CHAPTER 37

An Introduction to Allometric Scaling and Its Uses in Raptor Medicine

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ABSTRACT: Allometric scaling provides a method for examining the structural and functional consequences of changes in size or scale among otherwise similar organisms (Schmidt-Nielsen, 1984). It has been found that many physiological and life-history variables can be related to body mass by simple mathematical relationships. For example, when the resting metabolic rates of members of a taxonomic group of animals are plotted against body mass on a log-log plot, the points fall close to a straight line. This relationship has been expressed for nonpasserine birds (including raptors) as $Y = 78\ (M)^{0.72}$ (Lasiewski and Dawson, 1967), where Y is the animal's resting energy output in kilocalories per 24 hours, and M is the bird's mass in kilograms. The exponent 0.72 is not significantly different for 0.75 and thus variable Y is said to "scale" with mass to the 3/4 power (Schmidt-Nielsen, 1984).

The finding that energy requirements increase with the 3/4 power of the mass of the animal has become well established in the practice of comparative animal nutrition (Robbins, 1983). Size exerts its influence upon many other areas of importance to veterinary medicine (such as pharmacokinetic half-lives, heart rate, and clutch size), but this has yet to gain common acceptance in veterinary medicine. The purpose of this review is to outline methods by which certain biomedical values may be estimated from an animal's body weight using an allometric approach. Areas of specific interest to raptor biology are emphasized, including scaling of resting metabolism to body size, scaling of the capacity of transport organs (such as cardiac stroke volume), scaling of cyclic frequencies (heart rate, respiratory frequency, and so on), the concept of metabolic time, and the applications of scaling to such topics as nutrition, anesthesia, and clinical pharmacology.

KEY WORDS: raptor, allometric scaling, metabolic relationship, chemotherapeutics, anesthesia.

Modern veterinary practice had its roots in the care of domestic animals. With this limited number of species, it was possible to consider the physiology of each species independently. For this reason, the influence of size on biology was not appreciated, nor was a knowledge of it deemed necessary. Today the profession is becoming involved with a much wider range of species (there are 20,000 or so terrestrial vertebrates, spanning a size range from 2 g to 5,000 kg), and medicine is becoming very complex. An understanding of the influence of body size on biology and the rates of physiological processes is essential, because this millionfold difference in weight causes variations in physiology that obscure the basic patterns of similarity. Even among raptors, there is more than a 100-fold variation in size.

The finding that energy requirements increase with approximately the 3/4 power of body weight has become well established as a key principle in the science and practice of animal nutrition (Robbins, 1983), but similar weight relationships have yet to gain common acceptance in practice in other branches of veterinary science. As biological parameters have become established for animals of a range of body sizes, the allometric relationships of many of these parameters have been examined (Calder, 1984). The nature of these relationships offers clues as to how animals "work." They can also be of immediate practical value in predicting response to captive management.

In this chapter, the methodology of size scaling and its value in various fields of veterinary science and practice are

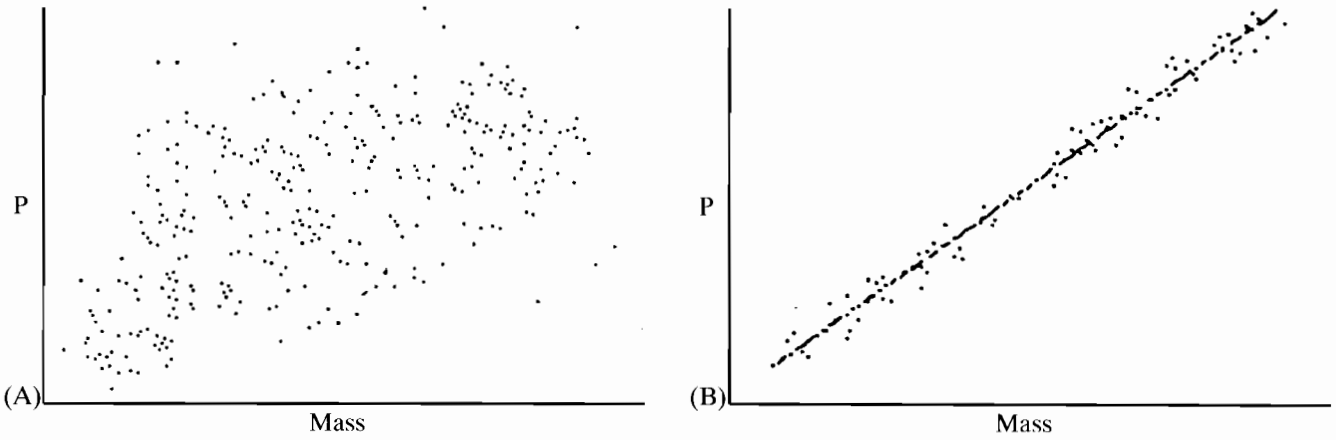


Figure 37.1. In allometry, many parameters (P), such as metabolic rate, life span, and kidney size, are found to vary between species with body mass in a curvilinear way (A). When logarithmically transformed, the points fall close to a straight line (B).

described. It must be borne in mind, first, that allometric relationships are not biological laws, but simply useful characterizations of data; and, second, that this field is in its infancy. As more data are gathered, new relationships will be found, and some of our existing theories will prove to be incorrect.

The Allometric Equation

Derivation

The allometric equation is a formula that can be used to summarize the relationship between the magnitude of any biological parameter (such as heart rate) and body weight. If the mean magnitude of the parameter P is plotted against mean body mass M for a variety of species, the points are often observed to cluster about a curved line (Fig. 37.1A). If these data are logarithmically transformed and then plotted, the points fall close to an approximately straight line (Fig. 37.1B). This line can be expressed in the traditional way ($y = bx + a$) by fitting a least squares linear regression equation:

$$\log P = \log a + b \log M$$

In the equation, b is the slope and log a is the y intercept. This then can be rearranged to the allometric equation:

$$P = aM^b$$

Although this equation was originally devised to describe the variation of P with M during the growth of an individual (Huxley, 1972), in this chapter we are concerned with its use in describing the variation of P among adults of different species. The following list summarizes several of the important mathematical techniques required to manipulate allometric equations (let A be equal to any number):

1. $A^m \times A^n = A^{m+n}$
2. $A^m + A^n = A^{m-n}$
3. $(A^m)^n = A^{mn}$
4. $A^o = 1$
5. $1/A^n = A^{-n}$
6. $A^{1/n} = \sqrt[n]{A}$
7. $A^{m/n} = \sqrt[n]{A^m}$

Examples and Interpretation

Some examples of allometric equations describing a selection of biological parameters are shown above. It is useful to have an insight into the significance of the values of b in the allometric equations. Fig. 37.2 includes two diagrams that show the pattern of the relationship of a parameter P to body weight M for various values of b on a generalized log-log scale.

Linstedt and Calder (1981) describe the various ways in which physiologic parameters are found to scale. Generally, the capacity of transport organs, such as blood volume, lung volumes, and cardiac stroke volume, tend to scale linearly with M ($b = 1$), so that their volume remains approximately in constant proportion to M as body size increases (Table 37.1).

Physiological volume rates such as oxygen consumption (ml O_2/min), glomerular filtration rate (GFR) (ml/min), and respiratory minute volume (l/minute), which have in common units of volume per time, tend to scale with $M^{0.75}$. These rates increase as animals increase in size, but note that the $b < 1$ slope (Fig. 37.2) means that a 5-kg animal will have a *lower* O_2 consumption per unit of body mass compared with a 50-g animal.

The frequency of cyclic events ranging from individual cycles (heart rate, respiratory rate, and so on) to population cycles (rate of population increase [r_{max}] or number of births/female/year, and so on) tend to scale with an exponent of approximately $M^{-0.25}$. For example, the heart rate

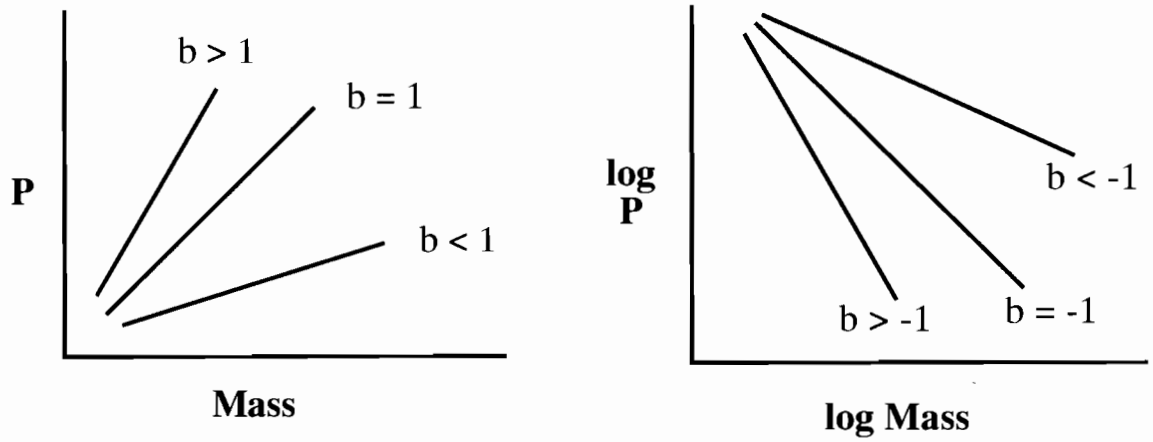


Figure 37.2. Patterns of the relationship of the magnitude of the parameter P to an animal's mass for various values of the exponent b.

of a large animal tends to be lower than that of a smaller animal.

Since cyclic frequencies vary with $M^{-0.25}$, the time to complete one cycle varies with $M^{0.25}$ (that is, $b = +0.25$). This means that the duration of one cardiac or respiratory cycle, the time to burn one unit of energy (kilocalorie, or kcal), or the time to excrete a given amount of a drug (the half-life) will tend to increase in a predictable fashion with the increasing size of the organism. The durations of many biological processes (time, for example, longevity or gestation period) tend to scale with $M^{0.25}$ (Fig. 37.3) (Linstedt and Calder, 1981).

Manipulation of Allometric Equa ions

If the correlation coefficients are very high, allometric equations can be manipulated as if they were simple equations, that is, as if they were exact rather than best-fit expressions. For example, in birds the growth time (t) is proportional to $M^{1/3}$ ($t \propto M^{1/3}$), and the length of the tarsometatarsus bone (L) is proportional to $M^{1/3}$ ($L \propto M^{1/3}$). The L/t (growth rate) is then $M^{1/3}/M^{1/3}$, which is equal to $M^{1/3-1/3}$, which is equal to M^0, which is 1. Thus, L/t is found to be proportional to a constant and independent of mass. This result is supported by Kirkwood et al. (1989), who found that tarsometatarsus growth rate was related to $M^{0.03}$ in a sample of 87 species of birds. The exponent 0.03 is not significantly different from 0.

Some Caveats

How useful is this equation as a general predictor of physiological, pharmacological, and other values? The points in Fig. 37.1 do not fall right on the line, but are scattered about it, so the equation provides an estimate of the value of P for a given M. Depending on the correlation coefficient, which provides an index of scatter about the line, the estimate may be good or may be of little value in practice. The confidence limits of an estimate of P for a given M can be calculated using techniques described in standard statistical texts.

Two important issues have a bearing on the value of the equations for predictive purposes. These methodological points have been discussed by Harvey and Mace (1982), Calder (1984), and others:

1. *The nature of the database*: The values of intercept a and slope b are wholly dependent on the data points (species) chosen or available for inclusion in deriving the regression equation. The line obtained may not represent the best fit through the data for the entire class or other subsets of it. The larger the data base and the greater the size range of the species included, the less likely it is that the line will be seriously biased. This point is particularly important when one is considering nonmammalian vertebrates, such as raptors. For many categories of data (physiological, population, and so on), our present extrapolations are based on small data sets from a limited number of avian species. Since one purpose of constructing allometric equations is to estimate values for an unknown species from a data set about its taxonomic group, the quality of the data determines the accuracy of the estimate. For this reason, it is imperative that additional, carefully collected, numerical data describing normal biological processes in healthy birds make their way into the literature.

2. *Statistical methods*: The equation also depends on the statistical method used in its derivation. There are a number of ways of fitting lines through scattergrams of data: least squares linear regression, major axis, or reduced major axis analyses. The pros and cons of these methods are described by Feldman and McMahon (1983), Smith (1984), and Calder (1984). When the correlation coefficient is high, the lines produced by these techniques are more or less superimposed and of equal predictive value in practice. But when

Table 37.1
Allometric formulae for nonpasserine birds

Parameter	*Formula*	*Reference*
Life span in captivity	yr = 28.3 $M^{0.19}$	Calder (1984)
Life span in the wild	yr = 17.6 $M^{0.20}$	Calder (1984)
Incubation period	days = 28.9 $M^{0.20}$	Calder (1984)
Length of respiratory cycle	sec = 3.22 $M^{0.33}$	Calder (1984)
Length of cardiac cycle	sec = 0.39 $M^{0.23}$	Calder (1984)
Heart rate (# per min)	155.8 $M^{-0.23}$	Lindstedt and Calder (1981)
Respiratory frequency (# per min)	17.2 $M^{-0.31}$	Lindstedt and Calder (1981)
Daily food intake (KJoule/day)	917 $M^{0.69}$	Farlow (1976)
Glomerular filtration rate (ml/min)	2.00 $M^{0.73}$	Calder and Braun (1983)
Tidal volume	13.2 $M^{1.08}$	Calder (1984)
Births per female per year (prop.)	$\propto M^{-0.22}$ to $M^{0.33}$	Calder (1984)
Oxygen consumption in birds (ml/min)	11.3 $M^{0.72}$	Schmidt-Nielsen (1984)

Note: M = body mass in kg. Basic requirements for every 100 kcals of MEC (for any species): water = 80-120 cc; sodium = 2.8 mEq; potassium = 2.2 mEq; chloride = 1.8 mEq.

the correlation coefficients are low, the prediction is influenced by the method used to draw the best-fit line.

Metabolic Rate and Body Size

Early in this century, comparative physiologists measured the metabolic rates of a variety of vertebrate species (Kleiber, 1947; Brody, 1945). As far as possible, these measurements were made on thermoneutral, postabsorptive, nonstressed animals. When the results of these studies were plotted, it was found that the energy required for minimal, resting body functions, including breathing, heart beat, peristalsis, and muscular support, did not increase linearly in proportion to increase in mass between species, but was proportional to body mass raised to about the 3/4 (or 0.75) power, indicating that smaller species had higher metabolic rates per unit mass than larger ones. Gessaman (1987) provides a good explanation of measuring the metabolism of raptors: the value of the exponent depends upon the species included in the analysis and the statistical techniques used. Typically, values in the range of 0.67 to 0.80 are found (Bennett and Harvey, 1987). Those who work with birds realize that these organisms both are smaller and have faster metabolic processes than domestic mammals. Observation reveals that birds also eat more food and excrete wastes more frequently than their equivalently sized mammalian counterparts.

When the lines relating metabolic rate to mass for various taxa have been compared, roughly parallel lines having a slope of about 0.75, but differing only in their Y intercepts, have been found (Fig. 37.4) (Hainsworth, 1981; Kleiber, 1947; Schmidt-Nielsen, 1984). It has been suggested that for various taxa these lines can be described by the following equation:

$$Y = K\,(M)^{0.75}$$

In the equation, Y = the resting animal's energy output in kcals per 24 hr, K = a taxonomically dependent constant, and M = an animal's body mass in kilograms. The following values of K have been suggested: passerine birds, 129; nonpasserines, 78; placental mammals, 70; marsupials, 49; and reptiles, 10 (at a species' preferred optimum temperature).

In practice, this equation allows us to estimate the basal energy expenditure for a wide range of species we might encounter. We refer to this basal energy expenditure as MEC, or minimum energy cost (Sedgwick et al., 1986). Two sample calculations will clarify the relationships:

1. The MEC of a 1,200 g owl can be estimated:
   $78 \times (1.2)^{0.75} = 89$ kcal/day.
2. The MEC of a 45 g passerine can be estimated:
   $129 \times (0.045)^{0.75} = 12.6$ kcal/day.

Mass-specific Metabolic Rate

When allometric rates are expressed per unit of body mass, they are termed mass specific or specific (SMEC). Mass specific scaling exponents are formed by dividing the rate equation by M:

$$Y = a(M)^{0.75}/\,M^1 = a(M)^{-0.25}$$

Thus, the mass-specific metabolic rate of an animal is a measure of the energy cost per unit mass to carry out its essential metabolic functions. In general, we can say that smaller animals require more energy per unit mass than large animals. For example:

The MEC of a 100-g raptor:
$\text{MEC} = 78 \times 0.100^{0.75} = 13.5$ kcals/day,
and therefore:
SMEC = 13.5/0.1 = 135 kcals/kg.
The MEC of a 1,000-g raptor:
$\text{MEC} = 78 \times 100^{0.75} = 78$ kcals/day,
and therefore:
SMEC = 78/1 = 78 kcals/kg (Fig. 37.5).

This can also be used to illustrate differences between taxa. For example, comparing the SMEC of an 850-g passerine bird with that of a placental mammal of the same mass:

The MEC of an 850-g passerine bird:
$\text{MEC} = 129 \times 0.85^{0.75} = 114$ kcal/day,

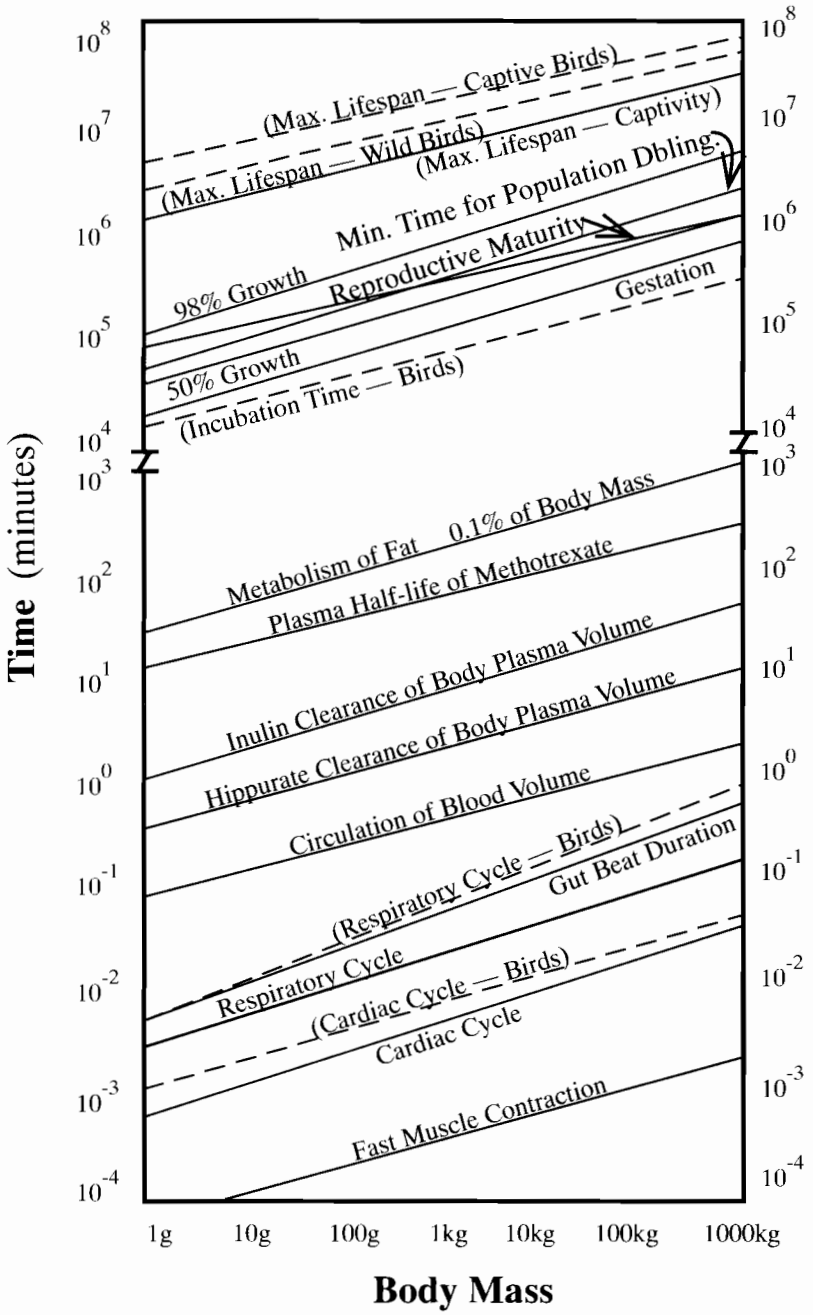


Figure 37.3. The relation between body mass and lengths of biological periods or cycles for mammals (solid lines) and for birds (dashed lines). Individual equations have been extrapolated to span the range of body sizes shown. Used with the permission of the *Quarterly Review of Biology* (Lindstedt and Calder, 1981).

and therefore:

$$\text{SMEC} = 114/0.85 = 134 \text{ kcal/kg/day.}$$

The MEC of an 850-g placental mammal:

$$\text{MEC} = 70 \times 0.85^{0.75} = 61.9 \text{ kcal/day,}$$

and therefore:

$$\text{SMEC} = 61.9/0.85 = 73 \text{ kcal/kg/day.}$$

Passerine birds have nearly twice (1.8 ×) the metabolic rate of a eutherian mammal of the same mass. This can also be seen by dividing the equations for MEC for the two taxa:

$$\frac{129\ M^{0.75}}{70\ M^{0.75}} = 1.8$$

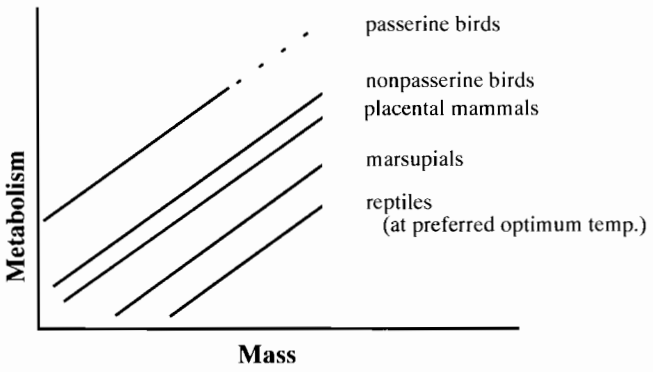


Figure 37.4. Regression lines representing the log-log plot of daily basal energy expenditure versus body mass for taxa of terrestrial vertebrates (after Hainsworth, 1981; Schmidt-Nielsen, 1984).

Allometric Calculation of Dietary Energy Requirements

Minimum energy cost is the amount of energy expended in sustaining vital functions when a resting animal is in a thermally neutral environment. The daily energy requirements exceed this (Kirkwood, 1981; Robbins, 1983; Calder, 1984). The amount by which requirements exceed MEC can be estimated under a variety of conditions as follows:

animal at rest	1.3-1.5 × MEC
animal with injury	1.5-2.5 × MEC
after surgery	1.5–2.5 × MEC
actively exercising	2-6 × MEC (depends on amount of exercise)
growing young	2-5 × MEC (depends on rate of growth)

Metabolic Scaling and Nutrition

We have already shown that the daily energy requirements of raptors are easily estimated. Food requirements can be estimated after consulting Fowler (1986), Exler (1987), Kirkwood (1981), or Watt and Merrill (1963) to find out how much metabolizable energy is contained in given food items. For example:

1. For a bald eagle weighing 5,000 g:
   $MEC = 78\ (5)^{0.75} = 260$ kcal/day.
2. Assume a low level of activity in captivity:
   $260 \times 1.5 = 390$ kcal/day.
3. How many adult rats should it be eating daily?
4. Rats contain 1.5 to 2 kcal/g of metabolizable energy (Fowler, 1986; Kirkwood, 1981).
5. Therefore, the bird is likely to require about 195 g of rat per day just for maintenance in captivity.

Sedgwick (1973, 1988a) and others have introduced to veterinary medicine the concept that specific nutrient requirements can also be scaled according to metabolism. For example, work by several authors (cited in Robbins, 1983) on water turnover rates has shown that for a variety of avian species, water turnover (Y = liters per day) scales to body mass with an exponent of 0.75 ($Y = 0.119\ M^{0.75}$) (Walter and Hughes, 1978; cited in Robbins, 1983).

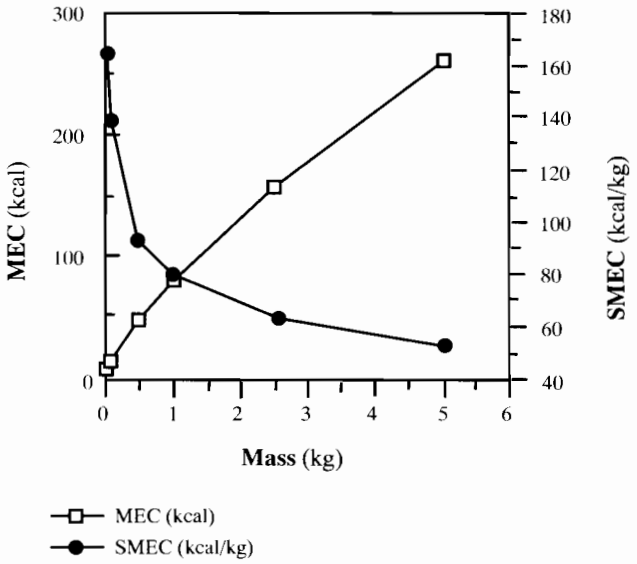


Figure 37.5. Graphic illustration of calculated minimum energy costs and specific metabolic rates for raptors from 50 g to 5 kg.

Other nutrients, both macro and micro, may tend to be utilized in proportion to the metabolic needs of an animal. Therefore, once the MEC for an animal has been calculated, an approximation of the daily requirement of other nutrients, including water, can be estimated allometrically per 100 kcal of daily energy cost (Table 37.2).

Physiologic (Metabolic) Time

Biologists have long made the association that large animals tend to live longer than small ones. In addition, larger animals tend to have slower heart rates and to reach sexual maturity at later ages. In 1945, Brody originated the term "physiological time," recognizing that smaller animals seem to "live" according to a faster time scale than large animals. It is helpful to look at a comparison of the specific metabolic rates of two birds of different weight. Returning to an example used in the previous section:

1. The MEC of a 100-g raptor:
   $MEC = 78 \times 0.100^{0.75} = 13.5$ kcals/day,
   therefore:
   $SMEC = 13.5/0.1 = 135$ kcals/kg/day.
2. The MEC of a 1,000-g raptor:
   $78 \times 100^{0.75} = 78$ kcals/day,
   therefore:
   $SMEC = 78/1 = 78$ kcals/kg/day.

Table 37.2
Suggested nutrients for mammalian or avian parenteral alimentation (per 100 kcal daily energy cost) [Reprinted with permission from the American Animal Hospital Association.]

Nutrient	*Adult*	*Infant*
Protein as essential amino acids (g)	3-7	5-9
Fat as essential fatty acids (g)	3-7	5-9
Carbohydrate as simple sugars (g)	10-13	3-6
Water (ml)	50-95	95-100
Vitamins		
A (IU)	300	300
D3 (IU)	25-35	50-75
E (IU)	2	3
C (mg)	10-15	10-15
K (mg)	3-6	15
Folic acid (μg)	25-50	25-50
Thiamin (μg)	100	200-800
Riboflavin (μg)	100-200	200-400
Niacin (mg)	1-2	800-1000
Pyridoxine (μg)	100-200	90-200
Cyanocobalamin (μg)	0.5	0.5
Biotin (μg)	10-20	10-20
Choline (mg)	20-100	20-100
Inosital (mg)	5	5
Pantothenic Acid (μg)	600-900	600-900
Minerals		
Calcium (mg)	5-100	100-200
Phosphorus (mg) (Ca:P = 1:1 to 2:1)	3-66	50-100
Sodium (mg)	75-100	35-50
Potassium (mg)	150	120
Chloride (mg)	75-100	50
Iron (mg)	1.1	2
Magnesium (mg)	25	10
Copper	0.1	0.1
Zinc (mg)	0.94	0.94
Iodine (μg)	10	10
Manganese (mg)	0.2	0.2

It could be said that the smaller raptor is "living" at nearly twice (1.7×) the rate of the larger. Linstedt and Calder (1981), in their extensive review of the literature on physiological time, remark that for homeotherms, a large number of developmental, physiological, and ecological cycles tend to scale in proportion to the quarter power of the body mass (about $M^{0.75}$) (Fig. 37.3). This elegant statement from Mordenti (1985) is useful:

> Physiologic time is measured by biologic clocks which use internal, physiologic parameters such as heartbeats, breath cycles or blood circulation velocities as units of measurement. When physiologic events in different mammals are measured by biological clocks, they occur in equivalent physiologic time. . . . Thus, the lifespan of an elephant and a mouse is the same when measured with a biological clock (i.e., heartbeats), although their life spans vary significantly when measured in years.

In the section on metabolic scaling and anesthesia below, we include an example of how one may use heartbeats as a measure of physiologic time. Fig. 37.6 is a graphic representation of the difference between chronological and physiological time, from Mordenti (1985).

Metabolic Scaling and Chemotherapeutics

Traditionally, veterinary and human medicine have calculated drug dosage and nutritional requirements based on body weight. Estimations of dose, treatment interval, toxicity, tissue levels, and routes of excretion are based upon measurements made in common, economically important domestic animals. No linear trend among these variables has been demonstrated; various authors have commented on the "random" nature of variables (Baggott, 1977). This approach has been acceptable where extrapolation occurs between species of similar size and metabolic rates, although variation in other factors (for example, species differences in drug metabolism) is known to occur.

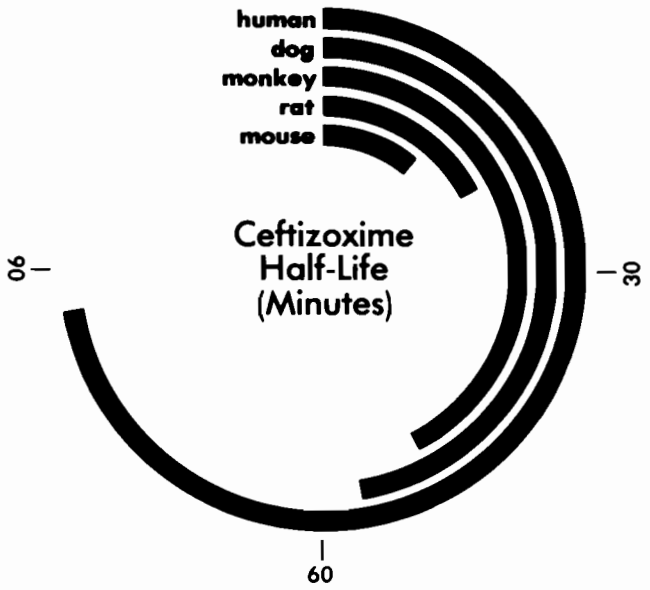
For avian, wildlife, and zoo veterinarians, the traditional means of extrapolation based on weight have proven to be less than satisfactory. We must all too often apply drug therapy to patients by extrapolation from a nebulous array of sources and therapeutic philosophies. This section introduces a metabolic scaling approach to the problem of interspecies drug extrapolation based upon physiological principles.

The Rationale of Pharmacokinetic Scaling

We have reviewed some of the ways in which allometry allows us to predict structural and functional characteristics of organisms. Allometry has proved to be of practical significance in the field of comparative nutrition (Robbins, 1983; Sedgwick, 1988a).

Newer and more controversial is the application of the power function to studies of pharmacology and toxicology. The action of toxins or drugs is linked to physiological mechanisms such as the blood supply to organs of excretion and the metabolic processes of cells for removal from the body. It seems reasonable to think that since we can form allometric equations to describe blood flow and metabolic rate, we may in a similar way describe the drug-disposition parameters that are dependent upon them. The relevance of body size to variation between species in the pharmacokinetic parameters describing elimination rates has been demonstrated for a range of drugs (Kirkwood and Merriam, 1990).

When a drug is administered to an animal, it first undergoes the processes of absorption from the site of administration and distribution to tissues. These processes are controlled by blood flow and extent of tissue perfusion (as



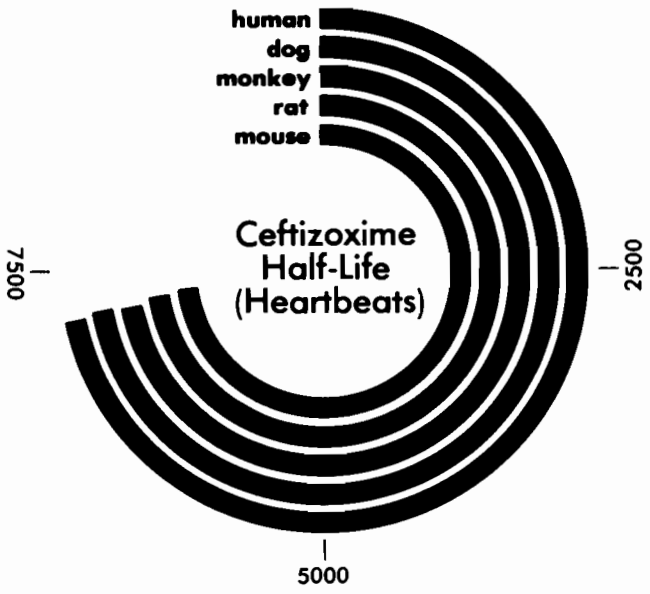


Figure 37.6. Perceived differences in the half-life of ceftizoxime in various mammals depend on the reference system used to denote time. (A) When half-lives are reported in minutes, the smaller mammals eliminate 50 percent of the drug more rapidly than the larger species. (B) When half-lives are reported in heartbeats, all mammals eliminate 50 percent of the drug in an equivalent time. Adapted from Mordenti (1985) with permission of the American Society for Microbiology.

well as by the local factors of pH, protein binding, and solubility). The drug may be taken up by various organs and either biotransformed or excreted unchanged. Rates of biotransformation are thought to be a function of such factors as membrane transport, enzyme kinetics, and concentration gradient. Although drugs vary as to the extent to which they are biotransformed, disposition kinetics are influenced by hemodynamics and rates of cell metabolism.

Based on the differences in physiology and metabolic rate between passerine birds and mammals, we form an intuitive sense of how drug disposition will vary between the two taxa. The 1-kg bird may have more rapid absorption and distribution of a drug from an injection site than the 1-kg mammal. Thus, the time to produce an effect is expected to be shorter in the bird. If the duration of action is governed by the rate of clearance of the drug from the plasma, then we may expect that the duration of effect will tend to be shorter in the bird than in the mammal (assuming they start with the same peak level). If the therapeutic object is to obtain some steady-state level of the drug, then doses may need to be given to the bird more frequently, or at higher levels, than to the mammal. However, this is not necessarily the case (see the discussion below concerning the difference between mammals and birds in glomerular filtration rate).

The little work that has been done in avian pharmacokinetics (Kirkwood and Merriam, 1990) provides evidence to suggest that relative volumes of distribution (V_ds) of drugs will vary with the type of drug. For most classes of drugs, it is not even known how V_d varies among orders of birds (Dorrestein et al., 1984).

Regarding routes of elimination, Dorrestein and van Miert (1988) remark: "In general, there is minimal variation among species in the manner by which polar compounds (like gentamicin) are handled by excretory mechanisms. This is in contrast with the wide interspecies variations and unpredictability associated with the biotransformation of extensively metabolized drugs (like chloramphenicol and sulfonamides)." The lack of information for avian species means that pharmacokinetic scaling in birds is in a more rudimentary stage than in mammals. Interspecies scaling in mammals is beginning to find its way into practical consideration (Mordenti, 1985; Mordenti and Chappell, 1989).

The following section presents (1) an introduction to interspecific scaling using an example of the drug inulin, (2) a basic scheme for scaling therapeutic regimens as outlined by Mordenti (1986; Mordenti and Chappell, 1989) in mammals, and (3) a method proposed by Sedgwick (1988b; Sedgwick et al., 1986) for scaling from mammals to birds.

Inulin Clearance, Scaling Therapeutic Regimens, from Mammals to Birds

A good first example is inulin, a drug that is filtered and excreted unchanged by the kidney. Edwards (1975) determined from published values of inulin clearance in mammals that

$$C_{in} = 5.36\ M^{0.72}$$

where C_{in} is the inulin clearance in ml/min, and M is the weight of the animal in kg. (The exponent 0.72 is not considered to be significantly different from 0.75.) Clearance is a drug-disposition parameter that has the units of a volume per time, just as cardiac output, minute ventilation, and oxygen consumption do; and clearance appears to vary with size in the same way. The data that Edwards used were collected from 26 species of mammals ranging in size from 0.15 to 590 kg.

Calder and Braun (1983) estimated inulin clearance from data on eight species of birds and found that

$$\text{avian } C_{in} = 2.00\ M^{0.73}.$$

Note that the constant 2.00 is lower than that for mammals (5.36), which implies that birds have a lower rate of inulin clearance than mammals of the same size (Edwards, 1975; Calder and Braun, 1983). Since inulin clearance is proportional to glomerular filtration rate (GFR), this suggests that birds also have a lower GFR than mammals of the same size. Although there are few data at the present time for birds, this finding could have important consequences in avian pharmacotherapeutics.

The lower clearance of inulin and perhaps lower GFR in birds compared with mammals seems in contrast with our expectation that clearance rates might be higher in birds due to their higher weight-specific metabolic rate. Perhaps it will be found that drugs that are excreted by simple glomerular filtration are more slowly cleared in birds than in mammals of the same size. This appears to be the case with gentamicin (Kirkwood and Merriam, 1990). The areas of avian physiology and pharmacology are certainly in need of an expanded data base.

A Basic Therapeutic Scaling Scheme

Mordenti and Chappell (1989) remark that, in mammals, the allometric exponents for the clearance of drugs usually range between 0.6 and 0.8. An exponent of less than 1.0 signifies that the mass-specific clearance, or Cl/kg, is lower in a large animal than in a smaller animal. Thus, one should expect that the same mg/kg dosage given to a 5,000-g eagle will result in a much longer "duration of action" than in a 100-g kestrel. To maintain effective drug levels, one must give the drug to the smaller animal more frequently.

This scaling principle may be applied toward three basic pharmacotherapeutic goals in approximating dosing schedules for an "unknown" subject based on pharmacokinetic data from a model animal (Mordenti and Chappell, 1989).

Goal 1 is the achievement of average equivalent steady-state concentrations. This is the basic ambition of most antibiotic/antifungal drug therapy and many other therapeutic agents. The plasma concentrations will oscillate around a constant average value. Mordenti reports an equation to predict dose for a subject animal (in this case the "subject" is a human) based on a dose in a "model" (animal) such that their steady-state concentration (C_{ss}) will be the same:

$$D_{human} = D_{animal} \left(\frac{F_{animal}}{F_{human}} \times \frac{T_{human}}{T_{animal}} \times \frac{W_{human}}{W_{animal}} \right)^{0.70}$$

D is the dose (mg, μg, and so on), F the bioavailability, T the treatment interval (min, hr, or the like), and W the body mass in kg. If T and F were the same for both animals, then the smaller of the two would require higher doses, which would result in higher peak concentrations (assuming equivalent V_d in the two animals). Mordenti uses the value for the exponent of 0.70 as a compromise between proponents of the 0.67 and 0.75 values.

In veterinary medicine, this means that if the smaller animal can tolerate the higher dose, and thus peak concentration, then the treatment interval may not need to be altered. If the predicted dose (mg/kg) is above the accepted toxic threshold, then the equation can be used to shorten the treatment interval, thus lowering the peak dose while maintaining "pharmacokinetic similarity." Although the above equation has many terms, it is a relatively simple matter to insert the values from a known situation to derive a dose for an animal for whom nothing is known but its weight.

Goal 2 is the achievement of similar peak concentrations. There are two instances in which calculation of doses to achieve equivalent minimum or maximum concentrations would be desirable. The first is if it is known that exceeding a certain concentration produces toxicity, as in the case of the drug gentamicin. The second is if a certain minimum concentration needs to be obtained. The equation given by Mordenti to achieve equivalent peak concentrations is as follows:

$$D_{human} = D_{animal} \left(\frac{F_{animal}}{F_{human}} \right) \left(\frac{V_{human}}{V_{animal}} \right) = D_{animal} \left(\frac{W_{human}}{W_{animal}} \right)^{1.0}$$

where V is the volume of distribution (ml, l, and so on), an estimate of the extent of distribution of the drug within the body (Baggot, 1977). The reduced equation assumes F is similar and volume scales as $W^{1.0}$.

Goal 3 is the achievement of similar "area under the curve" (AUC). AUC is important when cumulative dose becomes an issue, such as with the relatively toxic antineoplastic drugs. The equation given for this, in which hum = human and an = animal, resembles the equation given for Goal 1 above:

$$\#doses/day_{hum} = \#doses/day_{animal} \left(\frac{F_{an}}{F_{hum}} \times \frac{D_{an}}{D_{hum}} \times \frac{W_{hum}}{W_{an}} \right)^{0.70}$$

These three equations are based on the work of Mordenti (1986) and Mordenti and Chappell (1989) and apply to extrapolations within the taxonomic group of placental mammals. Extrapolation between taxonomic groups based on variations in metabolic rates (K factors) rather than body size are considered in the next section.

A Proposed Method of Scaling from Mammals to Birds

Sedgwick et al. (1986), Sedgwick (1988b), and Kirkwood (1983a, 1983b) have proposed that if drug disposition is influenced by metabolic rate over a range of sizes within a taxon, then the K factor constants (mentioned above in the section on metabolic rate and body size) should also be considered when one is predicting dosage. In other words, the K factors should relate parameters that scale with the 0.75 exponent, as dose for equivalent C_{ss} does. If all else is equal, we might expect dose (mg) for C_{ss} per unit of energy expenditure to be roughly constant between species. The following example shows how dose can then be calculated, remembering that K for nonpasserine birds is 78 and for mammals is 70:

1. Using a species for which reliable laboratory data are available (model species), find a reliable dose and treatment interval.

Example: Cephalothin, 2.0 g IM QID for a 70 kg "model" human (Sanford, 1988). Then, 2,000 mg × 4 = 8,000 mg/day for the total dose.

2. Calculate the MEC for this species:

$$MEC = K \times M^{0.75},$$

or

$$MEC = 70 \times 70^{0.75} = 1{,}694 \text{ kcal/day}.$$

M is the weight of the animal in kg and K is the K factor constant for placental mammals, or 70.

There are currently two models for how the above quantities can be used to calculate an allometric, or MEC, dose. Methods 1 and 2 are illustrated in Steps 3 through 5. Conceptually, these methods differ in that Method 1 concludes that smaller species with higher metabolic rates must *both* receive an increased dose of a drug (mg/kg) and receive these doses at more frequent intervals. Method 2 concludes that simply increasing the frequency of administration should be sufficient to account for metabolic variations.

Method 1 gives numerical results that are in agreement with Mordenti and Chappell's (1989) pharmacokinetic data for several mammalian taxa. Proponents of Method 1 believe that scaling drug dosages is most appropriately performed by extrapolating from the quantity of drug a model species is given per treatment interval, whereas proponents of Method 2 advocate that extrapolations should be performed from the 24-hr total drug dose received by the model species. As more pharmacokinetic data become available, we anticipate that one of these models will be verified. At present the technique illustrated by Method 1 is in use at the Tufts Wildlife Clinic.

Method 1

3. Divide the per treatment dose (mg) by the MEC and get a dosage in mg/kcal:

$$2{,}000/1{,}694 = 1.18 \text{ mg per kcal.}$$

Assume that this dosage rate is applicable to any species.

4. Calculate the appropriate dose for an 890-g peregrine falcon (subject species):

a. Calculate the MEC:

$$78 \times 0.89^{0.75} = 71 \text{ kcal.}$$

b. Multiply by 1.18 mg/kcal to get the dose:

$$71 \times 1.18 \text{ mg/kcal} = 83.78 \text{ mg/treatment.}$$

5. Calculate a metabolically appropriate dosing interval:

a. Calculate specific metabolic rate (SMEC, expressed as kcal/kg) for both model species and subject species:

$$\text{Human: } 1{,}694 \text{ kcal}/70 \text{ kg} = 24.2 \text{ kcal/kg.}$$

$$\text{Falcon: } 71 \text{ kcal}/0.89 \text{ kg} = 79.7 \text{ kcal/kg.}$$

b. Utilize these values in the following formula:

$$\text{Dose Interval}_{\text{subject}} \text{ (hours)} = \left(\frac{\text{SMEC}_{\text{subject}}}{\text{SMEC}_{\text{model}}} + \text{Dose Interval}_{\text{model}} \right)^{-1}$$

For this subject (peregrine) this would work out in this manner:

$$\text{Dose Interval} = [(79.7/24.2) + 6]^{-1} = 1.8 \text{ hrs.}$$

This means that ideally the falcon's daily dose should be divided into 12 doses of 84 mg to be given once every 2 hr, or 1,008 mg/day.

Method 2

3. Divide the total daily dose (mg) by the MEC and get a dosage in mg/kcal:

$$8{,}000/1{,}694 = 4.72 \text{ mg per kcal.}$$

4. Calculate the appropriate dose for an 890-g peregrine falcon (subject species):

a. Calculate the MEC:

$$\text{MEC} = 78 \times 0.89^{0.75} = 71 \text{ kcal.}$$

b. Multiply by 4.72 mg/kcal to get the dose:

$$71 \times 4.72 = 335 \text{ mg/day.}$$

5. Calculate a metabolically appropriate dosing interval: The calculation for dosing interval is identical to that in Method 1, however, subsequent reasoning differs. We now must take the total daily dose of 335 mg and divide it into equal intervals to be given every 1.8 hr. When rounded to unit hours, this means that the falcon's daily dose should be divided into 12 doses of 28 mg to be given once every 2 hr.

Obviously, such brief treatment intervals are impractical under most circumstances. If a drug were safe, it would probably be appropriate simply to give a larger dose less often. It is possible to use the equation for steady-state concentrations from Mordenti and Chappell (1989) for a longer and more practical treatment interval, as long as the new dose is not toxic. The toxic dose can be estimated from the model animal, if available, by using the peak-concentration equation given above from Mordenti and Chappell. The following list summarizes the differences in the two methods:

Step	*Method 1*	*Method 2*
3. mg/kcal dose	1.18	4.72
4. dose for 0.89 kg falcon	83.8 mg/ treatment	335 mg/day
5. determine interval	84 mg every 2 hr for 12 treatments per day = 1,008 mg/day	28 mg every 2 hr for 12 treatments per day = 335 mg/day

The dramatically different results obtained from these two models point clearly to the need for further laboratory studies of avian pharmacokinetics. Clearly, until pharmacokinetic studies are performed in a broader range of species, one must be very cautious about the use of drugs with known tissue toxicity in small species with high metabolic rates. We hope that this knowledge about the effects of metabolic scaling on pharmacokinetics will provide the impetus for the development of new techniques for drug administration in small wildlife species. In theory, such techniques as implantable osmotic pumps, slow-release drug-impregnated polymers, and adhesive patches for transcutaneous absorption might provide the slow, constant levels that small species appear to require.

The rates and efficiency of absorption from the digestive tract of birds appear to be quite variable. This is an area in which it is very unreliable to apply mammalian dosing schedules to birds, owing to the great variation in avian gastrointestinal anatomy and function. Dorrestein and van Miert (1988) present a good review of the methods of drug administration in birds.

Table 37.3
Calculated doses for nonpasserine birds based on an MEC dose of 0.23 mg/kg of ketamine compared with published data for empirically derived doses of ketamine

Body weight (kg)	*MEC (kcal)*	*Total ketamine dose (mg)*	*Calculated dose (mg/kg)*	*Empirical dose (mg/kg)*[a]
0.040	6.9	1.6	40	40
0.100	13.8	3.1	31.7	30
1.187	88.7	20.4	17.1	20
2.0	131	30.1	15	16
4	220.6	50.7	12.6	16
8	371	85.3	10.6	16

[a]Samour et al. (1984).

Extensions of Scaling Principles to Other Aspects of Raptor Biomedicine

Metabolic Scaling and Anesthesia

In a retrospective study of several injectable anesthetics, Samour et al. (1984) examined the use of these drugs in 154 species of birds ranging from 40 g to more than 8 kg. Table 37.3 includes a sampling of their data for a variety of nonpasserines.

The allometric (or MEC) dose of 0.23 mg/kcal utilized in Table 37.3 was derived as described in the above section on chemotherapeutics. By comparing the last two columns of Table 37.3, one can see that the doses predicted by allometric scaling closely approximate those derived empirically. Kirkwood and Wathes (1984) plotted Samour's data for ketamine allometrically and found that doses of ketamine required for adequate sedation scale with body mass to 0.78. This suggests that the dose rates are a function of the animals' metabolic rates, although other explanations are possible. However, the principles of allometric scaling may assist in making reasonable approximations for the use of injectable anesthetic agents on unknown species before subjecting any patients to an actual trial.

Studies at the Wildlife Clinic of Tufts University School of Veterinary Medicine (Sedgwick et al., 1986; Sedgwick, 1988b) have found that a combination of equal volumes of the injectable anesthetic agents ketamine (100 mg/ml) and xylazine (20 mg/ml) also scales allometrically for a wide variety of species. The ketamine-xylazine (50:50 mixture by volume) MEC dose of between 0.0022 and 0.0044 ml per kcal of basal energy requirement will chemically immobilize most vertebrates, including raptors, from small kestrels to the largest eagles. The lesser rates of administration should be used in the larger species, otherwise considerable respiratory depression may occur.

Metabolic Scaling and Heart Rate

One of the most useful indicators for measuring depth of anesthesia is heart rate. Knowing that the heart rate of raptors scales according to $156\ M^{-0.23}$ (Schmidt-Nielsen, 1984) allows us to calculate what the resting heart rate of any species should be. The Tufts Wildlife Clinic uses a functional definition of bradycardia as any rate more than 20% below the calculated rate.

Metabolic Scaling and Surgical Issues: Heart Rate and Oxygen Consumption

A knowledge of metabolic time is also critical for successful anesthetic technique. For example, common knowledge has it that humans can live for 5 to 6 min without oxygen before sustaining brain damage. Most veterinary students learn that dogs can survive for about 4 min under the same conditions. According to metabolic time, this should indicate to us that any vertebrate should be able to live for about 500 heartbeats before serious damage occurs. If this is so, what does it mean for our raptor patients? We already know that birds have slower heart rates than mammals of the same mass (Calder, 1984). Calculating the heart rate for a 6,000-g raptor reveals that it is likely to have a resting rate of approximately 100 beats per min. A 50-g raptor, on the other hand, would have a calculated rate of about 310 beats per min. We contend, therefore, that, all else being equal, the large raptor should survive about 5 min unharmed, but that our smaller patient might suffer irreversible damage in less than 2 min.

Hypothermia

Smaller patients have a proportionately greater surface area from which to lose heat than large ones. A surgical plane of anesthesia eliminates the patient's ability to generate additional heat by movement, shivering, or other adaptive actions. Additionally, ventilation is conducted with relatively cool, low-humidity gases. So even before an initial incision is made on a small avian patient, the bird may be approaching hypothermia.

Once the bird's body is opened surgically, we have not only eliminated the insulative protection of its feathers, but we have drastically increased the surface area available for cooling. So it is apparent that the provision of external sources of heat, an ocassionally used option for larger patients, is critical to surgical success with small birds.

In metabolic time terms, every minute on the surgical table for a 6-kg eagle is metabolically equivalent to 3 min of surgical time for a 50-g owl. Therefore, in planning the length of stressful procedures with small patients, attention must be paid to the metabolic clock—*not* the one on the wall. A 1-hr surgery on the tiny owl could be expected to cause the same amount of physiological stress as subjecting the eagle to a 3-hr procedure.

Conclusion

As stated at the outset, this chapter provides only a brief introduction to allometric scaling. We have not addressed such topics as population biology (where scaling has been used to explain the differences in population cycles of several species), island biogeography (where scaling has been useful in explaining the distribution of variously sized animals), the evolutionary limits of growth (where scaling has contributed strong support for the theory of the warm-blooded dinosaurs), and dozens of others. Schmidt-Nielsen (1984) and McMahon and Bonner (1983) provide a basic introduction to allometric scaling, while Calder (1984) gives a much more detailed and mathematically more rigorous approach.

For anyone wishing to try scaling drug dosages and periodicities, but intimidated by the mathematics entailed in allometric scaling, Pokras (1987), Pokras and Sedgwick (1987), and Sedgwick et al. (1986) offer simplified introductions to working with these concepts.

References

Baggott, J. D. 1977. Principles of drug disposition in domestic animals. W. B. Saunders, Philadelphia, Pennsylvania.

Bennett, P. M., and P. K. Harvey. 1987. Active and resting metabolism in birds: allometry, phylogeny and ecology. Journal of Zoology, London 213:327-363.

Brody, S. 1945. Bioenergetics and growth. Hafner Publishing, New York.

Bush, M., et al. 1981. Pharmacokinetics of cephalothin and cephalexin in selected avian species. American Journal of Veterinary Research 42:1014-1017.

Calder, W. A., III. 1984. Size, function and life history. Harvard University Press, Cambridge, Massachusetts.

Calder, W. A., III, and E. J. Braun. 1983. Scaling of osmotic regulation in mammals and birds. American Journal of Physiology 244:R601-R606.

Dorrestein, G. M., H. van Gogh, and J. D. Rinzema. 1984. Pharmacokinetic aspects of penicillins, aminoglycosides and chloramphenicol in birds compared to mammals. Veterinary Quarterly 6:216-224.

Dorrestein, G. M., and A. S. J. P. A. M. van Miert. 1988. Pharmacotherapeutic aspects of medication of birds. Journal of Veterinary Pharmacologic Therapy 11:33-44.

Edwards, N. A. 1975. Scaling of renal function in mammals. Comparative Biochemistry and Physiology 52A:63-66.

Exler, J. 1987. Composition of foods: finfish and shellfish. Agricultural Handbook No. 8-15 (USDA). U.S. Government Printing Office, Washington, D.C.

Farlow, J. O. 1976. A consideration of the trophic dynamics of a late cretaceous large dinosaur community. Ecology 57:841-857.

Feldman, H. A., and T. A. McMahon. 1983. The 3/4 mass exponent for energy metabolism is not a statistical artifact. Respiratory Physiology 52:149-163.

Fowler, M. E. (ed.). 1986. Zoo and wild animal medicine. W. B. Saunders, Philadelphia, Pennsylvania.

Gessaman, J. A. 1987. Energetics. *In* Raptor techniques manual, B. A. Pendleton et al. (eds.). National Wildlife Federation Science & Technology Series 10:289-320.

Hainsworth, F. R. 1981. Animal physiology: adaptations in function. Addison-Wesley, Reading, Massachusetts.

Harvey, P. K., and G. M. Mace. 1982. Comparisons between taxa and adaptation trends: problems of methodology. *In* Current problems in sociobiology, King's College Sociobiology Group. Cambridge University Press, Cambridge, England, pp. 346-364.

Huxley, J. S. 1972. Problems of relative growth, 2nd ed. Dover Publications, New York.

Kirkwood, J. K. 1981. Maintenance energy requirements and rate of weight loss during starvation in birds of prey. *In* Recent advances in the study of raptor diseases, J. E. Cooper and A. G. Greenwood (eds.). Chiron Publications, Keighley, West Yorkshire, England, pp. 153-157.

_____. 1983a. Dosing exotic species. Veterinary Record 112:486.

_____. 1983b. Bodyweight and drug dosage rates. British Veterinary Zoological Scoiety News 16:5-7.

_____. 1983c. Influence of body size in animals on health and disease. Veterinary Record 113:287-290.

Kirkwood, J. K, and J. Merriam. 1990. Variation in plasma half-life of gentamicin between species in relation to body weight and taxonomy. Research in Veterinary Science 49:160-165.

Kirkwood, J. K., and K. Thompson. 1984. Food and energy consumption of some large raptors at the Bristol Zoological Gardens. International Zoological Yearbook 23:114-117.

Kirkwood, J. K., and C. M. Wathes. 1984. Size, time and ketamine. Veterinary Record 115:390-391.

Kirkwood, J. K., and A. J. F. Webster. 1984. Energy-budget strategies for growth in mammals and birds. British Society of Animal Production:147-155.

Kirkwood, J. K., et al. 1989. Patterns of cell proliferation and growth rate in limb bones of the domestic fowl (*Gallus domesticus*). Research in Veterinary Science 47:139-147.

Kleiber, M. 1947. Body size and metabolic rate. Physiological Review 27:511-541.

Lasiewski, R. C., and W. R. Dawson. 1967. A re-examination of the relation between standard metabolic rate and body weight in birds. Condor 69:13-23.

Lindstedt, S. L., and W. A. Calder III. 1981. Body size, physiological time and longevity of homeothermic animals. Quarterly Review of Biology 56:1-16.

McMahon, T., and J. Bonner. 1983. On size and life. Scientific American Books. W. H. Freeman, New York.

Mordenti, J. 1985. Forecasting cephalosporin and monobactam antibiotic half-lives in humans from data collected in laboratory animals. Antimicrobial Agents and Chemotherapeutics 27:887-891.

_____. 1986. Man vs. beast: pharmacokinetic scaling in mammals. Journal of Pharmaceutical Science 75:1028-1040.

Mordenti, J., and W. Chappell. 1989. The use of interspecies scaling in toxicokinetics. *In* Toxicokinetics in drug development, A. Yacobi (ed.). Pergamon Press, Elmsford, New York.

Peters, R. H. 1983. The ecological implications of body size. Cambridge University Press, New York.

Pokras, M. A. 1987. Secrets of medical math. *In* Proceedings of the Sixth Symposium of the National Wildlife Rehabilitators Association, D. J. Mackey (ed.). National Wildlife Rehabilitators Association 6:33-38.

Pokras, M. A., and C. J. Sedgwick. 1987. Scaling nutrition and drug dosage based on metabolism. Proceedings of the 8th Annual Meeting of the Mid-Atlantic States Association of Avian Veterinarians, pp. 181-186.

Robbins, C. T. 1983. Wildlife feeding and nutrition. Academic Press, New York.

Samour, J. H., et al. 1984. Comparative studies of the use of some injectable anaesthetic agents in birds. Veterinary Record 115:6-11.

Sanford, J. P. 1988. Guide to antimicrobial therapy. Antimicrobial Therapy, Bethesda, Maryland.

Schmidt-Nielsen, K. 1984. Scaling: why is animal size so important? Cambridge University Press, New York.

Sedgwick, C. J. 1973. Methods of feeding animals. Proceedings of the American Association of Zoo Veterinarians, pp. 177-222.

_____. 1988a. Finding the dietetic needs of captive native wildlife and zoo animals by allometric scaling. Proceedings of the 55th Annual Meeting of the American Animal Hospital Association, Washington, D.C., pp. 149-154.

_____. 1988b. Anesthetic and chemical restraint techniques for zoo animals and wildlife. Proceedings of the 55th Annual Meeting of the American Animal Hospital Association, Washington, D.C., pp. 162-168.

Sedgwick, C. J., A. Haskell, and M. A. Pokras. 1986. Scaling drug dosages for animals of diverse body sizes. *In* Proceedings of the Fifth Symposium of the National Wildlife Rehabilitators Association, P. Beaver and D. J. Mackey (eds.). National Wildlife Rehabilitators Association 5:3-11.

Sedgwick, C. J., and M. A. Pokras. 1988. Extrapolating rational drug doses and treatment periods by allometric scaling. Proceedings of the 55th Annual Meeting of the American Animal Hospital Association, Washington, D.C., pp. 156-157.

Smith, R. J. 1984. Allometric scaling in comparative biology: problems of concept and method. American Journal of Physiology 15:R152-R160.

Thompson, D. W. 1917. On growth and form. Cambridge University Press, New York.

Walter, A., and M.R. Hughes. Total body water volume and turnover rate in fresh water and sea water adapted glaucous-winged gulls, *Larus glaucescens*. Comparative Biochemistry and Physiology 61:233-237.

Watt, B. K., and A. L. Merrill. 1963. Composition of foods. Agriculture Handbook No. 8 (USDA). U.S. Government Printing Office, Washington, D.C.

Zar, J. H. 1969. The use of the allometric model for avian standard metabolism-body weight relationships. Comparative Biochemistry and Physiology 29:227-234.

CHAPTER 38

Appetite Stimulation in Raptors

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ABSTRACT: The effective management of anorexia in raptors requires identification of the causes and use of the appropriate therapy for its control. Successful management consists of a blend of good husbandry practices, presentation of familiar foods, familiarization to novel diets, and the use of pharmacological agents. B-complex vitamins, corticosteroids, anabolic steroids, probiotics, and benzodiazapine derivatives have been employed to stimulate appetite where provision of reduced-stress environments and familiar foods have been insufficient. Based on a mix of largely unpublished experiences of various avian clinicians as well as extrapolations from human and other areas of veterinary medicine, the use of B-complex vitamins at a rate of 10 mg/kg thiamine, dexamethasone at 2-4 mg/kg, stannizol at .5 mg/kg, diazepam at .25-.5 mg/kg, and Lactobacillus cultures are recommended for pharmacological management of anorexia in raptors.

KEY WORDS: raptor, anorexia, appetite stimulation.

Anorexia can be a significant clinical problem in wild birds, and a concerted effort is often required by the clinician to induce feeding. Factors inhibitory to a bird's feeding behavior include reaction to the stress of injury and captivity, debilitation, injury, and organic disease. Anorexia is managed through recognition of the underlying cause(s); good husbandry practices, such as provision of a reduced-stress environment and recognizable food; and medical therapy. Little specific information exists on methods for medically managing anorexia in birds. The purpose of this chapter is to summarize the major clinical trends in managing this problem in birds based on the limited published information, personal communications, my own experiences, and extrapolation of the use of procedures used in human and other areas of veterinary medicine.

Management of Anorexia by Traditional Methods

Captivity may cause stress to wild animals. Among raptors, buteos, falcons, and owls generally are more tolerant of captive environments, while bald eagles (*Haliaeetus leucocephalus*), accipiters, and especially ospreys (*Pandion haliaetus*) exhibit poorer responses. Ospreys seldom feed spontaneously in any but the most stress- and disturbance-free environments. Astute attention to individual response to stress is important for inducing spontaneous feeding.

The state of health and injury of birds at admission will have an impact on the appetite of the patient. Two different situations are commonly encountered: (1) acute injuries without debilitation, and (2) chronic injury with debilitation. The former is readily managed in most instances, since the patient, once stabilized, can be offered and will accept an appropriate diet if favorable husbandry practices (see below) are employed. The starving bird, on the other hand, often cannot digest a solid diet and should receive easily digested preparations (Redig, 1984).

The base of such diets usually consists of an electrolyte solution with simple sugars and amino acids. Products available for human uses[a] may be used for raptors, as well as several homemade solutions (Redig, 1984; McKeever, 1979, pp. 30-34). A commercially available avian product[b] may also be chosen. In severely emaciated birds, the simple diet is fed by gavage tube exclusively for the first day at a rate totaling about 10% of the bird's weight in 2 to 4 divided doses (see Pokras et al., chapter 37, this volume, for further information on establishing amounts to feed). The volume of the simple diet is gradually decreased as a more complex or solid-meat diet is accepted by the bird. This transitional process continues until the bird is taking a whole-animal diet, which may take more than a week.

Force-feeding may be required to induce recognition and acceptance of the novel diets that are often substituted for natural foods. Such items as ground-meat products[c] or day-old cockerels or turkey necks or white mice may be substituted (Garcelon and Bogue, 1977). The sight of another raptor feeding may also help stimulate feeding behavior.[1]

Pharmacological Solutions to Anorexia

Husbandry solutions to anorexia are not always successful, and medical therapy may be employed. The use of drugs should not suspend the search for a possible organic cause of anorexia, however, because the anorexia may only be a

sign of a specific disease. The use of various agents with appetite-stimulating properties may be attempted. The drug groups recommended are the B-complex vitamins, corticosteroids, anabolic steroids, benzodiazepines, and the probiotics.

B-complex vitamins are commonly used to stimulate appetite in mammals (Buffington, 1986; Jenkins, 1982) and birds (Redig, 1992). Vitamins are regulatory enzymes for various physiologic processes. They are divided into fat-soluble and water-soluble forms. The fat-soluble vitamins (K, A, D, and E) are usually stored in large enough quantities to survive periods of injury or disease, but the water-soluble forms, which cannot be stored in great amounts, must be constantly ingested. Animals that are injured or diseased will require higher levels of vitamins, but it is often at this time that the ingestion of vitamins is at its lowest point (Buffington, 1986). The combination of increased need, decreased intake, and rapidly diminishing reserves makes the use of vitamins logical (Lewis et al., 1987). The B-complex vitamins are thought to be the most helpful vitamins for anorexia, however, their mechanism of action is poorly understood (Jenkins, 1982). The dosages of B-vitamins in raptors have not been specifically established, and prescribed dosages are extrapolations from other species. Fortunately, the use of B-complex vitamins, except in very large doses, is considered harmless. Amounts of B-complex vitamins administered are determined as a function of the thiamine content of the preparation, so that the dosage rate of 10 mg/kg given daily by IM injection for the duration of the anorexia is recommended (Clubb, 1986).

The second group of drugs to be considered for treating anorexia are the corticosteroids (Lewis et al., 1987; Jenkins, 1982; see Kaufman et al., chapter 32, this volume). Corticosteroids are widely used in veterinary medicine and are commonly administered in emergency raptor care (Redig, 1992; Kaufman et al., chapter 32, this volume). Corticosteroids are usually given in a single large dose by intramuscular or intravenous routes and are not repeated except in cases where continued anti-inflammatory action is needed, such as cranial trauma. The side effects of steroid use include immunosuppression, decreased wound healing, and iatrogenic Cushing's disease, but a single dose is rarely contraindicated. The dose of dexamethasone for emergency use is 2 to 4 mg/kg (Redig, 1992). In mammals, the corticosteroid appetite-stimulating effect is thought to be the result of its ability to create a euphoric effect that may relieve depressive states and therefore stimulate food intake (McDonald, 1982).

Several researchers suggest the use of anabolic steroids (stanazolol[d]) as another alternative for anorexia management in mammals (Lewis et al., 1987; Jenkins, 1982). The action of anabolic steroids involves their tissue-building capabilities, and they are used mainly in animals recovering from debilitating diseases. A dosage recommended by Clubb (1986) for stanazolol for use in birds is 25 mg/kg once or twice weekly.

Benzodiazepines, tranquilizers with both anticonvulsant and antianxiety activities, are commonly used for appetite stimulation in small animals (Lewis et al., 1987; Lulich and O'Brien, 1988; Jenkins, 1982). Two theories of mechanism of action have been proposed. Benzodiazepines may inhibit the satiety center or activate the hunger center in the brain (Jenkins, 1982; Baile and McLaughlin, 1979). The second theory invokes suppression of emotional influences that inhibit feeding (Baile and McLaughlin, 1979). The benzodiazepines used for stimulation include diazepam,[e] oxazepam,[f] and flurazepam hydrochloride[g] (Lewis et al., 1987; Lulich and O'Brien, 1988). Degree of appetite stimulation, induction of ataxia, and length of effect vary among these compounds.

In one study, oxazepam proved to be the most successful drug in cats of those tested, but it is available only in oral form (Fratta et al., 1976). Oxazepam has been shown to continue its appetite stimulation for up to 12 hr after ingestion (Fratta et al., 1976). Flurazepam hydrochloride has been reported to last for 4 to 7 days in cats (Lulich and O'Brien, 1988). Diazepam, although not as powerful a stimulant as some of the other drugs, is used commonly in cats and is readily available in a variety of dosage forms.

Benzodiazepines are effective in overcoming many causes of feeding inhibition, including heat stress and food additives with unfamiliar or aversive flavors. Their ability to overcome anorexia with many disease states in a variety of species has been reported (Baile and McLaughlin, 1979). Different species also show different responses to the various drugs. Cats are several times more sensitive than dogs to the effects of the benzodiazepines (Della-Fera et al., 1980). Interspecific response variation among raptors is likely.

In my experience, diazepam has been an effective appetite stimulant in raptors and is the recommended benzodiazepine because of availability, oral and parenteral forms of administration, and safety with raptors. The drug has been given both IM and IV in dose ranges of .25 mg/kg to .5 mg/kg. A single dose is often effective, but dosing at daily intervals for 2 or 3 days can also be helpful.

Red-tailed hawks (*Buteo jamaicensis*), red-shouldered hawks (*Buteo lineatus*), great horned owls (*Bubo virginianus*), bald eagles, and several nonraptorial species have responded to diazepam therapy, although favorable results were not obtained in all situations. Common side effects have been sedation and ataxia; IV administration has produced more marked side effects than has the IM dose. Response time following either type of administration ranged from almost immediate to several hours. Further work is

Garcelon, D., and G. Bogue. 1977. Raptor care and rehabilitation. Night Owl Press, Walnut Creek, California.

Harrison, G. J. 1986. What to do until a diagnosis is made. *In* Clinical avian medicine and surgery, G. J. Harrison and L. R. Harrison (eds.). W. B. Saunders, Philadelphia, Pennsylvania.

Jenkins, W. 1982. Drugs affecting gastrointestinal function. *In* Veterinary pharmacology and therapeutics, 5th ed., H. H. Booth and L. E. McDonald (eds.). Iowa State University Press, Ames, p. 594.

Lewis, L. D., M. L. Morris, and M. S. Hand. 1987. Small animal clinical nutrition, vol. 3. Mark Morris Associates, Topeka, Kansas.

Lulich, J. P., and T. D. O'Brien. 1988. Feline idiopathic polycystic disease. Compendium on Continuing Education 10:1030-1040.

McDonald, L. 1982. Drugs affecting metabolism and hormones affecting reproduction. *In* Veterinary pharmacology and therapeutics, 5th ed., H. H. Booth and L. E. McDonald (eds.). Iowa State University Press, Iowa, pp. 535-536, 564-569.

McKeever, K. 1979. Care and rehabilitation of injured owls. W. F. Rannie, Lincoln, Ontario.

Redig, P. T. 1984. Fluid therapy and acid-base balance in the critically ill avian patient. Proceedings of the International Conference on Avian Medicine, Association of Avian Veterinarians, Toronto, Canada, pp. 59-74.

_____. 1992. Critical care of raptor patients. *In* Kirk's current veterinary therapy, vol. 12, R. W. Kirk and J. D. Bonagura (eds.). W. B. Saunders, Philadelphia, Pennsylvania, pp. 1134-1137.

Sable, R. 1986. Evaluation of droppings. *In* Clinical avian medicine and surgery, G. J. Harrison and L. R. Harrison (eds.). W. B. Saunders, Philadelphia, Pennsylvania.

Sandine, W. E., K. S. Muralidhara, P. R. Elliker, and D. C. England, 1972. Lactic acid bacteria in food and health: a review with special reference to enteropathogenic *Escherichia coli* as well as certain enteric diseases with their treatment with antibiotics and *Lactobacillus*. Journal of Milk Food Technology 35:691-702.

Soerjadi, A. S., S. M. Stehman, G. H. Snoeyenbos, O. M. Weinack, and C. F. Smyuser. 1981. The influence of *Lactobacilli* on the competitive exclusion of paratyphoid salmonellae in chickens. Avian Diseases 25:1027-1035.

Weinack, O. M., G. H. Snoeyenbos, and A. S. Soerjadi-Liem. 1985. Further studies on competitive exclusion of *Salmonella typhimurium* by *Lactobacilli* in chickens. Avian Diseases 29:1273-1276.

Wren, W. B. 1987. Probiotics: fact or fiction. Animal Health and Nutrition for the Large Animal Veterinarian, November-December.