

# Pharmacokinetics in the Elderly

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Animals undergo substantial changes in many physiologic and biochemical functions as a natural consequence of aging. In the absence of disease or other pathologic conditions, these changes occur in a gradual manner with time (generally expressed as a fractional or percentage change in that function per year or decade). Furthermore, for any given function and at any given chronologic age, there is large variation in that function among individuals. Given the increase in life expectancy, the substantial increase in the number of elderly (and aged elderly) in the population, and the escalating costs of health care, there is great interest in learning more about the risks associated with aging as a result of toxic exposure. Are the elderly at greater risk than younger adults to the toxic effects of drugs and environmental exposure? Is the elderly population an inherently more sensitive one? — *Environ Health Perspect* 102(Suppl 11):119–124 (1994)

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## Introduction

This brief review will examine the changes with age in the processes of disposition that drugs and toxic agents undergo in the body: absorption, distribution, excretion, and metabolism. Gastrointestinal absorption appears to be unimpaired with age in terms of the completeness of absorption (rate is often reduced), with the possible exception of those compounds having a high hepatic extraction ratio (i.e., high hepatic clearance). Absorption by other routes, including pulmonary and dermal, has not been well studied. Distribution may be altered, depending upon the chemical characteristics of the compound, as a result of reduced plasma protein binding (in response to a decrease in plasma albumin concentrations) and anatomical changes (especially an increase in the percentage body weight that is fat and a decrease in the lean mass). Renal function declines with age, which affects the clearance and elimination half-life of renally excreted compounds (and their metabolites). Hepatic clearance either decreases or remains unchanged but it is difficult to make any general rules because metabolism is affected by numerous factors. It appears that phase I processes are more affected by age than phase II reactions.

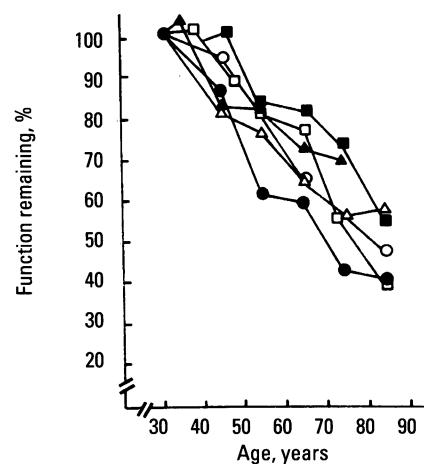
In recent years, there has been considerable interest in understanding how aging in humans may influence the disposition of

and the response to drugs and toxic agents. In addition to having recognized that age is a variable that may alter drug response and disposition in laboratory animals and, therefore, an analogous situation probably would exist among humans, the current interest in aging is driven by several factors. These considerations make the elderly a unique group within the population. Considerations involving the elderly, in comparison to younger adults, include the increasing percentage of elderly people as well as the aged elderly (those over 75 years) in the population (the “baby-boomers” have now reached middle age); a greater incidence of disease and physiological impairments; occupation of a greater percentage of hospital beds and long-term care facilities; greater drug ingestion per capita; and greater incidence of adverse drug effects and drug–drug interactions.

While there has been a substantial increase in the quality and quantity of the gerontology literature during the past decade, unanswered questions and numerous conflicting reports remain. The early literature particularly suffers from inadequate controls, poor experimental design, and insufficient methods of data analysis. Nowhere is this more apparent than in the pharmacokinetics literature in gerontology. These issues as well as a review of drug disposition in the elderly have been discussed elsewhere (1). It would be useful to keep in mind several of these concerns. For example, chronological age per se, while it is the only definition of age currently available, is a poor and variable predictor of biological activity (or function). Furthermore, what age defines elderly? Very often 65 years is used for such a demarcation, but this would appear to be artificial and without justification. Most studies are designed to

be cross-sectional rather than longitudinal; while the former provides results allowing conclusions about differences between ages, the latter gives more useful information about changes with age.

Figure 1, which is a plot of the percentage function remaining versus adult age, indicates a particularly important concept, body functions decline gradually at a relatively constant rate over time. This continuum tends to illustrate the uselessness of an arbitrary age to delimit young from elderly (1,2). The following discussion will attempt to summarize our current understanding of how aging influences the processes of drug disposition.



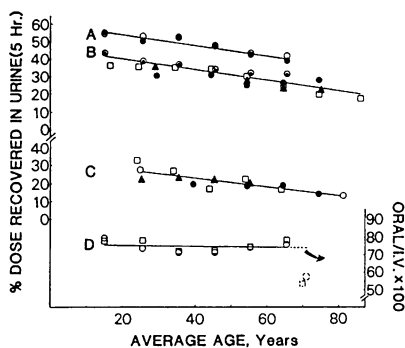
**Figure 1.** Percentage of function remaining versus age. The values shown are relative to those at age 30 years. (●) Maximal breathing capacity; (□) renal plasma flow by para-amino hippurate clearance; (○) renal plasma flow by diodrast clearance; (△) vital capacity; (■) glomerular filtration rate by inulin clearance; (▲) cardiac index. From Mayersohn (1) and Rowe and Besdine (2); reprinted with permission.

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## Absorption

The earlier gerontology literature contained numerous incorrect statements concerning the completeness of gastrointestinal absorption, and often the conclusion was that absorption declined with advancing age. This conclusion was based primarily upon poorly designed experiments, poorly analyzed data, or both. Perhaps the best illustration of this statement are studies conducted with *d*-xylose, which is often used as a diagnostic agent to assess malabsorption syndromes. The test procedure (often referred to as the xylose tolerance test) involves oral ingestion of 5 or 25 g *d*-xylose in solution and a subsequent total 5-hr urine collection. An analysis of the literature resulted in the relationships shown in Figure 2 (3). Reduced 5-hr urinary xylose recovery is seen as a function of adult age following 5- or 25-g oral doses (Figure 2B,C). This has been interpreted as indicating reduced intestinal absorption with advancing age. However, this does not explain a similar age dependence following an intravenous dose (Figure 2A), which, of course, cannot be a result of altered absorption. The ratio of urinary recoveries following oral and intravenous dosing (Figure 2D, y-axis on right) indicates constant fractional absorption with age. The explanation for these relationships has nothing to do with absorption but is a reflection of altered renal excretion of xylose, which, as will be discussed later, declines as a natural consequence of aging. A subsequent study of *d*-xylose absorption experimentally confirmed this conclusion (4). The neglect of some basic pharmacokinetic principles in study design and data analysis has



**Figure 2.** Percentage of xylose dose recovered in a 5-hr urine collection as a function of average age. Symbols reflect data obtained from different studies. (A) 5-g iv dose; (B) 5-g oral dose; (C) 25-g oral dose; (D) oral to iv urinary xylose recovery (y-axis on right) after a 5-g oral and 5-g iv dose. From Mayersohn (3); reprinted with permission.

resulted in incorrect conclusions about age-related alterations in drug disposition.

There are a number of changes that occur during aging, which may have an impact on absorption. These considerations include gastrointestinal pH and fluid contents, gastric emptying and intestinal transit rates, and gastrointestinal blood flow and effective membrane surface area. Other factors to consider would be alterations in nutritional intake and eating habits, the presence of age-related gastrointestinal disease states or disorders, and drug ingestion, which alters the absorption of other drugs.

The incidence of achlorhydria dramatically increases in the aged (5), and the resulting lack of acidity may have an effect on the dissolution of basic compounds and certain solid dosage forms that require an acid environment for disintegration and dissolution. Furthermore, some compounds administered as pro-drugs, such as chlorzapatate, must undergo acid hydrolysis in order to produce the pharmacologically active moiety (in this case *N*-desmethyldiazepam). To date there is no indication that gastrointestinal pH changes per se in the elderly are responsible for important alterations in absorption. There is a similar lack of information concerning the impact of age-altered gastrointestinal fluid contents and volume on absorption (e.g., bile secretion, enzyme concentrations, etc.).

Because the small intestine is the major site of absorption, any delay in movement from the stomach to the small intestine would result in a delay in absorption. This is a result of its large surface area. Gastric emptying rate or time is a measure of that transit, and it is influenced by a host of physical and chemical factors. The influence of age per se remains unresolved with two studies indicating a reduction in emptying rate and two additional studies reporting no change (6). A slowing of emptying will reduce the rate of absorption (and onset of response), but it should have little influence on the completeness of absorption, unless the compound is chemically unstable in gastric fluids. An example of the latter situation would be L-dihydroxyphenylalanine (L-DOPA), which is metabolized by decarboxylase enzymes present in the gastric mucosa (7). As noted for those compound absorbed high in the small intestine by an active process (e.g., riboflavin and ascorbic), in some instances a delay in emptying may actually increase absorption efficiency (8,9). For the latter vitamins, however, aging does not appear to influence the efficiency of absorption (A

Lopez-Anaya and M Mayersohn, unpublished data).

There is little information concerning the relationship between age and intestinal transit rates. The latter may be important in that prolonged residence in the intestinal tract might promote dissolution and absorption, whereas rapid transit would have the opposite effect. The general impression is that aging is associated with reduced gastrointestinal muscle tone and, therefore, decreased intestinal motility and perhaps prolonged transit times. However, one study suggests no difference in small intestinal transit times between an elderly group and a group of young subjects (10).

The gastrointestinal tract is well perfused by blood flow, which is consistent with absorption being one of its major functions. Normally, except for compounds with extremely high permeability coefficients, blood flow does not appear to rate-limit absorption. There is a reduction in splanchnic blood flow with aging (11) that might, under certain exacerbating circumstances (e.g., congestive heart failure), become the rate-limiting step in absorption. The reduced blood flow may decrease absorption rate in general.

The mucosal surface area appears to be reduced by about 20%, as determined in a group of elderly (60–73 years) compared to younger adults (16–30 years) (12). This decrease in surface area, unless there is a compensating increase in membrane permeability, would imply a reduction in absorption rate. Indeed, alterations of several of the factors noted above in the elderly (i.e., gastric emptying, intestinal transit, blood flow, surface area) would suggest a decrease in absorption rate. A review of the relevant literature supports that suggestion (1). As a general conclusion, the completeness of gastrointestinal absorption is unaltered with aging, but there is often a reduction in the rate of absorption.

The only exception to the general rule of unaltered completeness of absorption in the elderly is a group of compounds whose systemic absorption may increase with aging. Compounds with a high hepatic clearance (or high extraction ratio) undergo extensive hepatic first-pass metabolism and, if hepatic clearance declines with age, the absorption of the parent compound will be greater in the elderly adults compared to younger adults. There are now several drug examples to support this suggestion (e.g., L-DOPA, chlormethiazole, propranolol, lidocaine, nalbuphine) (13).

Unfortunately, little can be said about the influence of aging on the extent or rate of absorption across other membranes associated with different routes of administration (e.g., intramuscular, subcutaneous, rectal, pulmonary, dermal). One recent study indicates lower dermal penetration of hydrophilic compounds in the aged human skin but no age relationship for two lipid-soluble compounds (14). In terms of drug dosing and environmental exposure, these are relevant routes that require further study to determine the relationship between aging and absorption.

## Distribution

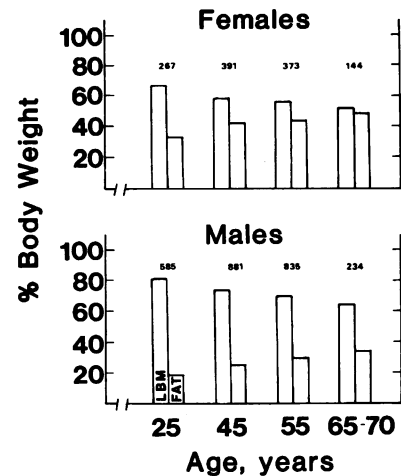
One needs to consider a variety of factors whose alteration with aging may have an impact upon the rate and extent to which a molecule distributes throughout the body. The major considerations include plasma protein concentration, body composition, blood flow, tissue-protein concentration, and fluid pH. Alterations in any of these factors will often express themselves in the value of the apparent volume of distribution of the compound or the apparent space that it occupies relative to blood concentration.

Alterations in plasma protein binding are particularly important because, depending upon the characteristics of the compound, such changes may modify the values of clearance and apparent volume of distribution and elimination half-life (1). Furthermore, such changes may alter the resulting steady-state unbound and bound blood concentrations that, in turn, affect the magnitude of response (1). Albumin, which is the major drug-binding protein in serum, decreases in concentration with age, and this decrease becomes more apparent during illness (15-17). An alteration in binding in the absence of a reduction in serum albumin concentration would indicate that factors other than protein concentration are involved. A likely possibility would be the presence of other drugs being ingested or the presence of metabolites of the drug that compete for binding (18). The role of such additional complicating factors that affect binding might not be recognized by determining binding in spiked blank plasma. This is in contrast to the determination of binding using authentic plasma samples (i.e., plasma from a subject ingesting the drug). In reviewing the literature about the relationship between plasma protein binding of drugs and age, one notes frequent inconsistencies and contradictions. Furthermore, the correlation coefficients for such rela-

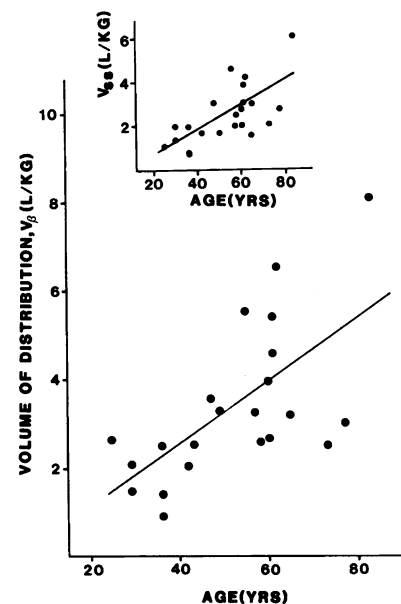
tionships are low (1). In general, plasma protein binding (usually involving albumin) either decreases or remains unchanged as a function of age. A possible exception to this rule is binding of basic compounds to the acute phase protein,  $\alpha_1$ -acid glycoprotein, whose concentrations may rise in response to a variety of diseases and disorders prevalent in the elderly and, in turn, may increase the degree of drug binding (e.g., propranolol) (19,20). It is not clear whether concentrations of this protein increase as a natural consequence of aging because the results of one study have shown no such age relationship in 68 normal subjects (21).

In contrast to plasma protein binding, we know far less about tissue binding processes and how they may change in response to age and other factors. The reason for this is the experimental difficulty in measuring tissue binding *in vitro* without disrupting the integrity of the tissue and its protein content. There may be reason to suggest decreased tissue binding in the aged as a result of reduced tissue mass and protein loss; however, there is little if any direct evidence to support that contention. Often, changes in tissue protein binding of a drug (actually a compartmental tissue or region in an abstract pharmacokinetic model) is inferred from the analysis of plasma concentration-time data. For example, if there is a change in the apparent volume of distribution of the compound in the absence of a change in plasma protein binding, one is tempted to conclude that there has been a change in tissue binding of the drug. Such is the case for the cardioactive drug, digoxin, whose reduced apparent volume of distribution and myocardium/serum concentration ratio in the presence of impaired renal function appears to reflect reduced muscle tissue binding of the drug (22).

A second major factor contributing to an age-dependent alteration in distribution is the change in body composition whose effect on distribution will in turn be a function of the physicochemical characteristic of the drug. This change in terms of lean body mass and fat for both females and males is shown in Figure 3. When expressed as a percentage of body weight, lean mass decreases while fat mass increases with age for both genders. This change results in an age-dependent decrease in the apparent volume of distribution for a water-soluble compound such as ethanol (23) and an increase in volume for a lipid-soluble drug such as thiopental (24). The latter relationship is illustrated in Figure 4.

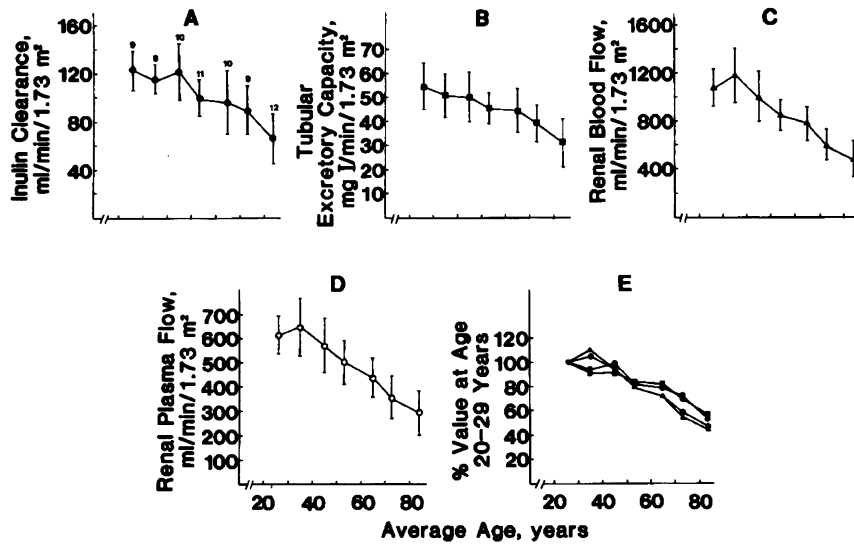


**Figure 3.** Percentage of body weight in males (bottom) and females (top) as a function of age and expressed as lean body mass and fat. The numbers above the bar graphs are the number of subjects. From Mayersohn (1); reprinted with permission.



**Figure 4.** Relationship between the apparent volume of distribution ( $V_d$ ) and the steady-state volume of distribution ( $V_{ss}$ , shown in the inset) of thiopental and age in 22 lean female subjects undergoing surgery. The solid lines represent linear regression analysis of the data:  $V_d$ ,  $r = 0.64$ ,  $p < 0.001$ ;  $V_{ss}$ ,  $r = 0.70$ ,  $p < 0.001$ . From Jung et al. (24); reprinted with permission.

Therefore, the direction of change of the apparent volume of distribution is a function of the solubility characteristics of the compound. Assuming there is no change in plasma protein binding, water-soluble compounds would be expected to show a decrease in the apparent volume, while



**Figure 5.** Various parameters of renal function versus average age in males. (A) Inulin clearance (●). (B) Tubular excretory capacity expressed as the transport maximum (T<sub>m</sub>) of iodopyracet (Diodrast) (■). (C) Renal blood flow (▲). (D) Renal plasma flow as measured by Diodrast clearance (○). (E) The values in A through D expressed as a percentage of the value of the youngest age group (20–29 years). The cross-hatched vertical bars represent the standard deviation, and the numbers above the bars in A are the number of subjects in each age group. From Mayersohn (29) and Davies and Shock (30); reprinted with permission.

lipid-soluble compounds would be expected to evidence an increase in volume. In reviewing the relationship between apparent volume and age for any given compound, only poor correlation coefficients were noted (1).

Cardiac output and cardiac index are known to decline substantially with age, and there is large variability among subjects in the degree of that change (25). In contrast to this conclusion, a more recent study indicates that there is no relationship between cardiac output and age when subjects with no evidence of coronary artery disease are selected for study; however, large variation among subjects at any given age remains (26). Therefore, age per se may not be associated with a decline in cardiac output. Any changes in blood flow that occur are not uniform throughout the body; cerebral flow declines at a slower rate with age in comparison with flow to the liver and kidney. This decrease in flow needs to be considered in relation to the organ or tissue weight, which may also decline with age. As a result, the effective flow per tissue weight may not decrease to an extent suggested by the absolute value of flow.

Reduced blood flow to eliminating organs may be important for those compounds that have a high clearance or extraction ratio (compounds that are non-restrictively cleared) because the elimination of such compounds depends upon blood flow. Furthermore, assuming there is

no change in distribution, the reduced clearance of such compounds will produce an increase in half-life as a result of decreased blood flow. Altered blood flow to sites of action may result in an increase in the onset time for a response to be initiated.

### Renal Excretion

Renal excretion of drugs (and metabolites) into the urine represents one of the major routes of elimination, in addition to hepatic metabolism. The influence of aging on renal function has been thoroughly studied. While there is considerable variation at any given age, all aspects of renal function appear to decline with age. In contrast to hepatic metabolism, one can accurately assess various aspects of kidney function such as glomerular filtration rate with measurements such as creatinine or inulin clearance. Processes of active secretion and reabsorption may also be accurately estimated. Quantitative relationships between drug elimination (usually measured as clearance or elimination rate constant) and creatinine clearance have been developed for many drugs, and they serve an important clinical function in being able to adjust a dosing regimen for renal impairment.

Creatinine clearance is the most frequently used index of glomerular filtration rate, primarily because creatinine is an endogenous material that makes it unnecessary to administer an exogenous compound. The measurement involves

determination of urinary creatinine excretion (often during 24 hr) and a serum creatinine concentration. Interestingly, while creatinine excretion decreases with age, there is little change in serum creatinine concentration. The steady-state serum creatinine concentration ( $S_{CR}$ ) may be written as a function of formation and elimination,  $S_{CR} = \text{production rate}/CL_{CR}$ , where production rate represents formation and creatinine clearance ( $CL_{CR}$ ) represents elimination. For  $S_{CR}$  to remain constant while  $CL_{CR}$  decreases with age, the production rate must be decreasing parallel to clearance. The latter is consistent with the biochemistry of creatinine, which is an end product of muscle metabolism. Because there is a reduction in muscle mass with aging, it is reasonable to expect that the production of creatinine will also decline. One important aspect of this relationship is that one cannot evaluate renal function across ages by measurement of serum creatinine concentration only, in the absence of any kidney disease. However, since  $S_{CR}$  is often a measured blood biochemistry value, it would be useful to be able to relate that value to creatinine clearance. One such relationship that incorporates several variables (body build or weight, age, gender) is given by (27)

$$CL_{CR} \text{ (ml/min)} =$$

$$\frac{[\text{ideal weight, kg}] [140 - \text{age, yr}]}{72 \times S_{CR} \text{ (mg\%)}}$$

The above relationship needs to be multiplied by 0.86 for females (as a result of a smaller muscle mass).

As the kidney ages, it undergoes anatomic and physiologic changes, including a decrease in mass and a reduction in the number and size of the nephrons (28). These changes are reflected in virtually all aspects of renal function, as shown in Figure 5 (29,30). It is particularly interesting to note that these various measures with age almost superimpose when they are expressed as a percentage of the youngest age group. This observation has been expressed as the intact nephron concept, which states that all aspects of kidney function decline uniformly. Therefore, as a general rule, renal clearance of compounds excreted by the kidney will decline with age and the elimination half-life will increase with age.

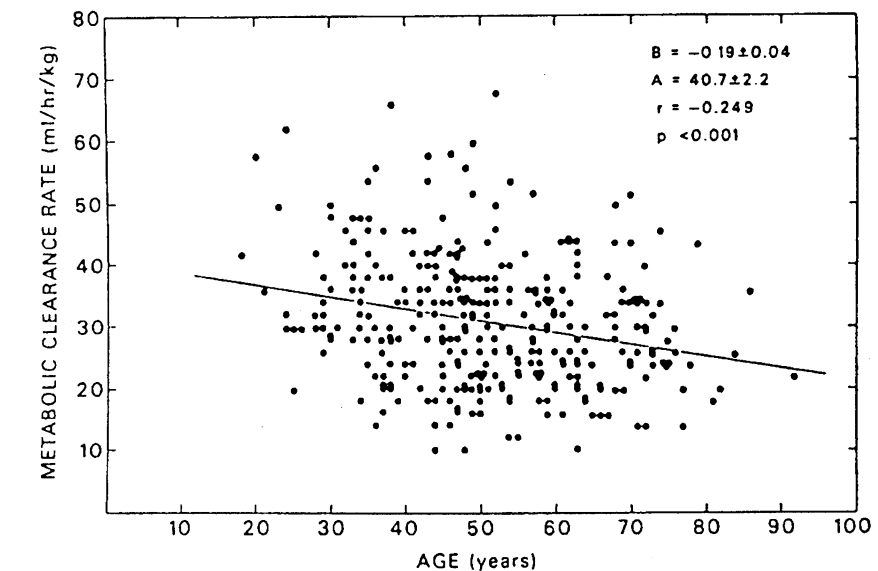
### Hepatic Metabolism

Hepatic metabolism and its relationship with aging is the most difficult of all of the

dispositional processes to discuss and reach general conclusions. There are at least two major reasons for this difficulty. First, unlike renal function, there is no measurement that is quantitatively related to and would allow us to assess hepatic metabolic function. Second, again unlike renal function, there are a host of factors that contribute to the enormous variability in hepatic function among subjects (i.e., factors that affect intrinsic enzymatic activity). The latter is true even within a normal, healthy, well-defined population of subjects of similar ages. Consider variability expected as a result of the following factors: blood flow, concurrent drug use (including alcohol, drugs of abuse, and caffeine), disease or physiologic disorders, environmental exposure (including smoking), gender, genetic differences, liver mass, nutritional intake, and physical condition. As a result, it is not surprising that it is extremely difficult to factor out age as a separate variable among the host of other considerations. To do so would require extreme care in the selection of subjects, the design of the study, and controlling as many variables as possible.

In a manner similar to the kidney, the liver undergoes a number of changes with age that includes a reduction in blood flow (31) and mass (or volume) (32,33). Reduced blood flow might suggest a reduction in the clearance of those compounds with a high hepatic clearance (or high extraction ratio, nonrestrictively cleared). It is more difficult to interpret the changes in liver mass. Several studies have shown a direct correlation between liver mass and clearance of compounds with a low clearance and that undergo oxidative metabolism (antipyrine and phenytoin) (33,34). The correlation coefficients, however, are quite low and would not be considered predictive. (The coefficients of determination generally are less than 0.5.)

Several observations need to be made at this juncture. First, there are conflicting results in the literature with regard to the relationship between age and estimates of metabolic efficiency for any given compound. This, in part, is a result of the use of very different populations of subjects, especially elderly subjects (e.g., with regard to health status and concurrent drug use). Confusion about the relative merits of clearance and elimination half-life in assessing metabolic activity remains. While the latter is a very useful parameter, it is not useful in the context of comparing metabolic efficiency of a given compound; clearance is the preferred parameter. The



**Figure 6.** Antipyrine clearance as a function of age in 307 healthy male subjects (18–92 years). Equation of the line is  $Y = -0.19X + 40.7$  ( $r = -0.249$ ,  $p < 0.001$ ). From Vestal et al. (36); reprinted with permission.

reason for this is the fact that half-life is a parameter dependent on clearance and volume of distribution. Thus, a difference in the half-life between two populations could be the result of differences in distribution volume as easily as it could be differences in clearance. In fact, this has been observed for several compounds (e.g., thiopental and diazepam) (24,35). Therefore, clearance, which is not dependent upon distribution volume but is a measure of the organ's ability to eliminate the compound, is the preferred parameter for measurement of metabolic efficiency and for comparing different populations. Because differences in plasma protein binding can affect the value of clearance, the ideal clearance parameter would be the one corrected for binding (i.e., unbound clearance). Unfortunately, the latter is seldom measured or reported in the literature.

The data illustrated in Figure 6 (36) indicate the challenge facing investigators who attempt to assess the relationship between age and hepatic metabolism. The most remarkable aspect of the data is the magnitude of the variation in antipyrine clearance at any given age. After reviewing the relationship between age and hepatic metabolism (37), the only general conclusion that may be made is that hepatic metabolism of compounds undergoing phase I metabolism is either reduced or unaltered. There are virtually no examples of increased clearance with age. Furthermore, while not thoroughly studied, the general impression is that com-

pounds undergoing phase II (conjugation) processes are not as affected by age. Further complicating this situation is the recent indication that there may be age-dependent differences in the enantiomeric metabolism of certain compounds. One example is the metabolism of the enantiomers of hexobarbital (38). Elderly male subjects had a lower oral clearance for the l-isomer in comparison to the value in younger adults, whereas there were no differences in the oral clearances of the d-isomer. This area has received little attention, but now there is great interest in studying the disposition of enantiomers because we now have the ability to separate enantiomers and perform quantitative analyses easily.

An additional issue that has not been thoroughly addressed is the possibility of age-related differences in metabolism as a function of gender. Another question that has not been examined rigorously is the relative enzymatic induction and inhibition ability as a function of age. Are the elderly more or less prone to enzymatic alteration than the younger adult?

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