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Interspecies Scaling, Allometry, Physiological Time, and the Ground Plan of Pharmacokinetics

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Interspecies variation in pharmacokinetics is considered and treated as a property and consequence of body size (allometry). Consequently, it is possible to reference (scale) pharmacokinetic parameters to the organism's individual anatomy, biochemistry, and/or physiology in such a manner that differences between species are nullified. Thus, in the mouse, rat, dog, monkey, and human, methotrexate plasma clearance always equals 133% of creatinine clearance and as such becomes invariant. Pharmacokinetic time (a variable in terms of chronological time) is shown to be a form of physiological time in which a pharmacokinetic event becomes the independent variable, e.g., disposition half-life. A relationship between pharmacokinetic time and body size is demonstrated. It is suggested that man's lesser quantitative ability to metabolize many drugs may be correlated with his enhanced longevity.

KEY WORDS: interspecies variations; scaling; heterogony; allometry; pharmacokinetics; physiological time; pharmacokinetic time; maximum lifespan potential.

What am I to be tonight—90 or 40?
Time is merely an accommodation to me.

—Ethel Barrymore

. . . time is also a process.

—L. K. Frank

INTRODUCTION

The subject of interspecies variations in pharmacokinetics has heretofore been rather empiric and descriptive. Typically, a drug is administered to two or more mammalian species, blood and urine levels are measured, parameters calculated, correlations sought, and the results are collated in

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tabular or graphical form. This approach has led to the conclusion that, in general, other species of mammals eliminate most drugs more rapidly than man. It appears then that body eliminating efficiency or total body clearance, when expressed in units of volume per unit of time per unit of body weight, is generally greater in animals than in man. Thus, the investigator might conclude that two species having different clearance values so expressed are discordant. But is this really true? Take, for example, the data for mouse and cow collated in Table I. The 0.030 kg mouse has a hypothetical drug hepatic clearance of 52.3 ml/min/kg body weight, and the 760 kg cow has a hepatic clearance of 14.1 ml/min/kg body weight. Because the liver weight in the mouse is 5.83% of body weight, whereas the liver weight in the cow is 1.57% of body weight, the respective clearance values are identical when adjusted to liver weight as opposed to body weight. And because hepatic perfusion rate in both species is approximately the same for each kg of liver weight (1), the mean hepatic extraction ratio in both species is approximately the same (0.60). We can see clearly that by adjusting clearance values to the organisms's individual anatomy and physiology, the apparent differences may disappear. But there is yet another way of looking at these data, i.e., by introducing the concept of "physiological time" (2,3).

Physiological time may be defined as a species dependent unit of chronological time required to complete a species independent physiological event. Take, for example, the process of aging in two species, dog and man, with life expectancies of 14 and 98 years, respectively. The dog ages at the rate of 7.14% of it's life per year; man ages at the rate of 7.14% of his life per 7 years. Thus 1 year in the dog and 7 years in the man are equivalent "physiological times" necessary to produce a species independent physiological event, i.e., living 7.14% of a lifetime. Applying this

Table I. Theoretical Data for a Hypothetical (Imaginary) Drug Undergoing Hepatic Metabolism in the Mouse and Cow

	(Mouse)	(Cow)
Body weight, kg	0.030	760
Blood volume, liters	0.0021	53.2
Liver weight, kg	0.00175	11.9
Hepatic blood flow, liters/min	0.00262	17.8
Hepatic clearance, ml/min/kg liver weight	898	898
Hepatic blood flow, ml/min/kg body weight	87.3	23.4
Hepatic clearance, liters/min	0.00157	10.7
Mean hepatic extraction ratio	0.60	0.60
Hepatic clearance, ml/min/kg body weight	52.3	14.1
Hepatic blood flow turnover time, min	0.802	2.99
Fraction of blood volume cleared of drug per turnover time	0.60	0.60

concept to the aforementioned example, we observe that on average, each microliter of blood in the mouse passes through the liver once each 0.802 min. For the cow, each microliter of blood on average passes through the liver once each 2.99 min. The reader will recognize these values as turnover times, equal to the volume of blood divided by hepatic blood flow. These times, or more properly "physiological times," are also equal to the amount of chronologic time it takes for the entire blood volume, on average, to pass through the liver once. That is to say, each 0.802 min in the mouse is equivalent to each 2.99 min in the cow. Looking at drug elimination in each species, 60% (hepatic extraction ratio as a percent) of the drug in the blood will be eliminated per turnover time. Looking at this yet another way, the ratio of turnover times is simply the inverse ratio of clearances, when the latter are expressed as ml/min/kg body weight.

While physiological time is gauged by the tempo of changes in living organisms (2–4), chronologic time is usually measured by the motion of pointers moving over a dial, which in turn is synchronized to some other movement or motion, e.g., the rotation of the earth about its axis. A good example of physiological time is given by Gould (4,5), Stahl (6), and Günther and Leon de la Barra (7). Both breath time and heartbeat time, which differ considerably among mammalian species, vary with the 0.28 power of body weight, as follows (4–7):

$$\text{Breath time (s)} = 0.169B^{0.28} \quad (1)$$

$$\text{Heartbeat time (s)} = 0.0428B^{0.28} \quad (2)$$

where B is body weight in grams.

Dividing breath time (pneumatochron) by heartbeat time (cardiochron) gives a value of 4.0. In other words, all mammals have 4 heartbeats for each respiratory cycle. Additionally, in many mammalian species, excluding the longer living primates (*vide infra*), lifetime also scales to the 0.28 power of body weight (4–6). This indicates that most mammals have nearly the same number of breaths and heartbeats during their lifetime. The fast-living mouse has a rapid heartbeat and a short lifetime, while the torpid hippopotamus has a slow heartbeat and a relatively long lifetime. The analogy to pharmacokinetics is apparent; the smaller short-lived animals generally clear drugs from their bodies more rapidly (chronologic time) per unit body weight than the larger long-lived animals. But measured by their own internal clocks, mammals may tend to clear drugs at a similar pace (*vide infra*).

When applied to pharmacokinetic events, physiological time becomes synonymous with pharmacokinetic time. An important characteristic of physiological, or pharmacokinetic time, is that it is generally age dependent.

Take for example, the most widely cited example of pharmacokinetic time, disposition half-life. For many drugs, this parameter increases with chronologic age.

The concept of disposition half-life may also be used to illustrate the relationship of physiological time to chronologic time. In general, rate processes in pharmacokinetics are described with chronologic time as an independent variable in the denominator, e.g., clearance is volume per unit (chronologic) time. That is, the pharmacokinetic event, in this case the clearing of a volume of blood, proceeds as a function of time. But in pharmacokinetic time, e.g., a disposition half-life, the 50% reduction of drug becomes the independent variable, and time becomes the dependent variable, i.e., time becomes the "process" (8). And therein lies a methodology for approaching many problems of interspecies variations in pharmacokinetics: normalize chronologic time to a suitable internal barometer or clock. As shall be discussed below, one method of approach consists of seeking relationships between pharmacokinetic parameters and body weights and/or lifespan potentials.

DATA ANALYSIS

The Dedrick Approach

The most obvious difference between commonly used species in pharmacokinetic research is size, but with the exception of Dedrick *et al.* (9), investigators have tacitly ignored this fact. This is unfortunate, given that the study of size and its consequences (allometry) probably expresses a major aspect of the ground plan for pharmacokinetics. In the context of this discussion, the ground plan for pharmacokinetics refers to the logical simplicity characteristic of pharmacokinetic events. As part of this ground plan, smaller mammals have relatively larger drug eliminating organs such as liver and kidneys than do larger mammals (1,10). An because blood perfusion rates to these organs are roughly proportional to their sizes (1,10,11), smaller animals, by virtue of anatomy and physiology alone, have a greater opportunity to dispose of drug molecules. No one in pharmacokinetics seems to have appreciated the subtleties associated with size more than Dedrick *et al.* (9). In their cogent analysis, the authors epitomized a basic tenet of interspecies variations in pharmacokinetics: that "small mammals can be regarded as true physical models of large ones in the engineering sense of the term" (12). Ostensibly, what these authors did was to take the plasma levels of methotrexate (MTX) from five mammalian species (mouse, rat, monkey, dog, and man), which differed by a factor of 17,000-fold, and normalized (scaled) them so they fit a single curve (MTX

is primarily eliminated by renal excretion). The normalization process, or scaling, proceeded as follows. In the conventional plot, log plasma level was plotted as a function of chronologic time. To appropriately scale this plot, two things needed to be done. First, differences in plasma levels due to differences in mg/kg dosages required attention. This was easily accomplished by dividing plasma levels by mg/kg dose. Secondly, differences in clearances (ml/min/kg body weight) required some sort of procedure to adjust chronologic time to pharmacokinetic time. Because the smaller species had greater clearance values (ml/min/kg body weight; *vide supra*), chronologic time in these species would have to be decelerated (time contraction) relative to the larger species. The authors accomplished this clearance normalization by dividing time on the x axis by body weight (B) to the 0.25 power. Whereas the former dosage adjustment methodology seems quite logical, this latter adjustment may appear superficially absurd—and therein lies the *pons asinorum*. What Dedrick *et al.* (9) realized and quite appropriately responded to, is the recognition that any process that includes chronologic time as a dimension is size dependent (13). All Dedrick *et al.* did was to remove the size dependency, i.e., they scaled chronologic time to pharmacokinetic time.

For the 0.022 kg mouse (a rapid MTX eliminator), $B^{0.25}$ is 0.385; for the 70 kg human (a slow MTX eliminator), $B^{0.25}$ is 2.89. By taking the ratio, 0.385/2.89, one arrives at a ratio of 0.13 to 1. Thus, 1 min of human chronologic time is equivalent to 0.13 min of mouse chronologic time. Restating this in more explicit pharmacokinetic terms, the mouse will clear the same volume of drug per kg body weight in 0.13 min as the human does in 1.0 min.

Seeking a physiological basis of the body weight power transformation, Dedrick *et al.* utilized the empirical relationships from Adolph (10):

$$CL_{Cr} = 4.2B^{0.69} \tag{3}$$

$$\frac{CL_{Cr}}{B} = 4.2B^{-0.31} \tag{4}$$

where CL_{Cr} is creatinine clearance (ml/h), and B is body weight (g). Thus, in a variety of mammalian species, creatinine clearance expressed per unit of body weight varies with body weight to the negative 0.31 power. Because MTX is primarily eliminated by the kidneys, it is logical that interspecies variations in MTX clearances would correlate with interspecies creatinine clearances, and 0.31 is close to 0.25.

Acknowledging the major contribution of Dedrick *et al.* (9), the author would like to add a few additional nuances. For this analysis, the original data on MTX were utilized (see ref. 9 for sources), and plasma clearance

values (CL_{MTX}) were calculated from dose and area under the curve. Figure 1 illustrates a log–log plot of CL_{MTX} vs. body weight (B). Note that CL_{MTX} (ml/min) varies with B (kg) to the 0.69 power:

$$CL_{MTX} = 10.9B^{0.690} \tag{5}$$

Equations (3) and (5) may readily be combined. However, Eq. (3) first needs to be rewritten so as to adjust units:

$$CL_{Cr} = 8.2B^{0.69} \tag{6}$$

where CL_{Cr} is creatinine clearance (ml/min), and B is body weight (kg). Dividing Eq. (5) by Eq. (6):

$$\frac{CL_{MTX}}{CL_{Cr}} = 1.33 \tag{7}$$

Thus, the interspecies ratio of CL_{MTX} to CL_{Cr} is a constant, independent of species and species size. In a sense, all species are alike, excreting MTX

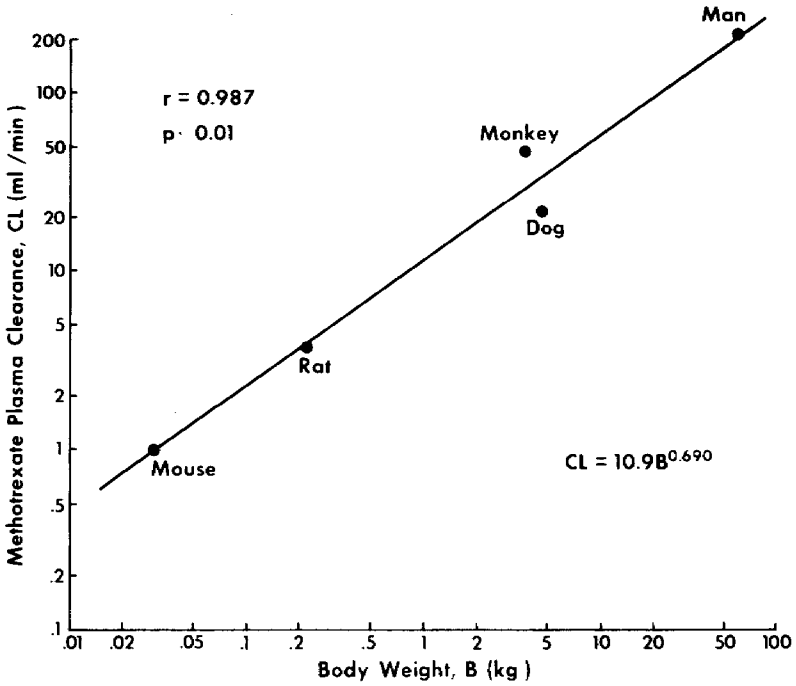

Fig. 1. Interspecies correlation between methotrexate plasma clearance and body weight. Linear regression analysis was performed on logarithmically transformed data. Intercept and slope values were used to calculate coefficient and exponent, respectively.

from their bodies at a pace correlated with internal factors contributing to their individual creatinine excretion.

MTX clearance may also be related to the total quantity of nephrons. Thus, according to Adolph (10):

$$N = 188{,}000B^{0.62} \tag{8}$$

where N is the total number of nephrons in a mammalian species, and B is body weight (kg). Dividing Eq. (5) by Eq. (8):

$$\frac{CL_{MTX}}{N} = (5.8 \times 10^{-5})B^{0.07} \tag{9}$$

$$\frac{CL_{MTX}}{N} \simeq 5.8 \times 10^{-5} \tag{10}$$

The exponent of 0.07 in Eq. (9) is termed the residual mass exponent, or RME (6); the closer the RME approaches 0, the closer B^{RME} approaches unity. Equation (10) indicates that for each 100,000 mammalian nephrons, MTX clearance is approximately 5.8 ml/min. This relationship suggests that glomeruli from different mammals are similar anatomically and physiologically. Support for this argument comes from Holt and Rhode (11), who demonstrated that the length of the average glomerular capillary is constant (733 μm), independent of the size of the mammal. Moreover, the average velocity through the glomerular capillary is also constant, as is the mean time in the glomerular capillaries (1.88 s). Other renal processes are also relatively invariant. Thus, Edwards (14) showed that regardless of mammalian species, renal blood flow is 25.9% of cardiac output (allometric analysis similar to that used in Eq. 9 was employed here, and the RME was 0.02).

Returning to the MTX data, there is a caveat to be added. In smaller species such as the mouse and rat, significant intact drug appears in the feces (biliary excretion) following parenteral administration (15). This amounts to approximately 30% of the dose in mice and 50% in rats. It may well be, as suggested by Dedrick *et al.*, that MTX pharmacokinetic time is more closely related to mean residence time in the vascular system than to creatinine clearance (*vide infra*).

Having considered interspecies variations in clearance, let us turn now to variations in volumes of distribution (V_β). Data were obtained from the sources noted in ref. 9. Figure 2 illustrates a log–log plot of V_β vs. B, where V_β is equal to CL_{MTX} divided by the terminal exponential rate constant. Accordingly,

$$V_\beta = 0.859B^{0.918} \tag{11}$$

where V_β is volume of distribution in liters, and B is body weight in kg.

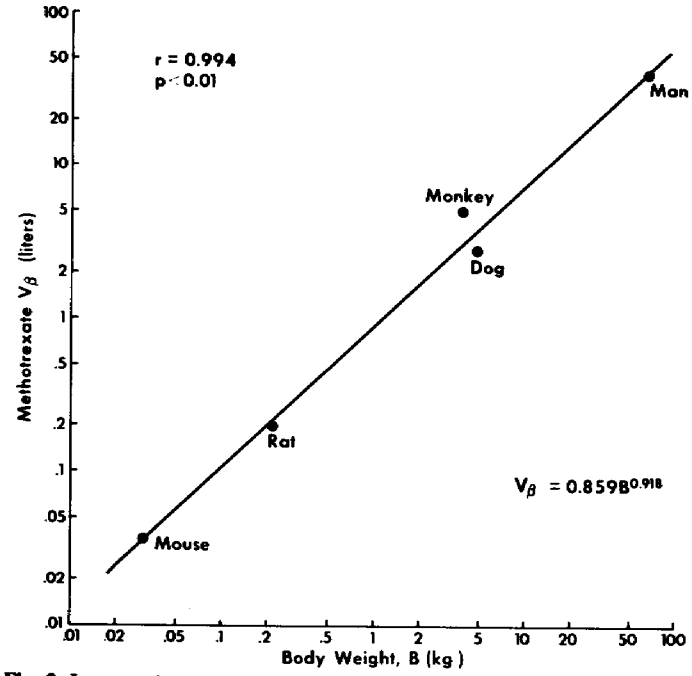

Fig. 2. Interspecies correlation between methotrexate volume of distribution and body weight.

It will be demonstrated subsequently in this work that total body water (TBW) in liters is given by:

$$\text{TBW} = 0.703B^{0.963} \tag{12}$$

Combining Eqs. (11) and (12):

$$\frac{V_\beta}{\text{TBW}} = 1.22B^{-0.045} \tag{13}$$

$$\frac{V_\beta}{\text{TBW}} \simeq 1.22 \tag{14}$$

Once again, an interspecies pharmacokinetic parameter has become relatively invariant when referenced (scaled) to a biological parameter within the organism. These latter two plots of log parameter vs. log body weight are specific examples of allometry (or heterogony).

Because both CL and V_β for MTX can be related to body weight using "the equation of simple allometry" (5), it seemed of interest to run simulations investigating the nature of the relationship between allometry

and the Dedrick plot. Figure 3 illustrates thecretical monoexponential plasma concentration time curves for a single hypothetical drug in two species, mouse and goat. Doses (mg/kg) are different, volume of distribution (V, liters/kg) is a constant fraction of body weight, and clearance is described by the equation of simple allometry with an exponent of 0.75. The most immediate and obvious question with regard to a Dedrick plot is, "By what factor is chronologic time to be scaled?" It may readily be demonstrated that if CL is proportional to B^x, then chronologic time needs to be scaled by dividing by B^{1-x}, in this example $B^{0.25}$. Such a procedure, together with adjustment of plasma levels by dividing by mg/kg body weight dose, will result in identical areas under the curves, given by (9):

$$AUC = \int_0^\infty \frac{C}{\text{dose}/B}\, d\left(\frac{t}{B^{1-x}}\right) \tag{15}$$

where AUC is area under the curve (0 to infinity), C is plasma concentration, B is species body weight, t is chronologic time, and x is the exponent of the equation of simple allometry relating clearance to body weight.

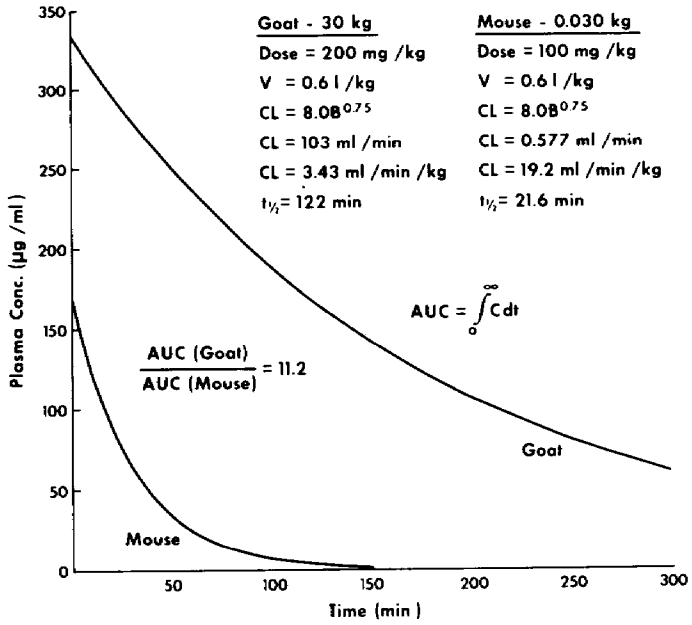

Fig. 3. Monoexponential decay curves for a hypothetical single drug in two species. Note that volume of distribution is a constant fraction of body weight. See text for discussion.

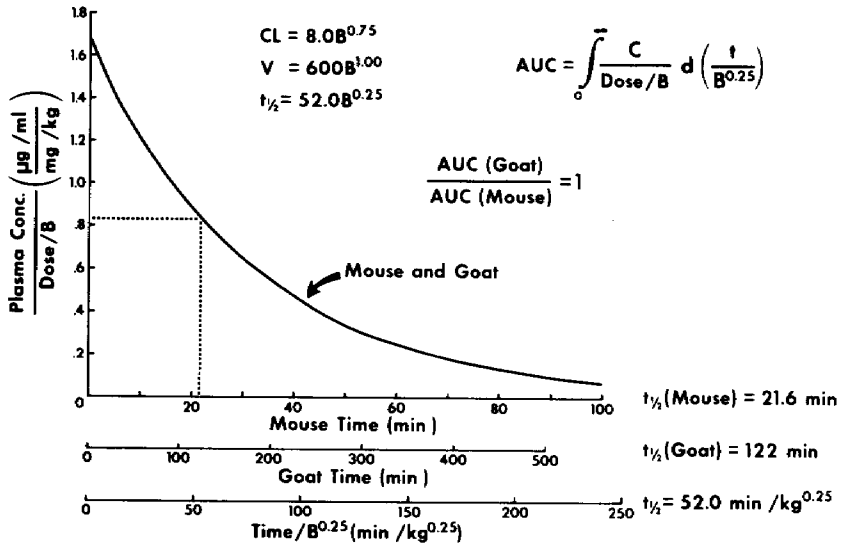

Fig. 4. Dedrick plot where volume of distribution is a constant fraction of body weight. See text for discussion.

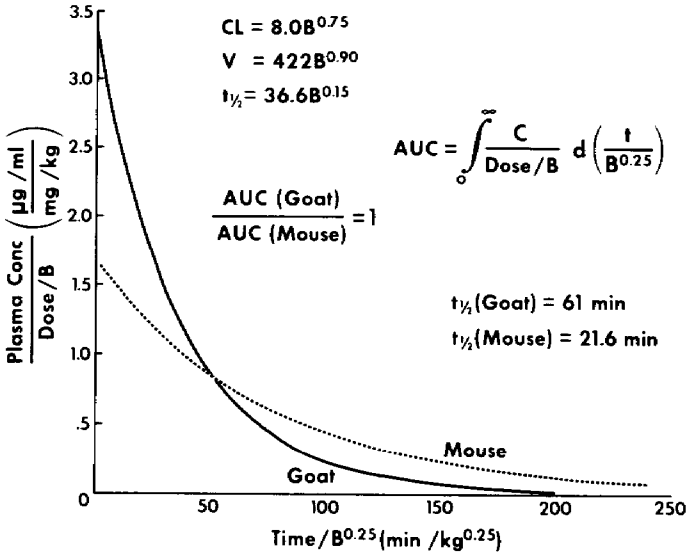

Fig. 5. Dedrick plot where volume of distribution is determined by the simple allometric equation, i.e., it is *not* a constant fraction of body weight.

Figure 4 illustrates a Dedrick plot with the same data as in Fig. 3. It is readily noted that transformations of these data result in superimposable curves. But suppose V is not a constant fraction of body weight. Figure 5 was constructed with data generated from the same allometric clearance relationship, but this time an allometric relationship was also presumed to describe volume of distribution, i.e., volume of distribution was *not* a constant fraction of body weight. In this situation, the Dedrick curves are not superimposable, but nonetheless, *AUC*s are identical. Thus it is apparent that Dedrick plots will only result in superimposable curves if V is a constant fraction of body weight, i.e., V is proportional to $B^{1.0}$. In the case of multiexponential disposition functions, superimposability will only be observed when the volume of the central compartment, V_β, and V_{ss} (volume of distribution at steady state) individually represent the same fraction of body weight between species.

History and Theory of Biological Scaling

Biological scaling can hardly be considered a new discipline. As early as 1637, Galileo (16,17) discussed the relationship of skeletal size to body mass. But with regard to physiological and pharmacokinetic problems, the work of Adolph (10) has probably been the most powerful influence. In his now classic 1949 paper published in *Science*, Adolph made the following comment concerning the use of the simple allometric equation, also termed the heterogonic equation: "It must be recognized that no limitation is imposed, by anything but the time and effort of investigation, upon the range of organisms and upon the array of properties that may be considered in interrelations."

At this point, however, the relationship between interspecies aspects of anatomy and physiology to that of pharmacokinetics requires development. Because organ sizes as well as biochemical and physiological processes are scaled in relation to body weight, and because these organs and processes affect drug disposition, one might well expect correlations between pharmacokinetic processes and normal day-to-day endogenous processes. In fact, the theories of Adolph (18) assume and require that such correlations exist:

1. Theory of interdependencies: No component is regulated independently of all others.
2. Theory of requirements: Rates of turnover of any one component depend upon the contents and rates of exchange of other components.
3. Theory of conservations: Rates of turnover are usually near the minimum compatible with indefinitely continued function.

4. Theory of time scales: Single components and groups of components tend among many species to unload in relatively similar times. [The author would only support this theory if the "times" referred to are physiological times.]

Because both physiologic and pharmacokinetic processes are regulated in one way or another by allometry, it seemed of interest to investigate whether or not endogeneous rate processes scale in a manner similar to that for drug disposition. On searching the literature, it soon became apparent that most of the available rate data on interspecies variations in physiological and biochemical processes were data on either turnover times or terminal exponential half-lives. Therefore, an attempt was made to see whether or not turnover times and half-lives for endogeneous processes are scaled to body weight in a manner analogous to the way in which drug elimination half-lives are scaled to body weight.

For endogenous substances at steady state, turnover time in the body is equal to mean residence time, i.e., the average lifespan of a molecule or particle in the body. For first-order processes at steady state, turnover time, t^*, is given by:

$$t^* = (1.44t_{1/2})\left(\frac{V_{ss}}{V_\beta}\right) \tag{16}$$

where $t_{1/2}$ is the half-life of the terminal β phase, V_{ss} is volume of distribution at steady state, and V_β is volume of distribution during the terminal β phase. For endogenous substances at steady-state, $1.44t_{1/2}$ approximates t^* inasmuch as V_{ss}/V_β approximates unity.

In the case of MTX, because both V_β and CL may be expressed in terms of allometric equations, $t_{1/2}$ may also be so expressed:

$$(t_{1/2})_{MTX} = \frac{(0.693)(1000)(0.859 \times B^{0.918})}{(10.9 \times B^{0.690})} \tag{17}$$

$$(t_{1/2})_{MTX} = 54.6B^{0.228} \tag{18}$$

where B is body weight in kg, and $(t_{1/2})_{MTX}$ is MTX half-life in minutes.

Analogous allometric relationships for CL and V_β may be developed for cyclophosphamide, CPM. This drug is eliminated primarily by metabolism, and data (19) are graphically illustrated in Figs. 6 and 7. Combining allometric relationships, the following is obtained:

$$(t_{1/2})_{CPM} = 36.6B^{0.235} \tag{19}$$

where $(t_{1/2})_{CPM}$ is cyclophosphamide half-life in min, and B is body weight in kg.

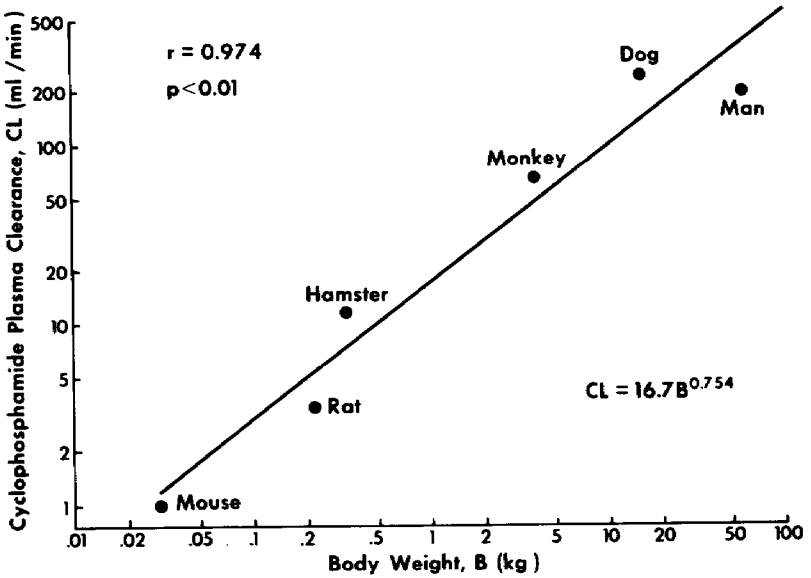

Fig. 6. Allometric relationship between cyclophosphamide plasma clearance and body weight.

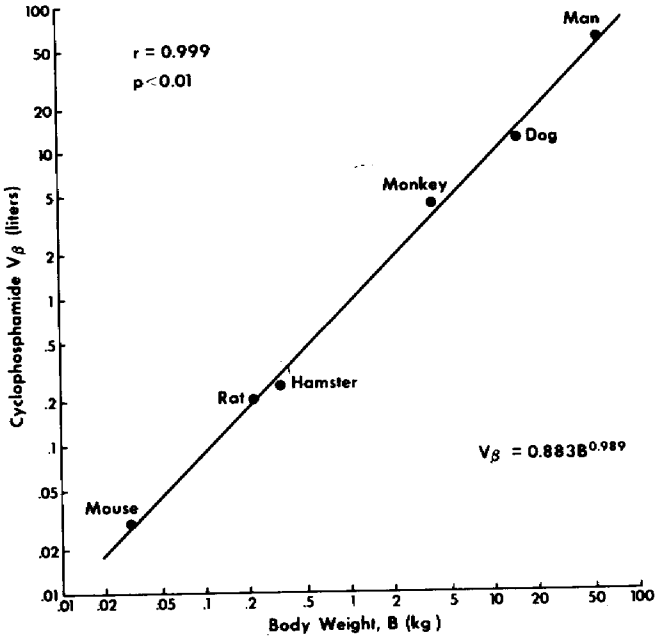

Fig. 7. Allometric relationship between cyclophosphamide volume of distribution and body weight.

In addition to methotrexate and cyclophosphamide, interspecies variations in the half-lives of antipyrine, digoxin, hexobarbital, phenylbutazone, aniline, and diazepam are summarized in Table II. This group represents a variety of compounds, with renal excretion being the primary elimination pathway for methotrexate and digoxin, and metabolism for the others. Although not all the regressions achieved satisfactory degrees of statistical significance, most certainly a trend does exist. The exponents of the allometric equations tend to cluster about a value near 0.25, as opposed to 0, 0.5, 0.75, or 1.0.

This is consistent with the ground plan of energy expenditure in mammals, and drug disposition is an energy consuming process. Body weight has long been recognized as a reference system for rhythmic phenomena (7,25), and the theory of similarity of chemical energy requires that energy turnover times be proportional to $B^{0.25}$ (26). Accordingly, body size scaling of resting oxygen consumption (proportional to basal metabolic rate) for poikilotherms and homeotherms results in identical allometric exponents of 0.75 (27,28), but with coefficients differing by a factor of about 30. Energy metabolism in plants and poikilotherms of similar body weight, however, is identical (29). As shall be discussed, energy expenditure is of extreme importance in understanding interspecies variations in pharmacokinetics, because it influences in one way or another the amount of energy to be directed towards xenobiotic and drug elimination. This in turn is reflected by the quantitative aspects of pharmacokinetics.

Returning to the discussion of metabolic rates and energy turnover times in mammals, Günther (25) has stated: "... increase in body size is generally associated with a progressive reduction of the metabolic rate per

Table II. Allometric Parameters Describing Interspecies Variation in Drug Elimination Half-Lives[a]

Drug[b]	Refs.	No. of species	Corr. coeff. (level of sig.)	Allometric coeff.	Allometric exponent
Methotrexate	9	5	0.994 ($p<0.01$)	54.6	0.228
Cyclophosphamide	19	6	0.752 ($p<0.1$)	36.6	0.236
Antipyrine[c]	1	10	0.503 ($p<0.2$)	74.5	0.069
Digoxin	19,20	5	0.941 ($p<0.05$)	983	0.234
Hexobarbital	19,21	5	0.912 ($p<0.05$)	80.0	0.348
Phenylbutazone[c]	19,22,23	7	0.335 ($p<0.5$)	340	0.060
Aniline	21	5	0.650 ($p<0.3$)	62.2	0.176
Diazepam[c]	24	4	0.989 ($p<0.05$)	122	0.428
				Mean	0.222

[a] Half-lives in minutes and body weight in kg.
[b] Only drugs for which half-life data were available in at least 4 species were considered.
[c] Data on man is an outlier and was excluded from analysis. If man were to be included, an analysis such as that illustrated in Figs. 9–11 would be more appropriate.

unit mass ... which influences the turnover rate at the cellular level and consequently could modify the biological timing process." In this regard, Kleiber (26) has shown that an organism's metabolic rate (M) is proportional to the 0.75 power of body weight:

$$M = aB^{0.75} \tag{20}$$

where a is a constant with appropriate units. In similometrically composed animal pools (contents proportional to body mass), energy content (thermodynamic potential energy) is directly proportional to body mass or weight. The turnover time, therefore, is proportional to $B^{0.25}$, as follows (26):

$$\text{turnover time} = \frac{\text{chemical energy content of body}}{\text{metabolic rate}} = \frac{a_1 B^{1.0}}{a_2 B^{0.75}} \propto B^{0.25} \tag{21}$$

where a_1 and a_2 are constants.

Thus, the turnover time of energy in an organism is proportional to $B^{0.25}$. Inasmuch as the whole is simply the sum of the parts, it follows, at least on average, that individual turnover times for similometric energy consuming processes will be related to body weight in an analogous fashion. This is demonstrated in Table III, where it may be observed that allometric expressions for turnover times of endogenous processes have exponents clustering about a value of approximately 0.25. Regarding drug disposition at steady state, inasmuch as the conditions described previously are satisfied, drug turnover times between species are approximately proportional to

Table III. Allometric Parameters Describing Turnover Times (or Estimates Thereof) for Endogeneous Substrates or Processes[a]

Substance	Ref.	No. of species	Corr. coeff. (level of sig.)	Allometric coeff.	Allometric exponent
Serum albumin[b,c]	30,31	6	0.993 ($p<0.01$)	5.68	0.296
Total body water[b,d]	32	8	0.940 ($p<0.01$)	6.01	0.161
Red blood cells[b]	33,34	11	0.778 ($p<0.01$)	68.4	0.102
Cardiac circulation[e]	14,24	≈11–12	—	0.422	0.210
				Mean	0.192

[a] B of allometric equation has units of kg.
[b] Turnover time in days, body weight in kg.
[c] Turnover time was approximated as $1.44t_{1/2}$.
[d] Total body water (*vide infra*) was divided by daily urinary water excretory rates to obtain turnover time estimates. The contribution of respiratory and sweat excretion was not considered, and desert animals were not considered.
[e] Mean residence time of blood in the vascular system. Estimated from two allometric equations; blood volume as a function of body weight divided by cardiac output as a function of body weight. Turnover time (or residence time) in minutes.

half-lives in the respective species. In other words, interspecies variations in drug disposition parameters in mammals are regulated to a large extent by the same factors quantitatively regulating other bodily processes, i.e., energy expenditure. Such a relationship is even more obvious when one considers that all living matter is basically a system for the capture, transformation, and release of energy (35). And, as has been discussed previously, energy expenditure in mammals is a simple function of body size, with a turnover time proportional to $B^{0.25}$. Günther (25) puts it this way: "... at all levels of biological organization we can observe that the ontogenetic and phylogenetic increase in size ... is directly associated with an increase of the duration of all periodic phenomena, a general trend which can be formulated by means of the power law for biological time: $T_B = aW^{0.27}$." Practically speaking, chronologic time is normalized to biological time by dividing by $B^{0.25}$, and therein possibly lies the basis for the transformation of time originally used in pharmacokinetics by Dedrick *et al.* (9) over 10 years ago (*vide supra*).

Pharmacokinetic elimination processes are primarily affected by the size and function of the liver and kidneys. As discussed by Gould (5), organs such as the liver and kidneys, by responding to the demands of metabolism, have increased their relative size so that their allometric exponents are approximately 0.85 (1,10). This may explain why some pharmacokinetic elimination parameters in the allometric equation are nearer 0.85 than 0.75. See, for example, Boxenbaum (1), who showed that the intrinsic clearance (unbound drug) for antipyrine in 10 mammalian species was a function of body weight to the 0.885 power (*vide infra*). In this case, pharmacokinetic time scales to $B^{0.115}$.

Returning to the previous discussion on interspecies variations of disposition half-lives, an obvious objection might be made. Because half-life is such a hybridized parameter, would it not be more appropriate to use a "more meaningful" pharmacokinetic parameter? First off, let it be said that the so-called lack of significance for disposition half-life is a consequence of teleological thinking (clinical relevance!) in clinical pharmacokinetics, particularly when the so-called "flow" models or "physiological" models are employed. For drugs completely metabolized by the liver, the author would agree that other parameters, particularly intrinsic clearance of unbound drug, are considerably more meaningful in that context. But in the context of allometry, it is precisely because half-life is so hybridized, and because it is so dependent upon such a variety of energy sources, that makes it a suitable parameter. That is, its weakness in clinical pharmacokinetics is precisely its strength in allometry.

There is still another way to rationalize a scaling factor of approximately $B^{0.25}$, and this has been discussed by Dedrick *et al.* (9). These

investigators noted that the tissues of smaller animals receive greater blood flows per unit volume of tissue than do larger animals. The mean residence time (chronologic) of blood in the vascular system (blood volume/cardiac output) scales to body weight to the 0.21 power (see Table III). Thus, smaller animals may eliminate drugs more rapidly than larger animals by virtue of circulation to any or all of the eliminating organs *per se*. There is herein the tacit assumption that drug clearance by an eliminating organ is blood flow dependent, an assumption probably true for methotrexate.

Allometric Collapsing in Pharmacokinetics

In his classic book, *The Mathematical Approach to Physiological Problems*, Riggs (36) noted the prevalence in nature of exponential (logarithmic) growth and decay and the overwhelming preponderance of log–normal distributions. Consequently, following the more generalized lead of Reiser (35), Riggs recommended adopting a logarithmic view of the universe. Consistent with that view is the prevalence of log–log relationships associated with the allometric equation in pharmacokinetics.

The usefulness of allometry in pharmacokinetics has already been demonstrated (1,9,10,19,24). Thus, for example, Boxenbaum (1) demonstrated that in 10 mammalian species (excluding man), antipyrine intrinsic clearance of unbound drug was related to body weight as follows:

$$CLu_{\text{int}} = 0.00816B^{0.885} \tag{22}$$

where B is body weight in kg, and CLu_{int} is intrinsic clearance of unbound drug in liters/min. It was also demonstrated that hepatic blood flow (Q_H, liters/min) was also related to body weight (kg):

$$Q_H = 0.0554B^{0.894} \tag{23}$$

The original data of Boxenbaum (1) were once again taken, and V_β was plotted against body weight on a double logarithmic grid. This is illustrated in Fig. 8. In the 11 mammalian species, V_β (liters) is related to body weight (kg) as follows:

$$V_\beta = 0.756B^{0.963} \tag{24}$$

From knowledge of CLu_{int} and V_β, and by assuming the liver is the sole eliminating organ, it is possible to calculate half-life from the following equations (37):

$$CL_M = \frac{f_B CLu_{\text{int}} Q_H}{f_B CLu_{\text{int}} + Q_H} \tag{25}$$

$$t_{1/2} = \frac{0.693 V_\beta}{CL_M} \tag{26}$$

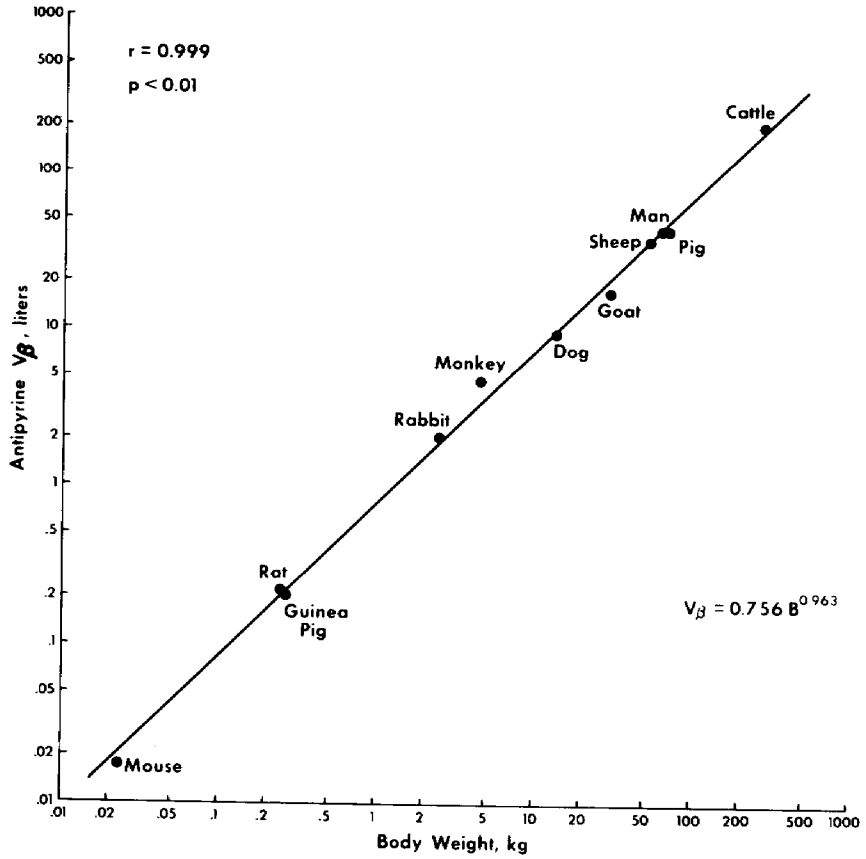

Fig. 8. Allometric relationship between antipyrine volume of distribution (V_β) and body weight.

where CL_M is metabolic clearance (also total clearance), and f_B is unbound fraction of drug in blood (taken as unity). Combining Eqs. (22)–(26), it is possible to express $t_{1/2}$(min) as a function of body weight (kg):

$$t_{1/2} \simeq 73.7B^{0.077} \tag{27}$$

Although the equations do combine in a complex fashion, combinations, cancellations, and removal of insignificant terms results in a major "collapse," so that the final relationship is considerably simplified. The parameters in Eq. (27) are very close to those reported in Table II, which were estimated by regression analysis. In all cases, the predicted half-life from Eq. (27) was between $\frac{1}{2}$- and 2-fold the observed value. Given the simplistic nature of the allometric equation (i.e., only one independent variable), this is indeed an interesting finding. A somewhat different but

analogous relationship was reported for the benzodiazepines (24). A log–log plot of the half-lives of 12 benzodiazepines in dog and man showed a significant correlation ($p < 0.05$).

Life, Death, and Pharmacokinetics

As has been discussed in previous sections, the allometric equation seems to have a great deal of utility in the analysis of interspecies pharmacokinetic data. However, not much consideration was given to the selection of parameters to be correlated with body weight. As just demonstrated, half-lives may correlate as a mathematical consequence of "collapsing." Clearance values may correlate for at least two reasons. For drugs solely metabolized by the liver, those with high extraction ratios have clearances approaching hepatic blood flow. These allometric relationships may be little more than secondary correlations, resulting as a consequence of the primary allometric relationship between hepatic blood flow and body weight. For drugs with low extraction ratios, clearance approximates $f_B CLu_{\text{int}}$ (well-stirred model), and correlations may now become a consequence of other biochemical and physiological factors. For drugs solely metabolized by the liver, probably the best parameter to correlate is CLu_{int} (1). The primary difficulty at present is finding sufficient data in enough mammalian species to make this plot. However, in the case of antipyrine, phenytoin, and clonazepam, sufficient data do exist (1,24). For all these drugs, CLu_{int} in man is considerably less than would be predicted from other mammalian species, i.e., man is an outlier. However, CLu_{int} for drugs of this type may be correlated with longevity in addition to body size.

The longevity of a species is genetically controlled by a characteristic aging rate and is a basic biological property of the organism (38). In other words, each species has a characteristic lifespan, and this is correlated with species specific timed functions such as gestation, puberty, heart rate, and metabolic rate (39). In the wild, most animals never realize their full lifespan potential, since they are killed by predators or by accidents before their performance is seriously compromised by aging (40). But excluding accidents, genetic diseases, predation, etc., mammals generally die from diseases which are themselves caused by failure of the circulatory and/or immune systems (39). Associated with this form of "natural" death, there exists a maximum lifespan potential (MLP) which is sequenced in part by a genetically controlled biological clock. This biological clock regulates the rate at which the improbable low entropy organization of the organism succumbs to the forces of nature tending to convert it into a random conglomeration, i.e., the death state (41). As shall be discussed, this biological clock may also be influencing the rate of drug metabolism.

The maximum lifespan potential calorie consumption (MCC) may be defined as the product of MLP and specific metabolic rate (SMR) (38,42). MCC is considered to represent total "life capacity" of an organism, and the rate at which one's allotted life capacity is expended is defined by the reciprocal of MLP (38). In other words, the pace of life (rate of energy expenditure) will affect longevity. Subsequently, the fast-living rat cannot survive as long as the torpid hippopotamus. In Drabkin's words (43), "the metabolic machine does wear out. We may call it the 'toxicity of living' or the 'tax upon living.'" It is precisely this "toxicity of living" which causes the reduction in the rates of drug disposition so commonly observed in the elderly.

From the foregoing discussion, it is apparent that in terms of enhancing longevity, it behooves an organism to economize on metabolic activity, including xenobiotic metabolism and excretion. This process of economization is such that enzyme amounts, including drug metabolism enzymes, generally exist at levels approximately twice the minimum required by the organism (44,45). This allows for a generally satisfactory "safety factor." The argument might be made that the amount of energy expended for the disposition of drugs is negligible, and that drugs are not even normally present in the body. The author will take up this subject in considerable detail in another paper. For the present, suffice it to say that drug disposition is simply a "model" for xenobiotic disposition, and that the ubiquitous presence of xenobiotics in nature is such that mammalian organisms are almost continually "detoxifying" xenobiotics at considerable metabolic cost. As a single example, analysis of coffee and chocolate (46) have indicated the presence of over 700 compounds that an individual's enzymes need to deal with as the price to be paid for enjoying a cafe mocha. Conceivably, the xenobiotics in these two substances *per se* could justify much of the qualitative drug metabolism machinery. Even so seemingly innocuous a beverage as natural orange juice contains at least 217 xenobiotics in the volative fraction *per se*! These xenobiotics include acids, alcohols, aldehydes, esters, hydrocarbons, ketones, etc. (47).

It follows as a consequence of the foregoing discussion, that the rate of some energy consuming processes may correlate inversely with MLP, and in fact some do (43). It therefore seemed of interest to investigate whether or not drug metabolism rates could be correlated in a similar fashion. For reasons discussed previously (1), the parameter which best gauges an organism's ability to fend off chemical assaults from ingested xenobiotics (or drugs) is intrinsic clearance of unbound drug, CLu_{int}. In this regard, metabolism of lipid soluble substances nonsaturably cleared by the liver can generally be described by the well-stirred model discussed by Pang (48). Accordingly, the mean, oral steady-state unbound drug blood

level is inversely proportional to CLu_{int} (37,49,50). Boxenbaum (1) has previously used this parameter successfully in the analysis of interspecies variations in pharmacokinetics. In 10 mammalian species other than man, this parameter was proportional to liver weight; man was unique, however, having a value one-seventh that which would be predicted from liver weight. Additional unpublished work by the author has indicated that the interspecies metabolism of lipophilic drugs tends to fall into two categories. In the first category, for which antipyrine is the prototype, other mammals tend to have values of $CL\mu_{int}$ per unit liver weight approximately 5–20 times greater than man. Examples are benzodiazepines and propanolol. In the second category, man seems to parallel other species; tolbutamide is an example in this latter category. Although it is still too early to make a definitive statement, the tendency seems to be that most oxidizable drugs fall into the former category (tolbutamide is an exception).

Because man is generally unique both with regards to low CLu_{int} values as well as enhanced longevity, it seemed of interest to determine if some manner of correlations could result from these anomalies. There is ample precedent for such correlations. Longevity correlates with anatomic, developmental, sociologic, and metabolic processes such as body temperature (51), body weight (42), brain size (42), gestation time (39), heart rate (39), basal metabolic rate (39), nitrogen outflow (43), biological intelligence (38,40), postnatal development rates (38), onset of specific physiological function (38), and age of sexual maturation (38).

As an initial step in establishing any such relationships, estimates of MLPs needed to be obtained. In this context, MLP is defined as the maximum documented longevity for a species (42), excluding man. In general, the bulk of MLP data comes from domesticated or zoo animals. One objection to this method is that MLP increases as the sample size from which the estimate is based increases (42); this generally does not present a serious problem except with respect to man, for which the sample size is considerably larger than other species. Accordingly, MLP in man is reduced 20% from 110 years to 90 years (41). Using multiple regression techniques, Sacher (42) developed the following equation:

$$\text{MLP} = 10.839(BW)^{0.636}(B)^{-0.225} \tag{28}$$

where MLP is maximum lifespan potential in years, BW is brain weight in grams, and B is body weight in grams. Table IV collates data from which calculations of MLPs were made.

Initially, the archetypical drug antipyrine was subjected to analysis. A number of different plots were empirically tried with varying degrees of success. The best fit to the data was obtained on a log–log plot of $CL\mu_{int} \times$ MLP vs. B, and this is illustrated for antipyrine in Fig. 9. Data on the

Table IV. Brain Weight, Body Weight, and Maximum Lifespan Potential Data[a]

Species	Adult body weight (g)	Adult brain weight (g)	Brain weight (% of body weight)	Calculated MLP (years)
Mouse	23.0	0.334	1.45	2.67
Rat	250	1.88	0.751	4.68
Guinea pig	270	3.42	1.27	6.72
Rabbit	2,550	9.97	0.391	8.01
Dog	14,200	75.4	0.531	19.7
Pig	77,200	58.2	0.075	11.4
Sheep	57,600	110	0.191	18.3
Goat	31,300	130	0.416	23.3
Cattle	310,000	252	0.081	21.2
Rhesus monkey	4,700	62.0	1.32	22.3
Human	70,000	1530	2.19	93.4

[a]See text for discussion. Brain and body weight data from refs. 1, 32, 34, 51–53.

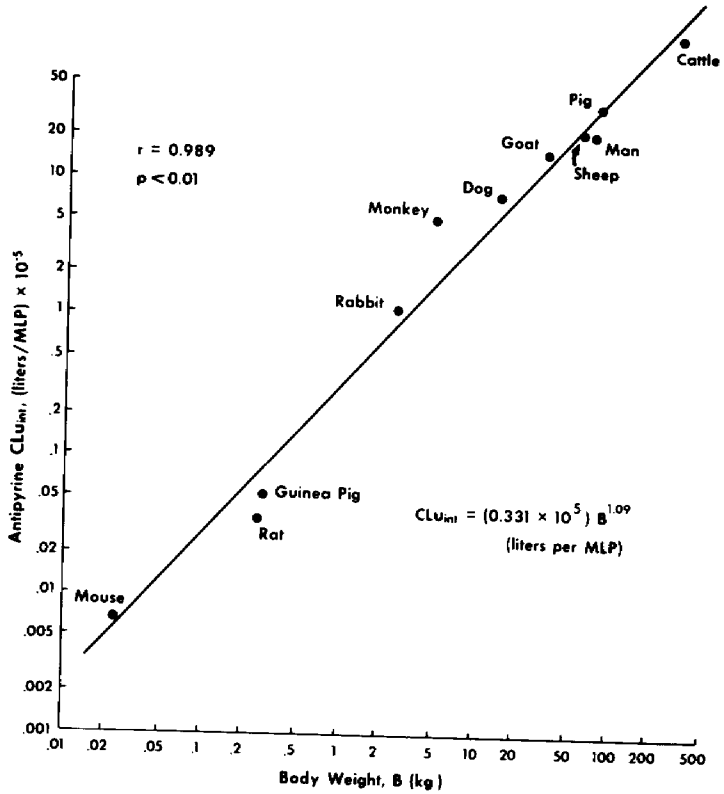

Fig. 9. Allometric relationship between unbound antipyrine intrinsic clearance per maximum lifespan potential and body weight. See text for discussion.

ordinate, $CL\mu_{int} \times MLP$, is the total volume from which drug would be cleared per MLP assuming constant drug exposure. In the context of chronologic time, MLP has units of years and is a variable between species. In the context of physiological time, MLP may be viewed as a unitless constant, with each species having a potential to live one MLP during its chronologic years. Thus, on the ordinate of Fig. 9, $CLu_{int} \times MLP$ (years) is equal to volume cleared per MLP in terms of physiological time. Interestingly, the regression indicates that volume cleared per MLP is approximately proportional to body weight. With regard to man, it could appear that his relatively low CLu_{int} (with respect to liver weight) is paced to his longevity; i.e., activity is conserved so as to be extended over a relatively longer chronologic MLP. Whether this observation is teleological or merely fortuitous remains to be established. Figures 10 and 11 illustrate similar plots of data for phenytoin (1) and clonazepam (24), respectively. Phenytoin data were obtained from linear, nonsaturable blood concentration-time data. Once again, good fits may be observed. Thus, it may very well be that this type plot will have utility in predicting or extrapolating data from one species to another.

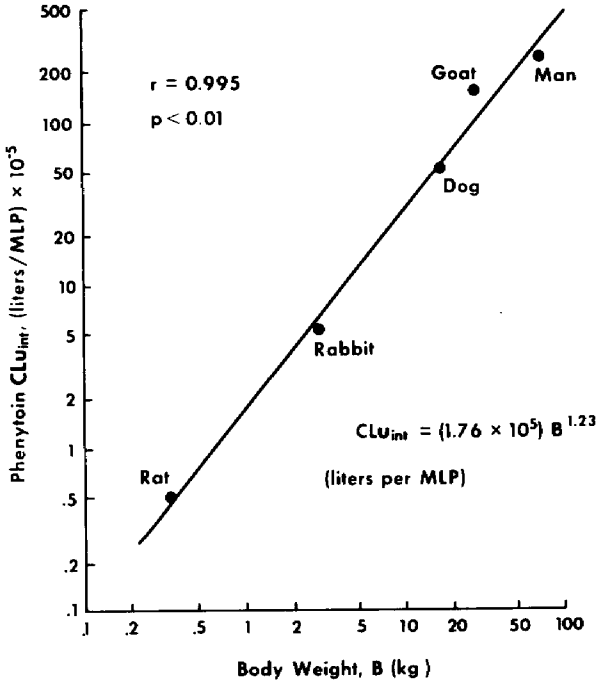

Fig. 10. Allometric relationship between unbound phenytoin intrinsic clearance per maximum lifespan potential and body weight.

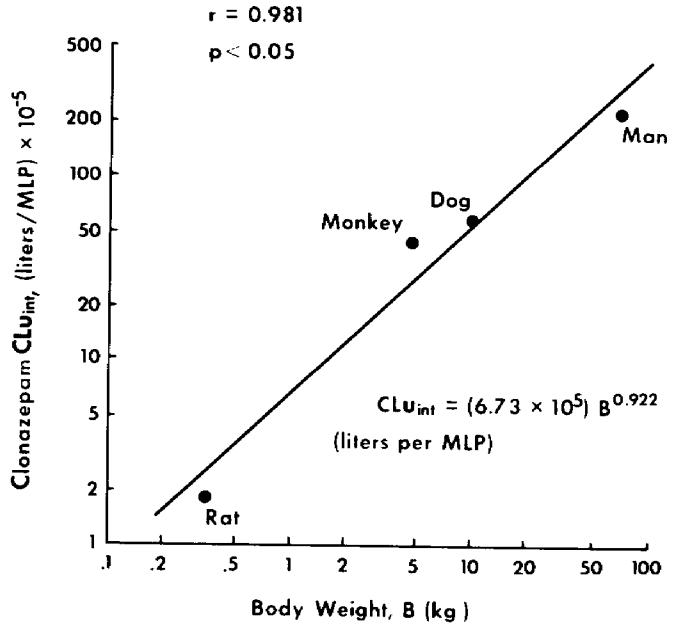

Fig. 11. Allometric relationship between unbound clonazepam intrinsic clearance per maximum lifespan potential and body weight.

Interestingly, the regression equations illustrated in Fig. 9–11 may be rearranged so that time (chronologic MLP) becomes what L. K. Frank (8) calls a "process," i.e., physiological time becomes the dependent variable. Thus, from the regression of the antipyrine data in Fig. 9, the following equation is obtained:

$$\text{MLP} = \frac{63.0B^{1.09}}{CLu_{\text{int}}} \tag{29}$$

where MLP is maximum lifespan potential in years, B is body weight in kg, and CLu_{int} is intrinsic clearance of unbound drug in ml/min. This is not to imply CLu_{int} of antipyrine or any other drug or xenobiotic has an appreciable influence on MLP *per se*, but rather that the rate of xenobiotic or drug metabolism in particular, and pharmacokinetics in general, is indicative of a more generalized biological ground plan.

NOTE ADDED IN PROOF

Subsequent to manuscript acceptance, the author became aware of two extremely relevant papers. One paper entitled "Body size, physiological time, and longevity of homeothermic animals" by S. L. Lindstedt and W. A. Calder III, *Quart. Rev. Biol.* **56**:1–16 (1981), provides a trenchant analysis of many of the principles upon which this present work is based. A paper entitled "Dependence of pharmacokinetic parameters on the body weight" by M. Weiss, W. Sziegoleit, and W. Förster, *Int. J. Clin. Pharmacol.* **15**:572–575 (1977), delineates an allometric approach to pharmacokinetic data very similar to that discussed herein.

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