digoxin in the elderly. Renal clearance of digoxin averaged 53 ml/min per 1.73 m^2 in the old and 83 ml/min per 1.73 m^2 in the young men. Although serum creatinine levels in the old and young subjects were not different, creatinine clearance averaged 56 ml/min per 1.73 m^2 in the elderly and 122 ml/min per 1.73 m^2 in the young subjects.

A report from Europe showed that the total plasma clearance of cimetidine decreased by half between the ages of 30 and 65 years, largely as a result of a profound decrease in the renal clearance of cimetidine with age.[74] The clearance of ranitidine was also found to be significantly lower in an elderly group compared with a group of young adults, consistent with the difference in creatinine clearance between the two groups.[75] These investigators predicted that ranitidine levels in plasma would be about 60% higher in the elderly compared with young adults, but suggested that dose reduction may not be necessary because ranitidine is substantially free of dose-related adverse effects.

Other investigators found marked differences in the disposition of the angiotensin-converting enzyme inhibitor enalapril and its active metabolite, enalaprilat, between healthy young and elderly subjects.[76] The apparent clearance of enalapril after oral administration and the clearance of enalaprilat after iv administration were about 30% lower in the elderly subjects. The clearance of each was significantly correlated with creatinine clearance, which averaged 92 ml/min in the younger group and 66 ml/min in the older group.

The decreased clearance and higher blood levels of enalaprilat may explain in part the greater hypotensive effect and prolonged converting enzyme inhibition observed in elderly subjects. Some dosage adjustments based on creatinine clearance may be necessary.

During the development of a new diuretic/antihypertensive combination product of triamterene (T) and hydrochlorothiazide (HCT) (Maxzide), with bioavailability characteristics superior to the original combination product (Dyazide), Williams et al.[77] compared the two formulations in patients with mild to moderate hypertension. For each product, they found higher blood levels of HCT than they had observed in earlier studies with healthy subjects. The clearance of HCT appeared to be lower in the patients than in healthy subjects.

An important difference between the two groups was age. The mean age was 50 years for the patients and 24 years for the healthy subjects. Age in the patient population ranged from 22 to 69 years. Those patients less than 60 years of age had a peak HCT concentration in plasma of 455 ng/ml, whereas those greater than 60 years of age had a mean peak level of 600 ng/ml. Similar differences were noted with regard to the plasma levels of the principal metabolite of T, hydroxytriamterene sulfate (HTS), which like HCT is eliminated by renal excretion. Relatively small differences in levels of T were observed.

Analysis of the data suggested that age is an important factor in determining the elimination of HCT and HTS. The investigators observed that "because increasing age is associated with reduced renal function, decreasing renal function might also have contributed to the alteration in drug disposition seen in our data." In fact, highly significant correlations were observed between the renal clearance values of HCT, T, and its active metabolite,

HTS, and both age and measured creatinine clearance when the data from both the patients and the healthy subjects were combined.

Hydrochlorothiazide is eliminated primarily by renal excretion. Between the ages of 25 and 50 years, the renal clearance of HCT declined by about one-third. In subjects older than 60 years, the clearance of HCT may be reduced 50% or more. Therefore, a given dose of HCT will result in higher blood levels in elderly individuals than in young adults. Because of the important role of metabolism in the elimination of triamterene, little accumulation occurs in the presence of renal impairment. On the other hand, renal excretion is the major route of elimination of HTS, and considerable accumulation occurs in older patients.

In evaluating renal function in the elderly patient one must bear in mind the decline of muscle mass and lean body mass relative to total body weight that occurs with old age. Since serum creatinine concentration depends on creatinine turnover, which is a function of muscle mass, as well as renal creatinine clearance, the decline in renal function may not be accompanied by an elevation in serum creatinine. Estimates of creatinine clearance from serum creatinine levels must take the patient's age into account.

Changes in drug metabolism with age are not nearly as predictable as changes in the renal excretion of drugs. There is a growing list of drugs subject to oxidative metabolism that are cleared less efficiently in the elderly, but this is not the case for all such drugs. Drug conjugation reactions, on the other hand, seem to be largely independent of age.

Hepatic blood flow declines with age, partly because of reduced cardiac output. Accordingly, the clearance of drugs with liver blood flow-dependent elimination may decrease in the elderly. Important age-related changes have also been reported for drugs showing marked first-pass metabolism.

The prototypical drug for studying metabolic oxidation in humans has been antipyrine. Swift et al.[78] measured liver volume and antipyrine kinetics in two groups of healthy individuals aged 20 to 29 years and 75 to 89 years. Liver volume and antipyrine clearance were reduced in the elderly group. On the average, clearance was 42 ml/min in the young subjects and 24 ml/min in the elderly subjects. The investigators concluded that "hepatic drug oxidation as measured by antipyrine clearance declines in man with aging and this is partly due to a decrease in liver size and partly to reduction in microsomal enzyme activity."

Most studies examining the effect of age on human liver size in vivo have used ultrasound. Swift et al.[78] found a reduction in estimated liver volume from a mean of 1300 ml in subjects 30 to 39 years of age to 990 ml in subjects aged 75 to 86 years. Bach et al.[79] reported a 17% decrease in liver volume over a similar age range. In a review of age-related changes in liver size and blood flow, and the implications for drug metabolism in the elderly, Woodhouse and Wynne[80] noted that the largest study of this kind found a significant negative correlation between estimated liver volume and age. A 28% fall in liver volume was noted in those over 65 years of age compared with those under 40.

Other investigators measured the plasma clearance of antipyrine after intravenous injection in normal male subjects aged 22 to 72 years.[81] They found that antipyrine clearance declined with age in the group as a whole, but that the change was much greater in smokers than nonsmokers. Antipyrine clearance was higher in smokers than nonsmokers among subjects less than 40 years of age but there was little difference between them among subjects older than 40. These findings suggest that the enzyme-inducing effects of smoking diminish with age.

The effects of aging on the pharmacokinetics of anticonvulsants is also of interest. Investigators determined the pharmacokinetics of phenytoin after an intravenous injection of 100 mg to a group of young healthy adults with a mean age of 29 years and to a group of elderly patients with a mean age of 83 years.[79] The clearance of phenytoin appeared to be similar in each group, about 50 ml/min, but plasma protein binding was considerably decreased in the elderly. Therefore, the clearance of unbound (free) phenytoin was significantly lower in the older patients (309 vs 569 ml/min), suggesting a need for lower doses of phenytoin in such patients.

The pharmacokinetics of valproic acid were compared in healthy young and elderly subjects during repeated dosing with oral valproate, 250 mg every 12 hr.[82] Steady-state concentrations of valproic acid were practically identical in both groups, about 40 to 45 mg/L. Free fraction in plasma, however, was significantly larger in the elderly than in the young subjects (0.11 vs 0.06). Calculation of unbound valproic acid concentrations indicated that

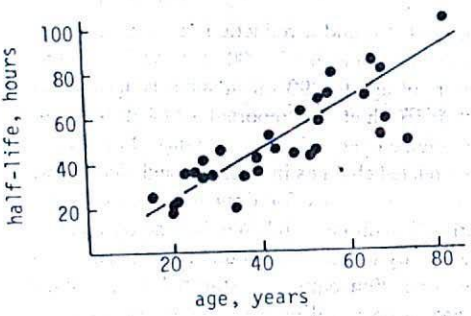

Fig. 12–7. Relationship between the half-life of diazepam and age in a group of healthy subjects. (Data from Klotz, U., et al.[83])

free drug levels at steady state are almost twice as high in the elderly as in the young subjects.

Changes in plasma protein and tissue binding on aging complicate the evaluation of the effects of age on drug metabolism. For example, Klotz and associates found a striking increase in the half-life of diazepam as a function of age in a panel of subjects ranging in age from 15 to 82 years; half-life increased from 20 to 90 hr (Fig. 12–7).[83] The clearance of diazepam, however, was independent of age. The entire change in half-life can be accounted for by an age-dependent increase in the apparent volume of distribution of diazepam secondary to changes in tissue binding of the drug. A similar situation has been reported for nitrazepam.[84]

An even more striking increase in the half-life of chlordiazepoxide with age has been reported. Unlike the situation with diazepam, this age-related increase in half-life is the result of both an increase in apparent volume of distribution and a decrease in the metabolic clearance of chlordiazepoxide.[85]

The effects of aging on the elimination of two short-acting benzodiazepines, triazolam and midazolam, have also been studied. The elimination of both drugs principally involves hepatic metabolism to hydroxylated metabolites.

Plasma triazolam concentrations were measured in male and female subjects, ranging in age from 21 to 87 years after a single 0.5-mg oral dose.[86] The apparent oral clearance of triazolam in male and female elderly subjects (>61 years) was only about half that observed in the younger subjects (<34 years). The initial hypnotic dose of triazolam in elderly patients with insomnia should be about half that recommended for a young adult of similar weight.

Similar but less pronounced effects have been observed with midazolam.[87] Elderly are not only less efficient in their ability to metabolize midazolam, they are also much more sensitive to the effects of the drug.[88]

Several benzodiazepines, including oxazepam, lorazepam, and temazepam, are not subject to oxidative metabolism but are eliminated by conjugation with glucuronic acid. Several studies have shown little or no effect of age on drug clearance. In regard to these drugs, Greenblatt and his colleagues have observed in a widely-cited literature review[89] that "total clearance tends to decline with age, but the amount of variability attributable to age is small, making age-related changes in clearance either insignificant or of border-line significance."

Early population pharmacokinetic studies suggested a need to lower theophylline doses in elderly patients because of reduced clearance. Subsequent studies, however, indicated that these preliminary observations may have been confounded by not controlling for disease state and smoking habits. These later reports suggested that theophylline clearance was independent of age in both smokers and nonsmokers and that cigarette smoking increased the clearance of theophylline in both young and elderly subjects.[90,91]

A carefully controlled investigation of the effect of age on theophylline metabolism in young and old cigarette smokers, using stable isotope methodology, may have resolved this controversy.[92] These investigators found that the plasma clearance of theophylline in old nonsmokers was about one-third less than in young nonsmokers. Theophylline clearance was also lower in older smokers than in young smokers but the difference, in the order of 20%, was less than that observed in nonsmokers. It appears the metabolism of theophylline is slightly impaired in the elderly but the change is difficult to detect because the variability in theophylline kinetics is large.

Age-related changes in hepatic blood flow and in the effects of smoking on microsomal drug metabolizing enzyme activity can also complicate the evaluation of the effects of age on drug metabolism. Vestal and co-workers determined in a group of 27 healthy subjects, consisting of smokers and nonsmokers and ranging in age from 21 to 73 years, that the systemic clearance of propranolol, deter-

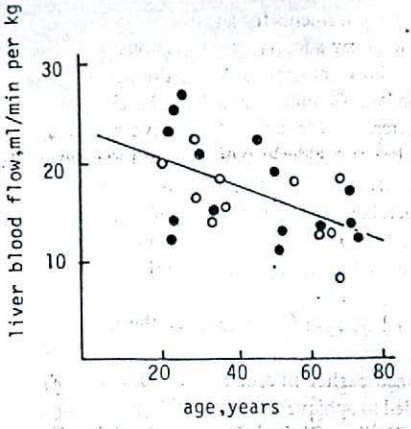

Fig. 12–8. Relationship between liver blood flow and age in smokers (●) and nonsmokers (○), r = 0.55. (Data from Vestal, R.E., et al.[93])

mined after intravenous administration, decreased as a function of age.[93] Propranolol has a high metabolic (hepatic) clearance that depends on both hepatic blood flow rate and the intrinsic ability of the hepatic enzymes to metabolize the drug (intrinsic clearance). The decline in the systemic clearance of propranolol as a function of age is largely the result of an age-dependent decrease in liver blood flow (Fig. 12–8). A similar age-related decline in the systemic clearance of indocyanine green has also been reported.[94]

Vestal and co-workers also found that the intrinsic hepatic metabolism of propranolol (determined after oral administration) decreased with age in smokers but not in nonsmokers.[93] Cigarette smoke induces hepatic microsomal enzymes involved in the metabolism of propranolol. Young smokers metabolize propranolol more efficiently than young nonsmokers; however, there is little difference in the intrinsic metabolic clearance of propranolol in elderly smokers and nonsmokers. The results are consistent with a decreased induction of drug-metabolizing enzymes with aging. This age-related effect on enzyme induction has also been found with antipyrine.[94]

The effects of aging on the kinetics of other beta-blockers have also been investigated. The bioavailability of metoprolol, which like propranolol undergoes substantial first-pass metabolism after oral administration, was studied in healthy young and elderly subjects.[95] Large intersubject differences were observed in both groups, but no significant difference in area under the drug concentration in plasma versus time curve (AUC), peak concentration, or half-life was found between the groups.

The pharmacokinetics of labetalol, a mixed alpha- and beta-blocker has also been studied after oral and iv administration to a small group of patients with hypertension, ranging in age from 28 to 75 years.[96] Labetalol bioavailability, incomplete because of first-pass metabolism, varied from 9 to 68% but was significantly correlated with age. The regression equation predicts a bioavailability of 15 to 20% in a 20-year-old patient and 55 to 60% in a 70-year-old patient.

These preliminary findings were confirmed by Abernethy et al.[97] On comparing the pharmacologic effects and pharmacokinetics of labetalol in young and elderly patients with systemic hypertension, they concluded that "the combination of increased antihypertensive effect and decreased clearance suggests that smaller labetalol doses may be required in elderly hypertensive persons to achieve antihypertensive effects comparable to those in young hypertensive patients."

In another study,[98] a prolonged-release tablet containing oxprenolol, a beta-blocker used outside the United States, was given once daily for 8 days to normal young adult subjects and elderly hypertensive patients. The elderly patients had a significantly higher AUC and peak drug concentration after the first and last dose of oxprenolol, presumably related to decreased clearance. Although it is not possible to sort out the effects of disease from those of age per se on the kinetics of oxprenolol, it is clear that the results of pharmacokinetic studies in young healthy subjects do not apply to an older population with hypertension.

This important distinction of age and disease may apply to other beta-blockers. Rigby et al.[99] measured steady-state blood levels in elderly patients with hypertension and in young healthy adults after repeated oral dosing of atenolol, metoprolol, oxprenolol, and propranolol. In each case, drug levels were considerably higher in the elderly patients than in the young healthy subjects. The ratios of steady-state concentrations (elderly: young) were 2.0 for atenolol, 1.6 for metoprolol, 1.5 for oxprenolol, and 2.1 for propranolol.

Calcium channel blockers produce a greater hypotensive effect in elderly patients than in younger ones. Studies with verapamil, nifedipine, and fel-

odipine indicate age-related changes in drug disposition contribute to the enhanced effects.

Abernethy et al.[100] studied the pharmacodynamics and pharmacokinetics of verapamil in young (23 to 36 years), elderly (61 to 74 years), and very elderly (75 to 102 years) male patients with hypertension. After a single 10-mg dose of iv verapamil, mean arterial blood pressure decreased more in elderly and very elderly patients than in young patients. The plasma clearance of verapamil was lower in the elderly and very elderly patients, resulting in prolonged elimination half-lives in these patients.

It is worth noting that few studies have included subjects beyond 75 years of age. Although statistically significant differences between the elderly and very elderly patients were not seen in this study, the investigators point out "there was a trend toward even greater changes in the very elderly compared with the young hypertensive patients in both pharmacodynamic and pharmacokinetic data." Age-related changes appear to continue with advancing age into the eighth and ninth decades of life.

Robertson et al.[101] studied the kinetics of nifedipine in healthy normotensive subjects aged 22 to 35 years and 73 to 83 years. Following a small iv dose, the clearance of nifedipine was 348 ml/min in the elderly compared with 519 ml/min in the young but volume of distribution was similar in each group. Mean peak concentration and AUC after oral administration were also much higher in the elderly than in the young subjects.

No hemodynamic effects were observed in the group of young subjects after oral nifedipine. In contrast, nifedipine had a significant acute hypotensive effect in the elderly. The investigators concluded that the results are consistent with an age-related decrease in the hepatic clearance and first-pass metabolism of nifedipine, as well as impaired baroreceptor function, all of which contribute to its increased hypotensive effect in elderly patients.

Other dihydropyridine calcium channel blockers will probably be found to show age-related changes in pharmacokinetics similar to nifedipine. For example, Landahl et al.[102] found blood levels of felodipine, an investigational dihydropyridine, to be 3 times higher in elderly than in young subjects. Moreover, the effect on blood pressure correlated with plasma concentration of felodipine.

Anesthesiologists have long been concerned about dosing requirements for anesthetics in elderly patients undergoing surgery. There is considerable evidence to show that the dose of thiopental required to induce or maintain a light level of anesthesia decreases with age. Many have assumed that this is because elderly patients are more sensitive to the effects of thiopental than younger patients. In fact, there is a general clinical impression that the aged brain is pharmacodynamically more sensitive to sedative, hypnotic, and anesthetic drugs.

Homer and Stanski[103] reexamined the question of dosing requirements of thiopental in the elderly and confirmed earlier findings. The dose of thiopental needed to achieve a measured degree of suppression of brain activity, as determined by the electroencephalogram (EEG) decreased linearly with age. The regression equation predicted a dosage requirement of 10.4 mg/kg for a 20-year-old patient but one of only 4.4 mg/kg for an 80-year-old patient. For each 10-year increment in age, the dose of thiopental decreased about 1 mg/kg.

The decreased dosage requirement for thiopental could result from either age-related changes in brain response or pharmacokinetics. These investigators, however, were unable to find a relationship between age and serum concentration of either total or unbound thiopental needed to reach half-maximum EEG suppression. This means that the need for smaller doses of thiopental in older patients must be due to age-related changes in pharmacokinetics. This aspect was investigated further in patients ranging in age from 24 to 88 years, who were given a bolus or very short iv infusion of thiopental. Blood samples were taken frequently after administration.

After a bolus dose of thiopental or after terminating a short infusion, there is pronounced multiexponential decline of drug levels in serum with time. Although no age-related changes were found with respect to clearance, unbound clearance, volume of distribution, or half-life, marked differences in the initial distribution kinetics of thiopental were found. The apparent volume of the so-called central compartment changed markedly with age, ranging from about 25 L in young adults (20 to 30 years of age) to 5 L or less in patients more than 60 years old. This smaller initial distribution volume in the elderly results in much higher serum levels (and presumably brain levels) immediately after dosing.

The investigators concluded that "this pharma-

cokinetic difference explains the clinical impression of 'increased sensitivity' of the elderly to thiopental. Having a smaller central compartment, the elderly develop high serum levels of thiopental quickly and require less drug to show an effect. Thus, the dose of thiopental required to reach a surgical level of anesthesia significantly decreased with increasing age."

Considerable attention has also been given to the disposition of antidepressant drugs in the elderly. These drugs are widely used in older patients; some estimate that clinically important depression is present at any given time in at least 10% of the elderly population.

In 1977, Nies et al.[104] reported that older depressed patients treated with imipramine developed higher steady-state plasma levels of imipramine and desipramine, its active metabolite, than younger patients. The age related differences in imipramine and desipramine levels occurred despite the fact that all of the younger patients, less than 65 years, were receiving 150 mg imipramine per day, but the dosage for the older group ranged from 50 to 150 mg/day with a mean value of 92 mg daily. Despite the lower dose, higher drug levels were generated.

More recently, Abernethy et al.[105] studied the disposition of imipramine and desipramine directly in healthy subjects older than 65 years or younger than 40 years. Each subject was given iv and oral doses of imipramine and an oral dose of desipramine. After iv administration, imipramine half-life was considerably prolonged in elderly subjects compared with younger subjects (30 vs 17 hours). This change was almost entirely due to reduced clearance.

Still greater differences were noted after oral administration of imipramine because of a decreased first-pass effect in the elderly. Peak levels of imipramine in elderly men were about twice those found in younger men; a 4-fold difference was seen in women as a function of age. In contrast, small age-related differences were observed after oral desipramine.

These findings suggest that the metabolism of imipramine, a tertiary amine predominantly subject to demethylation, may be more sensitive to effects of age than the metabolism of desipramine, which largely involves hydroxylation. The investigators are cautious in offering dosage recommendations, pointing out that "total pharmacologic activity for both imipramine and desipramine may be related to the quantity of parent drug, demethylated metabolites, and hydroxylated metabolites present."

Unfortunately, the findings with imipramine and desipramine cannot be generalized to other tricyclic antidepressants. This is clearly illustrated by the findings of Schulz et al.[106] who studied the effects of age on the kinetics of amitriptyline after iv and oral administration. Although the half-life of amitriptyline was marginally longer in the elderly group (22 vs 16 hours), there was no change in clearance with age. Furthermore, drug levels were similar in both groups after oral administration; first-pass metabolism eliminated 52% of the dose in the young adult subjects and 57% in the older subjects. These findings indicate that amitriptyline kinetics in healthy subjects, unlike those of imipramine, are relatively insensitive to age.

On the other hand, the elimination of nortriptyline, the demethylated active metabolite of amitriptyline, is much lower in the elderly, at least in those who are hospitalized and depressed, than in young healthy subjects. According to Dawling et al.,[107] the apparent clearance of nortriptyline in young healthy subjects following an oral dose ranged from 16 to 115 L/hour, with a mean of 54 L/hour; the mean apparent clearance in elderly patients was only 20 L/hour, with a range of 8 to 38 L/hour.

These age-related differences in the pharmacokinetics of tricyclic antidepressants provide, at least in part, an explanation for the increased susceptibility of older patients to side effects, including postural hypotension, urinary retention, tachycardia, and mental confusion. They also provide a rationale for using lower doses in the elderly.

Reports of serious adverse reactions with benoxaprofen, a nonsteroidal anti-inflammatory drug (NSAID) subsequently recalled from the market because of toxicity, heralded the current era of heightened concern as to drug dosage in the elderly. No other drug class has undergone greater scrutiny in this regard. Some of the more important studies with NSAIDs are reviewed below.

Upton et al.[108] studied naproxen pharmacokinetics in healthy elderly and young men. They found a substantial decrease in plasma protein binding of naproxen in the elderly panel of subjects. Consequently, although serum levels of total naproxen were similar in each group, steady-state concentrations of unbound naproxen were about twice as great in the elderly individuals than in the younger subjects. These findings support the view

of some clinicians who recommend that geriatric patients be treated, at least initially, with only one-half the usual dose of naproxen.

The elimination of ketoprofen, one of the more recently introduced NSAIDs, also appears to be impaired in the elderly. On oral dosing, plasma concentrations of ketoprofen were consistently higher in elderly patients than in young adult subjects.[109] The mean apparent clearance of ketoprofen was 89 ml/min for the panel of young adults but only 37 ml/min in the elderly panel. Ketoprofen, like naproxen, is highly bound to plasma proteins, and even greater differences may exist in the unbound clearance of ketoprofen between young and elderly subjects but the investigators did not report binding data.

Conjugation with glucuronic acid, resulting in an ester glucuronide, is the major route of ketoprofen elimination. About two-thirds of an oral dose is recovered in urine as ketoprofen glucuronide; a negligible amount of unchanged ketoprofen is excreted in urine. The investigators concluded that the decreased elimination of ketoprofen in the elderly is due to decreased conjugation with glucuronic acid.

An alternative explanation, based on the susceptibility of ester glucuronides to hydrolysis in biological fluids, has been advanced.[110] "Since the elderly have reduced renal function, old age should also result in a decreased excretion of ketoprofen glucuronide. The resulting accumulation of this ester glucuronide may lead to increased systemic deconjugation (regeneration of the parent compound)."

In 1987, a leading representative of the Food and Drug Administration discussed guidelines for the clinical investigation of drugs for use by the elderly.[111] The underlying principle of these guidelines is that age-related differences in response to drugs can arise from either pharmacokinetic or pharmacodynamic changes, but studies to evaluate possible differences in the elderly should focus initial attention on assessment of pharmacokinetic differences between age groups.

The critical features of a proper evaluation of a new drug with respect to the elderly are the following: "1. Include the elderly in clinical trials if they will be exposed to the new drug after it is marketed . . . Although it is reasonable and necessary to exclude patients too infirm to participate in clinical trials, patients unable to provide meaningful informed consent, and patients with too much complicating illness, rigid age cutoffs and routine exclusion of all patients with concomitant illness and medication is unnecessary and counter productive. It tends merely to delay discovery of important problems and interactions: it cannot prevent them . . . 2. Analyze the influence of age on adverse events and effectiveness . . . In the past, it was uncommon to examine trial experience to see whether age affected response . . . Any attempt to relate benefit or adverse effect to factors such as age will be greatly improved by good pharmacokinetic data . . . 3. Seek and transmit via labeling better information on all of the factors that affect pharmacokinetics of the drug, including age."

We are still a long way off from understanding why some drugs show important age-related changes in clearance while others do not. Many factors have been examined but one factor that has not been considered is the possibility of age-related stereoselective changes in elimination. About 10 to 15% of all drugs are marketed as racemic mixtures. Racemic drugs whose enantiomers use different oxidative metabolic pathways could exhibit selective age-related changes in drug metabolism.

In pursuit of this idea, investigators in Kentucky studied the disposition of hexobarbital enantiomers in young and elderly healthy male subjects.[112] The well-recognized and striking difference in the elimination of d- and l-hexobarbital was clearly seen in the panel of young subjects. Oral clearance was 16.9 ml/min/kg for the l-form but only 1.9 ml/min/kg for the d-form.

Interestingly, the difference between the hexobarbital enantiomers was considerably less in the elderly subjects. The reason for this was that although the oral clearance of d-hexobarbital was about the same in elderly and young subjects (1.7 vs 1.9 ml/min/kg), the mean oral clearance of l-hexobarbital in the elderly panel was less than half that found in the young panel (8.2 vs 16.9 ml/min/kg). A substantial age-related fall in the clearance of the l-form of hexobarbital but not of the d-form was observed. The investigators pointed out that age-related preferential decline in metabolism of one enantiomer over another has never been reported for any racemic drug in animals or humans.

Gender

Large sex-related differences in the capacity of rats to metabolize drugs are widely recognized.[113]

These differences are routinely considered in designing toxicology studies for new drugs. An example may be found in a recent report by Trenk et al.,[114] who studied the pharmacokinetics of phenprocoumon, an oral anticoagulant, in female and male inbred Lewis-Wistar rats. The clearance of phenprocoumon was significantly lower in females than males (7.9 vs 24.5 ml/min/kg) and its apparent volume of distribution was also much smaller in females than males (288 vs 617 ml/kg).

The low clearance of phenprocoumon in female rats is consistent with a slower metabolism found for many drugs metabolized by P-450 enzymes in rats and appears to be related to differences in sex hormones. In this species, androgens strongly stimulate the activity of microsomal mixed function oxidases. The smaller distribution volume of phenprocoumon in females relates, at least in part, to a higher degree of plasma protein binding. Percent unbound was 0.96% in females and 1.24% in males.

Important gender-related differences in metabolism are not generally observed in the mouse, guinea pig, dog, rabbit, or human. A review of the literature in 1977 concluded that although sex-related differences in drug metabolism did exist in human subjects, the differences were small and did not warrant modification of dosage as a function of gender. This conclusion still applies, but today we recognize that if sex-related differences are to be found, other variables including age, smoking habits, and the use of oral contraceptives need to be controlled.

The kinetics of a large number of benzodiazepines have been studied with respect to sex-related differences. Findings with compounds that are largely eliminated by oxidative metabolism are inconclusive. More consistent results have been observed with benzodiazepines eliminated by metabolic conjugation. The clearance or apparent clearance of temazepam,[115] oxazepam,[116] and lorazepam[117] is significantly less in human female subjects than in males. These differences parallel those found in rats but are far smaller.

Two studies in human subjects with acetaminophen indicate that clearance is about 40% greater in males than in females. Based on the data provided by Miners et al.,[118] we can calculate that most of the difference is due to increased activity of the glucuronidation pathway in males; the formation clearance of acetaminophen glucuronide was 252 ml/min in males and 173 ml/min in females. The formation clearances for acetaminophen sulfate (105 vs 80 ml/min) and for acetaminophen oxidation products (38 vs 28 ml/min) were also higher in men than in women. The major elimination pathway for temazepam, oxazepam, and lorazepam also involves conjugation with glucuronic acid.

In another study by Miners and his associates,[119] salicylic acid clearance was found to be about 60% higher in male than in female subjects, an effect due largely to enhanced activity of the glycine conjugation pathway (salicyluric acid formation) in males. Still lower clearance values were found in women using oral contraceptives.

It is clearly established that combination oral contraceptives, consisting of a synthetic estrogen and a progestin, inhibit the oxidative metabolism of many drugs. Studies comparing users with nonusers have found that oral contraceptives decrease the clearance of antipyrine, chlordiazepoxide, diazepam, prednisolone, imipramine, and metoprolol, among other drugs. In one study, in women using the same oral contraceptive for 6 months to 4 years, antipyrine clearance was 28 ml/min during use but increased to 37 ml/min 4 weeks after stopping medication.[124]

Pregnancy

The possible effects of pregnancy on plasma drug concentrations have been reviewed by Eadie and co-workers.[121] Late pregnancy is associated with delayed gastric emptying and decreased motility of the gastrointestinal tract. These changes may reduce the rate of drug absorption.

The volume available for drug distribution increases during pregnancy, with the growth of the uterus, placenta, and fetus. Maternal plasma volume and ECF volume also increase. The concentration of plasma proteins tends to fall gradually during pregnancy, and drug binding may be reduced.

Perucca and Crema[122] reviewed the literature dealing with plasma protein binding of drugs in pregnancy. They noted that "experimental studies conducted mostly in vitro have shown that the plasma protein binding of many (but not all) drugs is decreased during pregnancy, particularly during the last trimester. Notable examples . . . include diazepam, valproic acid, phenytoin, phenobarbitone, salicylic acid, pethidine, lignocaine, dexamethasone, sulphafurazole and propranolol."

Chen et al.[123] studied the serum protein binding

of phenytoin and phenobarbital in vitro in healthy pregnant and nonpregnant women and in vivo in pregnant and nonpregnant women with epilepsy who were under treatment with phenytoin, phenobarbital, or combinations of either or both with other anticonvulsants. They found for both phenytoin and phenobarbital that binding to plasma proteins was reduced during pregnancy in both healthy women and women with epilepsy.

There was a clear trend toward decreased drug binding during the course of the pregnancy. Compared with the mean value found in nonpregnant women with epilepsy, the free fraction of phenytoin was 13% higher in the first trimester and 24% higher in the third trimester. The same applied to phenobarbital. The degree of impaired binding during pregnancy paralleled the decrease in serum albumin over this period. In the absence of changes in drug excretion or metabolism, impaired plasma protein binding alone during pregnancy should present few problems. One would expect to see a decrease in total drug concentration in plasma but no change in free drug concentration. Under these conditions, there is no need to change the dose. A decision to increase the dose because total drug concentration is below some preconceived therapeutic level may result in drug toxicity.

Plasma protein binding decreases in pregnancy but glomerular filtration increases. One study in pregnant women showed that creatinine clearance fell from 136 ml/min per 1.73 m^2 during the third trimester to 98 ml/min per 1.73 m^2 6 to 12 weeks postpartum.[124] In some cases, notably for drugs largely eliminated by renal excretion, this change may result in unusually rapid elimination and undermedication in pregnant patients.

For example, the plasma clearance of ampicillin is about 50% greater in pregnant women than in nonpregnant controls.[125] Consistent with this finding, ampicillin levels in plasma following treatment with pivampicillin, a prodrug, are much lower in pregnant women.[126] Controlled studies with ampicillin, cephradine, and cefuroxime have found 30 to 50% lower plasma levels and substantially shorter half-lives during pregnancy than after delivery.[127] Other investigators reported that the mean plasma clearance of cephradine was nearly 60% greater during pregnancy than afterwards.[128] Higher mg/kg doses of ampicillin and other antibiotics may be required in pregnant patients to avoid the risk of treatment failure.[129]

In parallel with the changes in glomerular filtration rate, the clearance of digoxin is also increased during pregnancy.[124] One study determined that renal clearance of digoxin fell from 103 ml/min per 1.73 m^2 during the third trimester to 86 ml/min per 1.73 m^2 postpartum and that digoxin renal clearance and creatinine clearance were significantly correlated. Consistent with these findings, the 24-hour urinary excretion of digoxin in patients treated with 0.375 mg/day oral digoxin fell from 186 μg during the third trimester to 134 μg postpartum.

These results suggest the possibility of inadequate serum levels of digoxin in pregnant patients treated with ordinarily adequate doses. Surprisingly, the opposite has been found.[124] Twelve of 15 patients evaluated had higher serum digoxin concentrations during pregnancy than after delivery. On the average, serum digoxin was 1.28 ng/ml in the third trimester and 1.0 ng/ml postpartum.

Several reasons come to mind to explain the elevated serum digoxin level during pregnancy in the face of increased renal clearance: a decrease in nonrenal clearance, an increase in the bioavailability of digoxin, or a combination of the two. Although it is usually assumed that digoxin is largely excreted unchanged, the nonrenal component is considerable, accounting for about 40% of digoxin clearance.

A substantial decrease in the nonrenal clearance of digoxin during pregnancy, on the order of 50%, could account for the higher serum levels of digoxin despite the enhanced renal excretion of the drug. Alternatively, an increase from about 60% (pre- or post-pregnancy) to about 85% (during pregnancy) in the bioavailability of digoxin would also produce the elevated serum levels that were observed. This explanation appears to be more likely, although one cannot rule out some decrease in the nonrenal clearance of digoxin during pregnancy.

In the later stages of pregnancy, bowel motility decreases as a result of high progesterone levels, leading to increased transit time in the small bowel and increased absorption of certain drugs. Studies have shown that decreased gastric emptying and intestinal transit time significantly increase the bioavailability of digoxin, particularly from slowly dissolving preparations.

Considerable attention has been given to the effects of pregnancy on the pharmacokinetics of anticonvulsants.[130] The major concerns in the pregnant epileptic patient are loss of seizure control and

the teratogenic effects of anticonvulsant drugs on the fetus. One investigator found that seizure frequency increased during pregnancy in 45% of the women treated for idiopathic epilepsy.[131]

Epileptic patients must be carefully monitored when they become pregnant. At least part of the reason for the seeming deterioration in seizure control during pregnancy is a decline in the plasma levels of anticonvulsant drugs even though the dose is maintained and compliance appears to be unaffected. This problem is well documented[132,133] and may be related to accelerated metabolism of anticonvulsants during pregnancy, but the interpretation is complicated by concomitant changes in drug binding to plasma proteins.

Phenytoin, phenobarbital, and valproic acid binding to serum proteins is significantly decreased in pregnant women, consistent with the mild hypoalbuminemia that occurs during pregnancy. As a result, there is a decrease in total drug concentration at steady state during pregnancy. However, Chen et al.[123] found that the fall in phenytoin and phenobarbital serum levels during pregnancy was greater than could be accounted for by changes in protein binding and free drug levels were lower in pregnant women than in nonpregnant women. The mean free concentration of phenytoin at steady state was 0.51 μg/ml in pregnant subjects and 0.75 μg/ml in nonpregnant controls; for phenobarbital, the respective values were 8.6 and 10.1 μg/ml.

These findings suggest either accelerated metabolism or reduced absorption of anticonvulsants during pregnancy. In view of the physiologic changes in gastrointestinal motility that occur during pregnancy, reduced absorption appears to be an unlikely explanation. Most investigators favor a mechanism involving decreased plasma protein binding and accelerated metabolism to explain the declining serum levels of anticonvulsant drugs during pregnancy. This hypothesis, however, remains to be proven.

Induction of hepatic drug metabolizing enzymes by circulating progesterone may be a factor contributing to the suspected increased clearance of anticonvulsants during pregnancy. One study found the apparent clearance of methimazole, the active metabolite of carbimazole, to be significantly higher in pregnant hyperthyroid patients than in nonpregnant hyperthyroid patients.[134] In one patient, the clearance of methimazole increased about 40% from the first trimester to the third trimester of pregnancy.

Further evidence for the accelerated metabolism hypothesis is found in studies with metoprolol, the cardioselective beta-blocker widely used in the treatment of hypertension during pregnancy. In one report, single 100-mg oral doses were given to pregnant women during the last trimester of pregnancy and again 3 to 5 months after delivery.[135]

Individual peak plasma levels in the last trimester were only 20 to 40% of those found postpartum. The apparent oral clearance ranged from 251 to 502 ml/min/kg with a mean value of 362 ml/min/kg./ In contrast, apparent clearance values determined after delivery ranged from 53 to 108 ml/min/kg with a mean of 82 ml/min/kg. These results suggest that pregnancy profoundly affects the intrinsic hepatic metabolism of metoprolol. The binding of metoprolol to plasma proteins is low, on the order of 10%, and changes in binding cannot explain the differences observed during and after pregnancy.

In another study, investigators examined the effects of pregnancy on the pharmacokinetics of metoprolol after both oral and intravenous administration.[136] Women who developed hypertension during pregnancy received in the third trimester a single 10-mg intravenous dose of metoprolol; 3 days later each patient received a single 100-mg oral dose of the drug. The procedure was repeated 3 to 6 months after delivery.

Again, the metabolism of metoprolol appeared to be markedly accelerated during pregnancy. The clearance of iv metoprolol decreased from 1.38 L/min during pregnancy to 0.65 L/min after delivery, and the apparent oral clearance fell from 9.56 to 1.71 L/min. The bioavailability of oral metoprolol, which reflects only first-pass metabolism because metoprolol is probably completely absorbed, was 21% in the third trimester and 42% postpartum.

These results convincingly demonstrate that the increased clearance of metoprolol during pregnancy is a result of increased hepatic metabolism and a substantially greater first-pass effect after oral administration. The investigators note that the recommended doses of metoprolol for hypertension do not differ from different patient categories and urge that dose-effect and plasma concentration-effect relationships be studied in pregnant women to determine if larger than average doses of metoprolol are needed.

GENETIC FACTORS

A major cause of intersubject differences in drug concentrations in the blood or plasma is variability

in drug metabolism. In any large population, one finds individuals who metabolize a drug much more slowly or much more rapidly than the average person. It is now evident that genetic factors contribute substantially to the large differences among people in metabolic clearance of drugs. The study of these differences is called *pharmacogenetics*.

Studies in Twins

The genetic component of individual variation in drug metabolism can be estimated by comparing the pharmacokinetics of a drug in identical and fraternal twins. If the differences among individuals are largely related to genetic factors, the variability in rates of drug metabolism will be much smaller in monozygotic (identical) twin pairs than in dizygotic (fraternal) twin pairs.

Estimation of the half-lives of antipyrine, dicumarol, and phenylbutazone, all of which are eliminated by oxidative metabolism, in identical and fraternal twins indicates that differences are appreciably greater in fraternal twins.[137] These data are summarized in Table 12–4. Similar findings have been reported for the metabolism of ethanol,[138] halothane,[139] salicylate,[140] and nortriptyline[141] in human twin pairs. For nortriptyline, plasma protein binding as well as metabolic clearance appears to be principally under genetic control.[142]

Polymorphic Acetylation

Isoniazid. The metabolism of most drugs in man seems to be under multifactorial or polygenetic control. This judgment prevails because frequency distribution plots of metabolic parameters usually yield continuous unimodal curves similar to a normal distribution curve. Metabolism data for some drugs, however, show a bimodal distribution.

Figure 12–9 is a frequency distribution histogram for isoniazid concentrations in the plasma 6

Table 12–4. Antipyrine, Dicumarol, and Phenylbutazone Half-Lives in Identical and Fraternal Twins*

Twin	Age	Sex	Half-life		
			Antipyrine (hr)	Dicumarol (hr)	Phenylbutazone (days)
			Identical Twins		
H.M.	48	M	11.3	25.0	1.9
H.M.	48	M	11.3	25.0	2.1
D.T.	43	F	10.3	55.5	2.8
V.W.	43	F	9.6	55.5	2.9
J.G.	22	M	11.5	36.0	2.8
P.G.	22	M	11.5	34.0	2.8
J.T.	44	M	14.9	74.0	4.0
J.T.	44	M	14.9	72.0	4.0
C.J.	55	F	6.9	41.0	3.2
F.J.	55	F	7.1	42.5	2.9
G.L.	45	M	12.3	72.0	3.9
G.L.	45	M	12.8	69.0	4.1
D.H.	26	F	11.0	46.0	2.6
D.W.	26	F	11.0	44.0	2.6
			Fraternal Twins		
A.M.	21	F	15.1	45.0	7.3
S.M.	21	M	6.3	22.0	3.6
D.L.	36	F	7.2	46.5	2.3
D.S.	36	F	15.0	51.0	3.3
S.A.	33	F	5.1	34.5	2.1
S.M.	33	F	12.5	27.5	1.2
J.H.	24	F	12.0	7.0	2.6
J.H.	24	F	6.0	19.0	2.3
F.D.	48	M	14.7	24.5	2.8
P.D.	48	M	9.3	38.0	3.5
L.D.	21	F	8.2	67.0	2.9
L.W.	21	F	6.9	72.0	3.0
E.K.	31	F	7.7	40.5	1.9
R.K.	31	M	7.3	35.0	2.1

*Data from Vesell, E.S.[137]

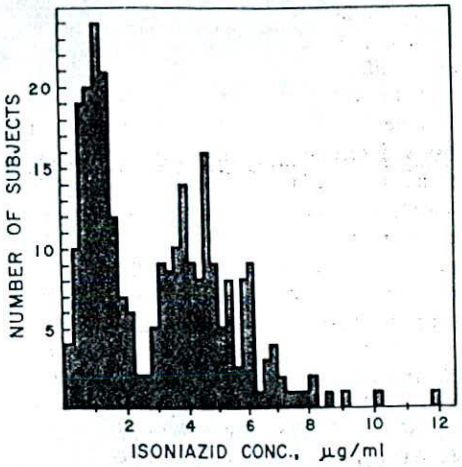

Fig. 12–9. Distribution of isoniazid concentrations in plasma 6 hr after an oral dose to 267 human subjects. (Data from Evans, D.A.P., Manley, K.A., and McKusick, V.C.[143])

hr after administration of a 10 mg/kg oral dose to 267 subjects.[143] A bimodality is evident with a mean of about 1 µg/ml for one subpopulation and a mean of about 4 to 5 µg ml for the other. The subpopulations are designated rapid inactivators and slow inactivators of isoniazid: they are assumed to represent two distinct phenotypes. The main route of elimination of isoniazid in man is conjugation with acetylcoenzyme A to form acetylisoniazid. Slow inactivators of isoniazid have less N-acetyltransferase in their liver than do rapid inactivators.

The half-life of isoniazid depends on how rapidly the drug is acetylated. In rapid inactivators the half-life of the drug ranges from 45 to 80 min; in slow inactivators the half-life of isoniazid is about 140 to 200 min.[144] At a given dosing rate, the steady-state plasma isoniazid level is lower in rapid inactivators than in slow inactivators. Rapid acetylators excrete small amounts of the drug unchanged in the urine (about 3% of the dose), whereas slow acetylators may excrete up to 30% of dose as unmetabolized isoniazid.

Widely different geographic and racial distributions of the acetylator phenotypes have been reported.[145] The upper extremes are the Eskimos and most populations of an Oriental origin; about 80 to 100% of these populations are rapid acetylators. The lower extremes investigated are Egyptians and certain groups of European origin; these populations consist of about 20 to 40% rapid acetylators. About one half of the United States population is classified as rapid acetylators.

Slow acetylators treated with isoniazid are more prone to develop peripheral neuropathy, are more prone to the adverse effects of phenytoin when simultaneously treated with isoniazid, and show greater tendency to develop antinuclear antibodies (ANA) and clinical signs of a systemic lupus erythematosus-like syndrome (SLE).[145] Rapid acetylators respond less favorably to treatment for pulmonary tuberculosis with a once-weekly isoniazid dosage regimen and may be more prone to develop isoniazid-related hepatitis.[145]

Polyneuritis is a well known adverse effect of isoniazid; it occurs more frequently in slow acetylators than in rapid acetylators. In one study, polyneuritis occurred during isoniazid therapy in 4 of 5 slow inactivators but in only 2 of 10 rapid inactivators.[146] Another study found peripheral neuropathy in 20% of slow inactivators compared with an incidence of 3% in rapid inactivators of isoniazid.[147]

As a consequence of the inhibitory effect of isoniazid on phenytoin metabolism, slow acetylators are more prone to the side effects of phenytoin than are rapid acetylators when both drugs are given together.[148] The dose of phenytoin should be reduced in such situations to avoid this complication.

Under certain conditions, slow acetylators show a higher cure rate than rapid acetylators. A study in 775 patients with pulmonary tuberculosis on standard isoniazid regimens showed that sputum conversion generally occurred earlier in slow than in rapid inactivators.[149] After 6 months, however, no clinically detectable differences were observed between rapid and slow phenotypes. If isoniazid is administered only once a week, then responses are better in slow than in rapid inactivator patients with tuberculosis.[150] A more recent report indicated that when patients were treated once a week for 12 months with isoniazid plus rifampin, 5% of the rapid acetylators had an unsatisfactory response; the treatment was completely successful in slow acetylators.[151]

Isoniazid is metabolized to acetylisoniazid and subsequently to acetylhydrazine, which can be converted to a potent acylating agent that produces liver necrosis. This metabolic sequence is the basis for the hypothesis that fast acetylators, who form more acetylisoniazid, are more susceptible to isoniazid-associated liver injury than slow acetylators.

Clinical evidence for this, however, is conflicting.[152] One reason that acetylator phenotype may not be a major determinant of isoniazid-induced hepatitis is that acetylhydrazine is inactivated by acetylation to form diacetylhydrazine, a nontoxic metabolite; this acetylation is subject to the same phenotype as the conversion of isoniazid to acetylisoniazid.[153]

There is a strong correlation of acetylator phenotype between isoniazid and many other drugs, including sulfadiazine, sulfamethazine (sulfadimidine), dapsone, procainamide, hydralazine, and nitrazepam.[145] Sulfanilamide, aminosalicylate, and aminobenzoate are also acetylated but show no correlation with phenotype, suggesting that the enzyme system or rate-limiting step for acetylation of these drugs is different than that of isoniazid. A recent investigation found no correlation between acetylator status and the formation of the acetyl metabolite of acebutolol, a β-blocker.[154] Unlike isoniazid and related drugs, where the acetyl metabolite is formed directly from the parent drug, acebutolol is probably first hydrolyzed to an amine which is then N-acetylated. This hydrolysis step is not genetically controlled and may be rate limiting.

Sulfonamides. Sulfadiazine, sulfamethazine, and sulfapyridine are subject to polymorphic acetylation. Sulfamethazine (sulfadimidine) is widely used to determine acetylator phenotype.[155] Urine is collected for 8 hr after oral administration of sulfamethazine (45 mg/kg) and assayed for unmetabolized sulfamethazine and "total" sulfamethazine. Acetylsulfamethazine is assumed to represent the difference between "total" and unmetabolized sulfamethazine. People who excrete more than 64% of the dose as acetyl metabolite are classified as rapid acetylators; those who excrete less are classified as slow acetylators. Phenotype can also be determined from the concentration ratio of acetylsulfamethazine to sulfamethazine in plasma at certain times after administration of a test dose.

The adverse effects of sulfasalazine are related to acetylator phenotype because it is metabolized by intestinal bacteria to sulfapyridine. Most of the toxic symptoms ascribed to the drug can be related to high serum concentrations of sulfapyridine. One study found that the mean serum concentration of sulfapyridine at steady state in patients with ulcerative colitis treated with sulfasalazine was 54 μg/ml for slow acetylators and 31 μg/ml for fast acetylators.[156] In another study, 24 of 28 patients with ulcerative colitis or Crohn's disease who experienced side effects during sulfasalazine therapy were phenotyped as slow acetylators.[157] Adverse effects to sulfasalazine regularly occur when serum concentrations of sulfapyridine exceed 50 μg/ml.[158]

Dapsone. Dapsone is used in the treatment of leprosy and dermatitis herpetiformis. Acetylation is an important elimination pathway of the drug. Slow acetylators treated with dapsone may be more prone to hematologic side effects; rapid acetylators may require higher doses for effective treatment.[145]

Dapsone has also been used for determining acetylator phenotype by calculating the concentration ratio of monoacetyldapsone (MAD) to dapsone (DDS) in plasma 3 hr after a single 100-mg dose of dapsone. A study of acetylator phenotype in 50 healthy Caucasians found 50% to be rapid acetylators (MAD DDS ratio of 0.14 to 0.28), 44% to be slow acetylators (MAD/DDS ratio of 0.42 to 1.06), and 6% to be of indeterminate phenotype (MAD/DDS ratio of 0.32 to 0.34).[159]

Procainamide. Procainamide (PA) is an orally effective drug for the treatment of ventricular arrhythmias. In patients with normal renal function, more than half the dose is excreted unchanged; from 20 to 40% of the dose is acetylated to give N-acetylprocainamide (NAPA). The amount of NAPA formed depends on the acetylator phenotype of the patient. The steady-state serum concentration ratio of NAPA to PA is about 1.3 in fast acetylators and about 0.5 in slow acetylators.[160] This ratio increases with decreasing renal function because urinary excretion is more important to the elimination of NAPA than to that of PA. For a given dosage regimen, steady-state blood levels of PA will be about 30% higher in slow acetylators than in fast acetylators. Accordingly, fast acetylators may require higher daily doses of PA than slow acetylators, to achieve comparable blood levels.[161]

The long-term use of PA is limited by the development of a systemic lupus erythematosus (SLE)-like syndrome, almost invariably preceded by high titers of antinuclear antibodies (ANA). Early reports estimated the incidence of ANA in PA therapy to be 50%, but with longer duration of therapy it rises to almost 100%. The incidence of clinical lupus has been estimated to be 30% but may be higher with a longer duration of PA treatment.[162]

It is widely held that NAPA is far less likely to induce SLE than is PA. Therefore, the acetylator phenotype of the patient may affect the onset or incidence of PA-related ANA or SLE.

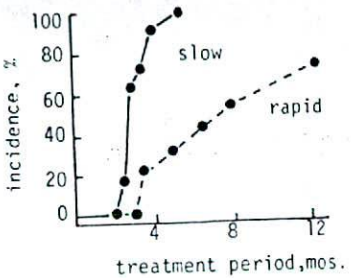

Fig. 12–10. Incidence (expressed as percent of patient population) of development of antinuclear antibodies (ANA) during treatment with procainamide (PA) in slow and rapid acetylators. (Data from Woosley, R.L., et al.[163])

Woosley and co-workers determined the rate of development of ANA in 20 patients, 11 slow acetylators and 9 fast acetylators, receiving chronic PA therapy.[163] As shown in Figure 12–10, the duration of therapy required to induce antibodies in 50% of slow and rapid acetylators was about 3 months and 7 months, respectively. After 5.5 months, ANA had developed in all the slow acetylators, but in only 36% of the rapid acetylators. After 1 year of treatment, antibodies had developed in all but two patients.

These investigators also evaluated the effect of acetylator phenotype on the rate of development of the lupus syndrome in 7 patients, 4 slow acetylators and 3 fast acetylators.[163] The mean duration of therapy before development of lupus was 12 months for the slow acetylators and 54 months for the rapid acetylators. These findings suggest that acetylation of the arylamine group of PA serves as a protective pathway of biotransformation, reducing the amount of drug or reactive metabolite available for initiating the immunopathology associated with drug-induced lupus.

Hydralazine. The metabolism of the antihypertensive drug hydralazine is complicated, but acetylation plays an important role. Plasma concentrations of hydralazine after a standard oral dose vary by as much as 15-fold among individuals, but are lower in rapid acetylators than in slow acetylators.[164] Current dosing guidelines for hydralazine specify a maximum of 200 mg/day for patients with unknown acetylator status and a maximum dose of 300 mg/day for fast acetylators.

Hydralazine, like PA, induces ANA and an SLE-like syndrome. In a study of 57 patients treated with hydralazine for hypertension, a 54% incidence of ANA was found; the incidence was 38% for rapid acetylators and 67% for slow acetylators.[165] More recently, 27 hypertensive patients were treated with hydralazine and followed for evidence of autoimmunity.[166] Acetylation phenotype profoundly affected this response: slow acetylators had a much higher incidence and larger amounts of autoantibodies than rapid acetylators.

Other investigators have studied the role of acetylator phenotype in determining the response to hydralazine in patients with hypertension.[167] Hydralazine was added to diuretic and beta-blocker at doses not exceeding 200 mg daily, consistent with current dosing recommendations for patients with unknown acetylator status. Phenotype was determined with sulfamethazine. About 37% of the 57 patients were classified as rapid acetylators and the rest were considered to be slow acetylators.

The addition of hydralazine satisfactorily lowered blood pressure in only 47% of the patient population. Most rapid acetylators reached the maximum dosage of hydralazine (200 mg/day), but only 27% of these patients were controlled at the end of the 6-month trial. In contrast, satisfactory control of blood pressure was achieved in 65% of the slow acetylators at daily doses of 50 or 100 mg.

The investigators recommended that patients who do not respond to hydralazine at daily doses of 200 mg and for whom continued use of hydralazine at higher dosage is deemed preferable to the use of another drug be phenotyped for acetylator status. They further suggested that about 70% of those evaluated will be rapid acetylators for whom the daily dose of hydralazine may be safely increased to 300 mg or even 400 mg.

Other Drugs. Amrinone is a positive inotropic agent with vasodilatory properties used to a limited extent in the treatment of congestive heart failure. In both animals and man, amrinone has been shown to be converted to its N-acetyl metabolites. Hamilton et al.[168] studied the influence of acetylator phenotype on the pharmacokinetics of amrinone in healthy human subjects. After being phenotyped, the subjects received iv amrinone 75 mg over 10 minutes.

The clearance of amrinone was significantly lower in slow acetylators than in fast acetylators (277 vs 620 ml/min). There was more than a 4-fold difference between the highest clearance in the fast acetylators and the lowest clearance in the slow acetylators. As expected, the ratio of N-acetylam-

rinone to amrinone in urine was much higher in fast acetylators.

Both isoniazid and sulfamethazine have been used to determine acetylator status but these agents may produce adverse effects in certain patients. The search for a safer phenotyping agent has focused on caffeine. The urinary ratios of two caffeine metabolites, 5-acetylamino-6-formylamino-3-methyluracil (AFMU) and 1-methylxanthine (MX) are closely related to acetylation phenotypes determined with the use of sulfamethazine.

Evans et al.[169] administered caffeine, in the form of a cola beverage, to children and adolescents and measured the ratio of metabolites in urine collected over the first 4 hours. Subjects with a molar ratio (AFMU:MX) less than 0.3 were defined as slow acetylators; those with ratios greater than 0.4 were classified as rapid acetylators. Fifteen children were ranked as rapid acetylators, nine were classified as slow acetylators, and two had intermediate metabolic ratios. It is likely that caffeine will become the probe of choice to determine acetylator phenotype.

Polymorphic Oxidation—Debrisoquin Type

The hydroxylation of debrisoquin, an adrenergic-blocker used in the treatment of hypertension is expressed as two phenotypes, designated extensive metabolizer (EM) and poor metabolizer (PM).[170] The ratio of debrisoquin to 4-hydroxydebrisoquin in urine collected for 8 hr after a 10-mg oral test dose of debrisoquin ranged from 0.6 to 1.5 in EM subjects and from 19.3 to 22.9 in PM subjects. The frequency of 4-hydroxylation defect (PM phenotype) was about 3% (3 of 94 subjects).

The metabolism of guanoxan, an antihypertensive drug chemically related to debrisoquin and guanethidine, and phenacetin was studied in healthy subjects previously phenotyped for their ability to hydroxylate debrisoquin.[171] From 31 to 60% of the guanoxan dose was excreted unchanged in the urine in PM subjects, whereas only 1.2 to 1.9% was excreted unchanged in EM subjects. The rate of formation of acetaminophen, an active metabolite of phenacetin, was considerably slower in the PM group than in the EM group. Therefore, the hydroxylation defect shown for debrisoquin also applies to the oxidative metabolism of phenacetin and guanoxan.

More recent studies suggest a correlation of oxidation phenotype between debrisoquin and nortriptyline,[172] phenytoin.[173] metoprolol,[174] phenformin,[175] and perhexiline.[176] but not antipyrine.[172] A correlation was also observed between the plasma clearance of nortriptyline and the debrisoquin to 4-hydroxydebrisoquin urinary excretion ratio in the same individual (Fig. 12–11).[172]

Fig. 12–11. Relationship between nortriptyline clearance (hr per kg) and the urinary excretion ratio of debrisoquin (D) to 4-hydroxydebrisoquin (HD). (Data from Bertilsson, L., et al.[172])

The clinical consequences of polymorphic oxidation continue to be examined. The small percentage of the population who are poor metabolizers may be at risk of adverse effects from the usual doses of many drugs.

Shah and co-workers have suggested a relationship between the incidence of neuropathy in patients with ischemic heart disease treated with perhexiline and the oxidative metabolism status of the patient.[176] The average debrisoquin/4-hydroxydebrisoquin ratio was 14.4 in patients with neuropathy but only 0.65 in patients with no signs of neuropathy.

Debrisoquin and sparteine have been used most frequently to study genetic polymorphism in oxidative metabolism of the debrisoquin type. The impaired metabolism of debrisoquin and sparteine in PMs has been shown to follow Mendelian inheritance. PM subjects are homozygous for an autosomal recessive gene.

The molecular mechanism of impaired drug oxidation is under study in laboratories throughout the world. The findings to date suggest impaired metabolism is the result of the absence of or altered catalytic properties of the P-450 cytochrome involved in the oxidative metabolism of debrisoquin and other drugs.

To better understand polymorphic oxidation, investigators from Germany and Switzerland studied sparteine metabolism in human liver microsomes prepared from liver samples obtained from patients undergoing cholecystectomy.[177] The patients had been phenotyped with sparteine before laparotomy. The ratio of sparteine to the sum of 2- and 5-dehydrosparteine in urine, termed the metabolic ratio (MR), was the basis for phenotyping. The study panel consisted of 6 patients with MR <1 (EMs), 4 patients with MR >20 (PMs), and 3 patients classified as intermediates with MR values ranging from 3 to 18.

In hepatic microsomes from PMs, the Michaelis-Menten constant (K_M) for the formation of 2-dehydrosparteine was 30 times larger than in microsomes from EMs (1880 vs 58 μmol/L). Intermediary metabolizers had an average K_m of 658 μmol/L. The K_m values for 2-dehydrosparteine formation correlated strongly (r = 0.98) with urinary MR values. There were no significant differences in V_{max} values between EM and PM subjects. 5-Dehydrosparteine was detected only in microsomal preparations from EMs. The investigators concluded that "the data obtained in this study indicate that the basis of the differences in oxidative capacity between PMs and EMs is more likely to be the result of a variant isozyme with defective catalytic properties rather than a decreased amount of enzyme."

Difficulty in obtaining debrisoquin as well as its potential for adverse effects have prompted investigators to evaluate other probes for phenotyping. Dextromethorphan (DM) is quickly becoming the agent of choice. There is a strong relationship between dextromethorphan O-demethylation and debrisoquin 4-hydroxylation.

Investigators in Sweden[178] determined serum concentrations of DM and its metabolites in healthy subjects given DM orally. The same subjects were phenotyped using the urinary ratio of debrisoquin and 4-hydroxydebrisoquin; 4 of 29 subjects were classified as PMs.

PMs had very low serum levels of the O-demethylated metabolite of DM, dextromethorphan (D), whereas the serum levels of DM were highest in these subjects. The opposite was seen in EMs. The two groups were characterized by a large difference in DM/D ratio and were easily identified after a single dose of DM. The ratios in PMs were 3.6 or more compared with ratios of 0.11 or less in EMs.

Evans et al.[169] reported the use of dextromethorphan to phenotype children and adolescents. These investigators also found that analysis of urine collected for 4 hours after coadministration of DM and caffeine permits the simultaneous determination of both oxidation (debrisoquin type) and acetylation phenotypes in an individual subject.

Gene frequencies for the loci involved in impaired metabolism may vary among racial and ethnic groups, resulting in differences in polymorphic distribution. A well-established difference between Caucasians and Orientals is the responsiveness to ethanol, involving differences in both alcohol and aldehyde dehydrogenases. More recently, interethnic differences in debrisoquin hydroxylation were studied in healthy white subjects living in the U.S. (n = 183) and Japanese subjects living in Japan (n = 100), using the 8-hour urinary metabolic ratio of debrisoquin to identify EMs and PMs.[179]

In white subjects, the frequency of PMs for debrisoquin was 8.7%. In contrast, no PMs of debrisoquin were found among the Japanese subjects. These findings are important because differences in polymorphic distribution of oxidative drug metabolizing ability have implications for interethnic efficacy and toxicity of drugs and other chemicals metabolized by the involved cytochrome P-450. "Given the international nature of drug development and use and the multiracial nature of the populations of many countries, it appears that the potential for genetically determined interethnic differences in drug responsiveness caused by drug dispositional factors should be given increased recognition."[179]

The relative importance of genetic and environmental factors in determining differences among individuals in debrisoquin hydroxylation was studied in 52 families in Sweden.[180] The major influence on interindividual variation was genetic heritability, accounting for 79% of the variance. Only a minor part of family resemblance was actually due to common culture and environment. The investigators concluded that "the debrisoquin metabolic phenotype seems to be extensively controlled by a monogenic system and not significantly influenced by environmental factors or age."

Genetic polymorphism in oxidative metabolism raises an intriguing question. What other tendencies cosegregate with the metabolism phenotype? There is some evidence that lung cancer is more frequent in EMs than in PMs, suggesting that metabolic activation of environmental carcinogens by

the involved hydroxylase has a part in the disease.[181,182] More recently, differences in personality between EMs and PMs have been reported.[183]

Fifty-one PMs and 102 EMs, matched for age and sex, were evaluated using standardized tests. Significant differences in personality were measured. Scores for PMs implied high vitality, alertness, efficiency, and ease of decision making. Consistent with lack of hesitation in making a decision was the significantly higher frequency of extreme responses in the PMs. The investigators speculated that "the relation between debrisoquin hydroxylation phenotype and personality may indicate that debrisoquin hydroxylase is also involved in the metabolism of endogenous substances important for central nervous system function."

Beta-Blockers. The metabolism of several beta-adrenoceptor blocking drugs (e.g., metoprolol, alprenolol, timolol) appears to be linked to debrisoquin oxidative polymorphism. Poor metabolizers of debrisoquin may have relatively high plasma concentrations of these drugs when treated with usual doses and may be susceptible to adverse effects.

Lewis et al.[184] studied timolol and atenolol in 6 EMs and 4 PMs of debrisoquin. Timolol is extensively metabolized in humans, largely by oxidative pathways. Atenolol undergoes little metabolism and is largely excreted unchanged.

Mean plasma concentration of timolol were more than twice as high in poor metabolizers of debrisoquin than in extensive metabolizers. Beta-blockade, determined by bicycle ergometry, following a 20-mg oral dose of timolol was also greater in PMs than in EMs. At 24 hours after the dose, the mean degree of blockade was 16% in the PMs and 6% in the EMs. Statistically significant correlations were found between the debrisoquin/4-hydroxydebrisoquin ratio in urine after a test dose and the AUC of timolol ($r = 0.75$) as well as between the urinary ratio and the degree of beta-blockade at 24 hours ($r = 0.66$). There was no relation between oxidation phenotype and plasma atenolol levels or the degree of beta-blockade following a single 100 mg dose of atenolol.

Other investigators studied propranolol in EMs and PMs of debrisoquin.[185] Dramatic differences were observed between the two groups with respect to the formation of 4-hydroxypropranolol (4-HP). Total AUC for unconjugated 4-HP following a single 160 mg oral dose of propranolol averaged 21 ng-hr/ml in PMs and 94 ng-hr/ml in EMs. The AUC for total 4-HP, determined after hydrolysis, was also more than 4 times greater in PMs than in EMs. Similar differences in plasma concentrations of unconjugated and total 4-HP were found after multiple oral doses of propranolol. At steady-state, 4-HP accounted for about 20–25% of drug-related material in urine in PMs but for less than 5% in EMs.

Despite the differences in 4-HP plasma levels and urinary recoveries, plasma concentrations of propranolol were about the same in EMs and PMs. Furthermore, although propranolol and 4-HP are equipotent, no difference in beta-blockade was found between the two groups. These findings suggest that formation of 4-HP is a minor pathway in the overall metabolism of propranolol and that 4-HP does not contribute significantly to beta-blockade during treatment with propranolol.

Encainide. Encainide is a class I antiarrhythmic agent recently approved for use in the United States. Disturbing findings suggesting excess deaths in patients treated with encainide, reported shortly after the drug's approval, foreshadow that the use of encainide will be limited in the United States. Nevertheless, its metabolism, pharmacokinetics, and pharmacodynamics are sufficiently interesting to merit discussion.

Encainide is extensively metabolized to form O- and N-desmethylencainide (ODE and NDE); ODE is further metabolized to 3-methoxy-O-desmethylencainide (MODE). Studies in laboratory animals suggest that all three metabolites are active, potency decreasing as follows: ODE > MODE = encainide > NDE.

Early clinical trials with encainide turned up a nonresponder who, paradoxically, had much higher plasma levels of encainide than patients responding to the drug. Further probing indicated that this patient was also a poor metabolizer of debrisoquin. These results prompted Wang et al.[186] to study encainide in EMs and PMs of debrisoquin.

Dramatic differences in the pharmacokinetics of encainide were observed. Total clearance, determined after intravenous administration, was 1.8 L/min in EMs but only 0.22 L/min in PMs. After an oral dose, bioavailability was 26% in EMs and 88% in PMs, reflecting large differences in first-pass metabolism. Plasma levels of ODE after a single oral dose of encainide were more than 10 times higher in EMs than PMs. Substantial plasma concentrations of MODE were also found in EMs but

this metabolite could not be detected in slow metabolizers.

Important differences were also found in the pharmacologic effects of encainide in EMs and PMs. Measurement of ECG changes after 3 days of oral encainide showed a significant delay in intraventricular conduction in EMs but not in PMs. Although poor metabolizers have substantially higher and more persistent levels of encainide than extensive metabolizers, PMs appear to be less responsive to the effects of the drug than EMs. These findings suggest an important role for ODE and MODE in the clinical effects of encainide.

These investigators also studied encainide in 8 patients with ventricular arrhythmias, 2 of whom were phenotyped as PMs of debrisoquin.[187] Encainide suppressed ventricular ectopic beats by greater than 90% in all patients. QRS interval on the ECG was prolonged by 31 to 62% in the 6 EMs and by 22% and 29% in the 2 PMs. At steady-state, encainide concentrations in plasma were about 5 times higher in the 2 PMs than in the EMs. On the other hand, unlike the PMs, the EMs had appreciable levels of both ODE and MODE.

In both PMs, arrhythmia suppression and prolongation of the QRS interval were significantly correlated with encainide levels in plasma. This was not the case in the EMs. Arrhythmia suppression and effects on the ECG in EMs were strongly correlated with concentrations of ODE and MODE.

These findings support the hypothesis that among EMs, who probably constitute more than 90% of the U.S. population, metabolites of encainide are primarily responsible for the clinical effects of the drug. On the other hand, encainide seems to be an effective antiarrhythmic agent in its own right, at least at the high concentrations found in poor metabolizers of debrisoquin.

"In both phenotypic groups, there is an active compound in plasma with a relatively long half-life: ODE in EMs ($t_{1/2}$ = >6 hours) and encainide in PMs (>8 hours)."[187] Frequency of dosing of encainide should reflect these half-lives rather the relatively short half-life of encainide itself, about 3 hours, found in EMs.

More recently, Barbey et al.[188] studied the pharmacokinetics and antiarrhythmic effects of ODE and MODE directly in 9 patients with ventricular arrhythmias, 2 of whom were PMs. Intravenous infusion of both ODE and MODE suppressed chronic ventricular arrhythmias. The clearance of ODE was also a function of debrisoquin phenotype. Mean clearance in EMs was 914 ml/min, with a range from 554 to 1314 ml/min. ODE clearance was 434 ml/min in one poor metabolizer and 298 ml/min in the other. MODE was detected during ODE infusion in all 7 EMs but in neither poor metabolizer. The clearance of MODE in EMs ranged from 180 to 410 ml/min. MODE clearance in one PM was well within this range but was only 78 ml/min in the other. Whether MODE clearance is a function of metabolic phenotype requires a larger panel of subjects to answer.

Propafenone. Propafenone is a new antiarrhythmic agent undergoing clinical testing in the U.S. At least one active metabolite of propafenone is recognized, 5-hydroxypropafenone, with antiarrhythmic properties similar to the parent drug. Large variability in blood levels has been observed during the early clinical trials with propafenone. Some patients, for no obvious reason, exhibit unusually long half-lives and high plasma levels.

The occurrence of high blood levels and slow elimination in a small fraction of the patients taking propafenone prompted Siddoway and his colleagues[189] to consider the possibility of polymorphic metabolism. These investigators studied the pharmacokinetics and pharmacodynamics of propafenone in symptomatic patients with more than 30 ventricular ectopic depolarizations (VEDs) per hour, who had been phenotyped with debrisoquin.

The half-life of propafenone was 5.5 hr in EMs and 17.2 hr in PMs. The apparent clearance after oral administration was about 4 times greater in EMs than in PMs, 1115 vs 264 ml/min. The concordance between debrisoquin and propafenone metabolism suggest a low capacity for hydroxylation of propafenone in PMs. Consistent with this hypothesis, the ratio of propafenone to the 5-hydroxy metabolite is much smaller in EMs than in PMs.

Surprisingly, the relationship between propafenone dose and concentration in plasma was also different in EMs and PMs. A total of 17 patients (13 EMs and 4 PMs) received doses of 600 mg/day and 900 mg/day. This 50% increase in dose, as expected, resulted in a mean increase of about 50% in steady-state trough levels in PMs, from 1340 to 2030 ng/ml. In EMs, however, this modest increase in dose resulted in more than a 200% increase in drug levels. These results suggest that the pharmacokinetics of propafenone are markedly nonlinear in EMs, whereas, over the dosage range

studied, the kinetics of propafenone appear to be linear in PMs.

The nonlinear kinetics of propafenone have been confirmed by Zoble et al.[190] These investigators followed 169 patients of unknown phenotype with chronic ventricular arrhythmia during treatment with various doses of propafenone. They found that for a doubling of the daily dose from 450 to 900 mg/day, mean steady-state trough propafenone concentrations increased 4.3-fold.

Siddoway et al.[189] also reported that the trough plasma concentrations of propafenone at which more than 70% suppression of VEDs was realized ranged from 40 to 1800 ng/ml. This range could be divided into two groups, based on metabolic phenotype: 42–1356 ng/ml for EMs and 1408–1801 ng/ml for PMs. Although higher levels of propafenone are found in PMs, this group appears to be less sensitive to the antiarrhythmic effects of the drug. Consequently, there were no significant differences in the mean effective dose of propafenone for EMs and PMs, 828 mg/day vs 800 mg/day, respectively.

In another study, examining the effects of food on the bioavailability of propafenone, Axelson et al.[191] found that food had no effect in poor metabolizers of propafenone, but resulted in a marked increase in bioavailability in extensive metabolizers. Bioavailability was increased by 250%, on the average. There was a strong correlation between the food-related increase in AUC and the fasting AUC. Those subjects showing the largest change in propafenone AUC due to food had the lowest AUC after oral administration of propafenone in the fasting state.

Other Drugs. Imipramine is eliminated by demethylation to the active metabolite desipramine and both imipramine and desipramine are subject to 2-hydroxylation. The demethylation of imipramine and the 2-hydroxylation of both drugs are carried out by at least two different isozymes of cytochrome P-450. The 2-hydroxylation expresses the activity of the isozyme also known to oxidize debrisoquin, sparteine, and other drugs.

Brosen and Gram[192] administered imipramine and desipramine intravenously and orally to extensive and poor metabolizers of sparteine. They assumed that the absorption of both drugs was complete and calculated the extent of first-pass metabolism in each subject. Consistent with theory, the mean degree of first-pass metabolism of imipramine was about 60% in EMs but only 30% in PMs. In other words, about 40% of a 50-mg oral dose of imipramine was systemically available in EMs compared with 70% of the dose in PMs.

Desipramine showed similar results but a closer relationship was found between the extent of first-pass metabolism and metabolic ratio (MR), determined from the ratio of sparteine to dehydrosparteine in a 12-hour urine sample. Mean first-pass metabolism was 44% in EMs with an MR of 0.31 or less, 27% in EMs with MR values ranging from 0.72–0.98, and 14% in PMs with MR values ranging from 62–140.

There is also evidence that the metabolism of flecainide, an orally effective antiarrhythmic agent, is under monogenic control. Interestingly, flecainide like encainide has been found to produce excess deaths in patients treated for arrhythmias. Flecainide is both metabolized and excreted unchanged. Urinary excretion is pH-dependent.

Mikus et al.[193] administered oral flecainide to extensive and poor metabolizers of the debrisoquin type. Urine pH was controlled, on the acid side, with oral ammonium chloride given before and after flecainide. This measure decreased variability but also maximized the urinary excretion of unchanged drug.

The average clearance of flecainide, assuming complete absorption and no first-pass effect, was 1,041 ml/min in EMs and 600 ml/min in PMs. Renal clearance, measured directly, was 315 ml/min in EMs and 308 ml/min in PMs. Renal excretion accounted for about 30% of the overall elimination of flecainide in EMs and for about 50% in PMs.

Mikus and his colleagues have shown that the total clearance of flecainide is dependent on debrisoquin phenotype whereas its renal clearance is not. The difference between total clearance and renal clearance is called the nonrenal clearance and in some cases may faithfully reflect metabolic clearance. Nonrenal clearance of flecainide was calculated to be 726 ml/min in EMs and 292 ml/min in PMs.

The investigators concluded that "under conditions of uncontrolled urinary . . . pH, renal excretion of flecainide will be reduced and the difference in disposition will be greater. In PMs with renal impairment, accumulation of flecainide to very high levels may be anticipated, and this may result in proarrhythmic effects." In patients with renal impairment, flecainide levels will be elevated in both PMs and EMs unless dosage is adjusted.

In patients with no renal function, one may calculate from the nonrenal clearance values reported in this study that flecainide levels will be 2.5 times greater in PMs than in EMs.

Polymorphic Oxidation—Mephenytoin Type

Poor hydroxylators of phenytoin have been recognized for about 25 years. These individuals are at risk of severe adverse effects because hydroxylation is the principal elimination pathway for phenytoin. Many investigators believe that this problem is an inherited one, but evidence for concordance with the debrisoquin phenotype has not been forthcoming.

The hydroxylation of mephenytoin, a closely related drug, also demonstrates polymorphism. In one study,[194] the urinary excretion of hydroxymephenytoin was determined after a single oral dose of mephenytoin in 118 Caucasians and 70 Asians. The urinary excretion of the metabolite was bimodal in these populations; 13% of the Asians and 4% of the Caucasians were classified as poor metabolizers. Hydroxymephenytoin accounted for about 40 to 45% of the dose of mephenytoin in EMs but for only 1 to 3% for the dose in PMs. Family studies have suggested that deficient hydroxylation of mephenytoin is genetically determined.

Mephenytoin is a racemate and its metabolism is stereoselective; hydroxylation strongly favors the S-enantiomer. It follows that the ratio of S- to R-mephenytoin in urine will be very small in EMs but nearly 1.0 in PMs. Wedlund et al.[195] tested this hypothesis by determining the urinary recovery of hydroxyphenytoin and the urinary S:R enantiomeric ratio of mephenytoin after a single 100-mg dose of mephenytoin.

On the basis of urinary excretion data, 4 of the 156 Caucasians studied were classified as PMs of mephenytoin. These individuals excreted negligible quantities of the hydroxy metabolite, whereas the rest of the panel excreted about 40% of the dose as hydroxymephenytoin. The mean S:R ratio of mephenytoin was 0.99 in the 4 PMs but only 0.16 in the EMs. This difference is consistent with the stereoselective metabolism of mephenytoin in EMs but not in PMs.

The panel was also phenotyped with debrisoquin. Using this probe, 11 subjects (7%) were classified as PMs. All 4 poor metabolizers of mephenytoin were classified as extensive metabolizers of debrisoquin and all 11 poor metabolizers of debrisoquin were found to be extensive metabolizers of mephenytoin. On the basis of these results, the investigators concluded that "4-hydroxylation of mephenytoin is a new polymorphism independent of that for debrisoquin."

More recently, Wedlund et al.[196] determined the plasma levels of the enantiomers of both mephenytoin and its pharmacologically active N-demethylated metabolite, phenylethylhydantoin (PEH), after a single oral dose of mephenytoin in subjects who had been phenotyped. In extensive metabolizers of mephenytoin, substantial plasma levels of both R-mephenytoin and R-PEH were measured, whereas very low levels of the S-form of mephenytoin and its metabolite were seen. A 100- to 200-fold difference in the oral clearance of S- and R-mephenytoin was calculated. Average values were 4700 ml/min for the S-enantiomer and 27 ml/min for the R-enantiomer. Mean half-lives were 2 hours for S- and 76 hours for R-mephenytoin.

In these same extensive metabolizers, R-PEH concentrations accumulated over several days after a single dose of mephenytoin and then declined with a half-life of about 200 hours. Plasma levels of S-PEH were negligible.

A different picture emerged in poor metabolizers of mephenytoin. The stereoselective elimination of mephenytoin essentially disappeared. Average oral clearance values in PMs were 29 ml/min for S-mephenytoin and 20 ml/min for R-mephenytoin. Almost comparable plasma levels of S- and R-PEH were also found. The investigators suggested that such large differences between EMs and PMs would be expected to have clinical consequences for both desired and untoward effects of mephenytoin when it is used as an anticonvulsant.

The rate of 4-hydroxylation of S- and R-mephenytoin has also been studied in human liver microsomes from 13 extensive metabolizers of mephenytoin and 2 poor metabolizers.[197] Microsomal metabolism of S-mephenytoin in the two subjects classified as PMs was characterized by a larger K_m (150 and 180 μmol/L versus a mean value of 38 μmol/L in EMs), a smaller V_{max} (0.8 and 0.7 nmol/mg protein per hour versus a mean value of 4.8 nmol/mg protein per hour in EMs), and loss of stereoselectivity. On the other hand, the formation of 4-hydroxymephenytoin from R-mephenytoin was not dependent on mephenytoin phenotype. The investigators concluded that "these results support our hypothesis that the mephenytoin polymorphism is caused by a partial or complete absence or in-

activity of a cytochrome P-450 isozyme with high affinity for S-mephenytoin."

Not surprisingly, reports are now being published suggesting that the metabolism of many drugs may be influenced by the mephenytoin phenotype. For example, Kupfer and Branch[198] found that the metabolism of mephobarbital cosegregates with mephenytoin hydroxylation. They measured the 8-hour urinary recovery of 4-hydroxymephobarbital (4-HP) after a single oral dose of racemic mephobarbital in 17 EMs and 6 PMs of mephenytoin.

The recovery of 4-HP in EMs ranged from 2.5 to 48%, with a mean value of about 10%. No metabolite was detected in the urine of poor metabolizers of mephenytoin. One extensive metabolizer received similar doses of R- and S-mephobarbital on separate occasions. Urinary recovery of the 4-hydroxy metabolite was 33% of the dose when R-mephobarbital was given but less than 1% of the dose when S-mephobarbital was administered. Studies as to absolute configuration have shown that S-mephenytoin is the analog of R-mephobarbital. Based on their findings, Kupfer and Branch suggested that "mephobarbital is stereoselectively hydroxylated by the same drug metabolizing enzyme that is responsible for the stereoselective aromatic hydroxylation of mephenytoin."

Investigators in Sweden studied the importance of genetic factors in the metabolism of diazepam.[199] They administered single oral doses of diazepam and its metabolite, desmethyldiazepam (DMD), on separate occasions to 4 poor metabolizers of debrisoquin, 3 poor metabolizers of mephenytoin, and 9 extensive metabolizers of both drugs.

Among the 16 subjects, a statistically significant correlation ($r = 0.83$) was found between the total plasma clearance of diazepam and that of DMD. There was no relationship between diazepam or DMD disposition and debrisoquin status. Diazepam clearance was 22 ml/min in EMs and 26 ml/min in PMs of debrisoquin. However, poor metabolizers of mephenytoin had less than half the plasma clearance of both diazepam and DMD than extensive metabolizers. Mean diazepam clearance was 26 ml/min in EMs and 12 ml/min for PMs of mephenytoin. Corresponding values for DMD were 11 ml/min and 5 ml/min. Mean half-life of diazepam was 88 hours in PMs and 41 hours in EMs. "This study shows that the metabolism of diazepam (mainly demethylation) and desmethyldiazepam (mainly hydroxylation) is related to the mephenytoin but not to the debrisoquin hydroxylation phenotype."[199]

Ward et al.[200] examined the relative contributions of the debrisoquin and mephenytoin isozymes to the stereoselective metabolism of oral propranolol in a panel of healthy subjects who had been phenotyped. Six subjects were extensive metabolizers of both drugs (EM), 4 were poor metabolizers of debrisoquin (PM_D), 5 subjects were poor metabolizers of mephenytoin (PM_M), and 1 subject was a poor metabolizer of both drugs ($PM_{D,M}$).

The total oral clearance of R-propranolol was significantly greater than that of the S-form in the EM, PM_D, and PM_M groups. The highest mean clearance of R-propranolol was seen in the EM group (2666 ml/min) and the lowest values occurred in the one individual who was deficient for both drugs (918 ml/min). Oral clearance values in the other two groups were similar and intermediary, 1860 ml/min for the PM_D group and 2012 ml/min for the PM_M group. The same pattern emerged for S-propranolol.

The partial metabolic clearance of each propranolol enantiomer to 4-hydroxypropranolol in the PM_D group was only about 25% that found in the EM and PM_M groups, suggesting a major contribution of the debrisoquin isozyme to this route of metabolism. The partial metabolic clearance to naphthoxylactic acid (NLA) in the PM_M group was about half that found in the EM and PM_D groups, suggesting that the mephenytoin isozyme contributes to the metabolic conversion of propranolol to NLA.

It appears that the 4-hydroxylation of propranolol cosegregates with the debrisoquin polymorph but the side-chain oxidation of propranolol to NLA is catalyzed in part by the mephenytoin isozyme. Propranolol is the first drug identified where two independent isozymes of cytochrome P-450, identified as being responsible for debrisoquin and mephenytoin hydroxylation, contribute to the two separate oxidative pathways. A deficiency in both routes will probably result in impaired total clearance of propranolol.

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