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Review

A Sceptics View: "Kleiber's Law" or the "3/4 Rule" is neither a Law nor a Rule but Rather an Empirical Approximation

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Abstract: Early studies showed the metabolic rate (MR) of different-sized animals was not directly related to body mass. The initial explanation of this difference, the "surface law", was replaced by the suggestion that MR be expressed relative to mass^{n}, where the scaling exponent "*n*" be empirically determined. Basal metabolic rate (BMR) conditions were developed and BMR became important clinically, especially concerning thyroid diseases. Allometry, the technique previously used to empirically analyse relative growth, showed BMR of endotherms varied with 0.73–0.74 power of body mass. Kleiber suggested that mass$^{3/4}$ be used, partly because of its easy calculation with a slide rule. Later studies have produced a range of BMR scaling exponents, depending on species measured. Measurement of maximal metabolism produced scaling exponents ranging from 0.80 to 0.97, while scaling of mammalian MR during growth display multi-phasic allometric relationships with scaling exponents >3/4 initially, followed by scaling exponents <3/4. There is no universal metabolic scaling exponent. The fact that "allometry" is an empirical technique to analyse relative change and not a biological law is discussed. Relative tissue size is an important determinant of MR. There is also a need to avoid simplistic assumptions regarding the allometry of surface area.

Keywords: allometry; basal metabolic rate; maximal metabolic rate; relative growth

1. Introduction

The subject of *allometry* concerns relative change in structure or function with change in body size. It has a long history stemming from detailed studies of relative growth and is defined as "the growth of body parts at different rates, resulting in a change of body proportions". Huxley and Teissier in 1936

coined the term *allometry* to replace "heterogony" (Huxley's previous term) and "disharmony" (Teissier's previous term), and thus coalesce the field of relative growth studies [1,2]. They also proposed the term *isometry* (to replace "isogony" and "harmony") and agreed on the symbolic formulation for allometric growth of $y = b \cdot x^a$, where y is some biological variable, x is body mass, a is the scaling exponent, and b is a constant (the value of y at unity body size, *i.e.*, when $x = 1$). Isometry is the case of allometry where the scaling exponent $a = 1$, and occurs when a biological variable varies directly with body size and remains thus a constant proportion of total body mass.

Huxley and Teissier were not the first to use a power function to describe relative growth (either for comparison of individual growth, or comparison between species of differing size). In 1897 Eugene DuBois [3] had used the equation $e = c \cdot s^r$ to describe the relationship between brain mass (e) and body mass (s) of mammals where c represented the "coefficient of cephalisation" and r was the "coefficient of relation". He calculated the value of the exponent r to be between 0.51 and 0.55 and such a scaling exponent means that for every 100% increase (*i.e.*, doubling) in body mass there is only a 42–46% increase in brain mass.

A historical perspective always enriches understanding and, in my opinion, researchers interested in biological scaling would appreciate a reading of the "On Magnitude" chapter of D'Arcy Thompson's classic *On Growth and Form* [4]. In it, he points out "*we are taught by elementary mathematics—and by Archimedes himself—that in similar figures the surface increases as the square, and the volume as the cube, of the linear dimensions*". Thompson then describes the implications of size for both structure and function of animals and plants. This means that different-sized objects (importantly they must have the same shape and density) have a surface area (SA) that is proportional to their mass to the 2/3 power; *i.e.*, $SA = k \cdot M^{2/3}$, where k is a constant determined by both the shape of the object and it's density. Following its original use for the study of relative growth, the techniques of allometry have also been used to analyse the relationships between a wide range of body functions and body size. In this contribution, I intend to apply a historical perspective to the analysis of the relationship between metabolic rate and body size of animals, and I will return to this fundamental surface area/size relationship.

2. Metabolic Rate and Body Size: The "Surface Law"

Lavoisier demonstrated in 1780 that animal metabolism was similar to combustion (e.g., a candle) in that it was a process that involved consumption of oxygen and the production of carbon dioxide, water and heat. With his wife as his major collaborator, he also demonstrated that the rate of oxygen consumption varied with: (i) food intake; (ii) environmental temperature; and (iii) the performance of muscular work. He thought this process of metabolism occurred in the lungs; it was not until 1837 that Magnus definitively resolved that the process of animal metabolism took place in the tissues in general [5]. In 1838 Sarrus and Rameaux [6] proposed what was called the "surface law". They suggested that the heat production of different-sized species should be related to their surface area rather than their body masses if they were to maintain the same body temperature. Their presentation was a theoretical proposal and thus implied that small animals should have greater mass-specific rates of metabolism than larger animals, just as relative surface area (*i.e.*, relative to body size) increases with decreased size of similar-shaped objects.

Regnault and Reiset [7] developed an innovative respirometer (one that provided oxygen at the rate it was consumed) and measured the metabolic rates of a number of animals (including rabbits, dogs, fowl, ducks, finches, sparrows, frogs, salamanders, lizards and beetles). Because their measurements were carried out at temperatures ranging from ~15 °C to ~23 °C (average ~18 °C), and generally on animals feeding, these were not measurements of basal metabolism. However, they did report a number of seminal findings: (i) mammals and birds of the same size had similar mass-specific rates of oxygen consumption; (ii) the mass-specific oxygen consumption of the small bird species (average mass ~23 g) was more than 8-fold greater than the larger birds (average mass ~1.4 kg); and (iii) there was a huge difference in the metabolic rates of the endotherms (mammals and birds) compared to the ectothermic vertebrates (amphibians and reptiles). For example, with respect to this last point, although they were approximately the same size, the mass-specific oxygen consumption rates of the small bird species was ~135 times that of the amphibians and reptiles.

Interestingly, Regnault and Reiset [7] also showed that when they kept rabbits and dogs in an atmosphere that had 2–3 times normal oxygen levels they had exactly the same metabolic rates as those in normal atmospheric oxygen. In other words, metabolic rate seemed to be an intrinsic characteristic of the species and was not limited by the supply of oxygen. In this way it differed from combustion.

In 1883, the nutritionist Max Rubner [8] calculated the daily metabolic rates (by detailed measurement of their food energy intake and waste elimination) of seven dogs ranging in size from 3 kg to 31 kg and demonstrated that mass-specific metabolic rate was greater in small dogs than in large dogs (~2.5 fold in smallest compared to largest dog). He also calculated the body surface area for each dog and, relative to body mass this was 2.1-fold greater in the smallest dog compared to the largest dog. When daily metabolic rate for each dog was expressed relative to its surface area, all dogs had similar metabolic rates (ranging from 1036 to 1212 kcal/m^2·day). Rubner's measurements supported the "surface law", although it should be remembered that they were also not measurements of basal metabolism, as they were made at room temperature (~15 °C) and all dogs were fed during the measurements.

Independently, Richet [9] also confirmed the "surface law" with observations on rabbits, while Voit [10] presented the first well-known interspecific confirmation of this "law". In his 1916 classic, Krogh [11] discusses many of these early studies of the "surface law". These studies were not allometric analyses as we know them today but rather were demonstrations that metabolic rates of different-sized animals were relatively constant when expressed per unit surface area, but when expressed per unit body mass the values dramatically increased as animal size decreased.

Towards the end of the nineteenth century a number of accurate respirometers, capable of measuring the metabolic rate of humans, were developed and investigators became very interested in whether human metabolic rates varied with age, sex, pregnancy, menstruation and various diseases [12]. This was especially stimulated when, in 1895, Magnus-Levy [13] showed that human metabolic rate was dramatically increased in exopthalmic goitre (*i.e.*, hyperthyroidism). These investigations required good knowledge of normal control subjects and necessitated the development of stringent conditions for measurement of metabolic rate. This led to the concept of the *Basal Metabolic Rate* (BMR) which required the subject to be: (i) resting (*i.e.*, undergoing no physical activity); (ii) fasting (*i.e.*, post-absorptive and finished processing any food previously ingested); and (iii) in a thermo-neutral environment. When applied to comparison of BMR between species, it was also specified that the animal should be healthy and not growing (*i.e.*, an adult), and also not be cold- or heat-acclimated.

During the early part of the twentieth century, before the development of the sophisticated analytical techniques used in clinical diagnosis nowadays, measurement of BMR of humans was commonly used clinically, especially in diagnosis of various thyroid diseases and it was common practice throughout this period that metabolic rate be expressed per unit of body surface area. For detailed discussion see DuBois [12].

The "surface law" did not specifically propose that BMR of different animals was proportional to 2/3 power of their body mass, but rather that it was proportional to their body surface area. BMR would only be proportional to $mass^{2/3}$, if all species were the same shape and of the same specific gravity. This is not the case. Animals vary both in shape and specific gravity (which is influenced by relative fat content as well as, for example, the presence of air sacs in birds). For this reason there were many different methods developed to measure the surface areas (SA) of animals and there was variation in the values determined by different techniques [14]. Within a single animal species, if it assumed that overall shape and specific gravity are constant with body size, then $SA = k \cdot mass^{2/3}$ [15], where k is a constant (called the Meeh factor) determined by the shape and specific gravity of the species. Once k has been determined empirically, it can be used to calculate SA (in cm^2) from body mass (in g). It varies for species of different shapes and specific gravity. For a cube of water, the Meeh factor is 6. It is greater for slim animals than for stout species. The Meeh factor determined for pigs is 8.7 while that for rats and mice is 11.4. Meeh factors are affected by the presence of substantial membranous areas. For example, the extensive gliding membranes of the sugar glider result in a value of 25.7 for this marsupial compared to values ranging from 10.6 to 13.8 for other marsupial species [16]. Because of the variation in shape and specific gravity of species, it should not be assumed that the surface area of animals is related to the 2/3 power of body mass. For example, one compilation [17] of empirical measurement of the surface area of mammals and birds provides allometric equations with exponents ranging from 0.65 to 0.73 and even within single species, changes in shape and specific gravity (e.g., due to relative adiposity) can produce exponents that differ from 2/3, for example the exponent is reported to be 0.56 for cattle (from 20–600 kg), 0.60 to 0.65 for rats (20–400 g) and 0.69 for humans (2–100 kg) [14].

From the early studies of metabolism, it became very obvious that simple body mass was an inadequate reference base for comparison of the metabolic rate. The power of the "surface law" was that surface area seemed a much better comparator (and resulted in its dominant use as the denominator in clinical BMR values). However, this "law" provoked much consideration and discussion as to what BMR actually was, and what mechanisms controlled it. The early concept that heat loss determined BMR was discarded when a number of experiments showed that conditions that influence heat loss (such as changes in fur insulation) do not change BMR. There was an emerging view that the difference in minimal metabolic rate between different-sized animals was due to intrinsic differences at the level of tissue metabolism, that BMR was relatively constant and fixed for particular species and that it was determined more by the species evolutionary past than its immediate environment, see [11].

While expression of BMR relative to surface area was dominant in clinical science, among the zoo-physiologists there was more ambivalence. For example, Krogh's discussion of the "surface law" ended with the conclusion that *metabolism should not therefore be expressed per sq. m. or any other unit of surface but as a function of* W^n [11]. In his book, he implied that the value of the exponent "n" should be determined empirically.

3. Metabolic Rate and Body Size: The Rise of "Kleiber's Law" or the "3/4 Rule"

With the technological development of very accurate respirometry systems, there accumulated a large database of BMR values for a wide range of animal species in the first part of the twentieth century. Three key contributors were Francis Benedict, Samuel Brody and Max Kleiber and all three published classic monographs in animal energetics towards the end of their careers. Benedict was the first of these investigators. Although his early publications were of either technical or clinical aspects of metabolism, in later years he measured the metabolic rates of a wide range of species, including elephants and large reptiles. Initially, he believed the BMR of each species was a firmly fixed value but after years of detailed meticulous measurement, especially on dairy cows, he revised his view that BMR was constant and emphasised the variability of BMR values. He determined the BMR of many species (much of his data were used later by Brody and Kleiber) and aggregated this data in his classic monograph, *Vital Energetics*: *a study of comparative basal metabolism* [18] in which he published a "mouse to elephant" BMR graph. He showed that BMR of different species was not constant when expressed both relative to body mass and relative to surface area. Thus he disagreed with Rubner's "surface law" and strongly opposed that any physical law was the explanation of the relationship between BMR and body size. He emphasised that different species of the same size often had different BMR values and suggested that because tissues differed greatly in their metabolic activity, that it was likely relative body composition determined the BMR of the whole animal. He used the term "*active protoplasmic mass*" of the animal to describe this concept.

Brody and Kleiber were agricultural scientists and their interest in metabolic rates was linked to the concepts of growth and efficiency of agricultural production. Brody's classic monograph was *Bioenergetics and Growth: with special reference to the efficiency complex in domestic animals* [14], whilst Kleiber's was *The Fire of Life: an introduction to animal energetics* [19]. However, long before the publication of their respective monographs, both Brody and Kleiber independently published papers in 1932 that examined the relationship between the BMR and body mass of warm-blooded animals [20,21]. They used log-log plots of BMR and body mass of selected mammal and bird species and Brody found the slope of this relationship to be 0.73 while Kleiber found the value to be 0.74. As an indication of relative change, a scaling exponent of 0.73 means for every doubling of body size BMR will increase by only 66%, and a value of 0.74 means the BMR increase is 68% for a 100% increase in body mass. The similarity in these values is not surprising in that there was considerable overlap between the two studies in (i) the species measured, and (ii) the BMR data used (much of the data were from Benedict). Both authors suggested that $mass^{2/3}$ was unsatisfactory as the reference base for comparison of basal metabolism. In view of the variability of BMR values, Brody rounded down and suggested $mass^{0.7}$ should be the unit of metabolic body size while Kleiber rounded up and suggested that $mass^{3/4}$ should be used.

Since these early studies, there have been BMR measurements of many other species, as well as several determinations of the allometric relationship between BMR and body size of different groups of mammals and birds. The exponents calculated from these studies vary substantially, often depending on the mixture of species analysed. For example, the compilation of various studies by Peters [17] gives exponents ranging from 0.61 to 0.79, while the compilation of Withers [22] gives a exponents ranging from 0.55 to 0.76 for interspecific studies, and from 0.56 to 0.91 for intraspecific studies.

In general, the majority of these values are less than the ¾ scaling exponent and while all values will have some statistical uncertainty associated with them, this variation is real and it is obvious that there is no universal ¾ scaling exponent for BMR applicable to all animal groups.

In 1928, Terroine and Sorg-Matter reported that the ratio of total endogenous nitrogen excretion to BMR was relatively constant in different sized mammals [23]. Furthering this observation, Brody and colleagues showed that the excretion rates of endogenous nitrogen and neutral sulphur by mammals varying in size from small rodents to cattle varied in proportion, respectively, to $mass^{0.72}$ and $mass^{0.74}$ [24]. Thus, Brody suggested that $mass^{0.7}$ could be used as the reference base for both basal energy metabolism and basal protein metabolism [14]. In 1935, the National Research Council's Conference on Energy Metabolism tentatively adopted the 0.73 power of body mass as the reference base for energy metabolism [14] (p. 373).

It should be remembered that prior to the introduction of electronic calculators in the late 1960s and the later introduction of programmable computers, most mathematical calculations were either by hand, use of logarithm tables or use of slide rules. Indeed, one of the explicit points made by Kleiber in arguing for the adoption of the ¾ power of body mass as the unit of metabolic body size was that it could be easily calculated using a slide rule (by taking the square root of the square root of the cube of body mass). The calculation of "metabolic body size" was useful in agriculture for determining such things as doses of dietary supplements or medicines. In 1965, the European Association for Animal Production adopted the ¾ power of body mass as the reference base for metabolic rate.

Over the years, knowledge of the contributions by several investigators to understanding this relationship between BMR of mammals and body size, outlined above, have largely become lost. Possibly because it replaced the "surface law", this relationship was referred to as "Kleiber's Law" or sometimes the "¾ Rule". The use of the words "law" or "rule" in biology is unfortunate. Their use often implies that there is an underlying simple physical principle, applicable to all animals, that explains the relationship. The variation in the natural world that is so much part of the evolutionary process argues against such biological "laws". Other examples of biological "laws" and "rules" are worth comment: (i) "Bergman's Law"—states that warm-blooded animals living in cold climates tend to be larger than those living in a warm climate; (ii) "Allen's Law" states that the limbs, ears and tails of endotherms living colder regions tend to be smaller than those living in moderate climates, and (iii) "Cope's Law" proposes that animals tend to increase in body size over evolutionary time. These are not "laws". They are trends, generalizations or tendencies and all have numerous documented exceptions. In the opinion of this author, the same concern applies to "Kleiber's Law" or the "¾ Rule". Whether "laws" (in the sense described for aspects of the science of physics) exist in the science of biology has been a topic of much discussion. Lawton [25] has argued that they do not exist in the science of ecology.

Kleiber outlived both Brody and Benedict by ~20 years and with his strong personality he greatly encouraged use of the ¾ exponent. In later publications, he sometimes uses "$mass^{3/4}$" instead of "metabolic rate". In a late publication [26], he proposed that when the Lilliputians calculated Gulliver's food requirements they must have used ¾ power of Gulliver's body mass. This proposition was based on his calculation that Gulliver was 26 times the height of the average Lilliputian. Yet, Johnathon Swift writes [27] that Gulliver said the following (with my bold text emphasis):

... his majesty's mathematicians having taken the height of my body by the help of a quadrant, and finding it to exceed theirs in the proportion of ***twelve to one****, they concluded, from the similarity of their bodies, that mine must contain at least 1724 of theirs, and consequently would require as much food as was necessary to support that number of Lilliputians.*

A height of 12 times that of a Lilliputian with the assumption of geometric similarity means Gulliver's body mass was 12^3 (=1728) times that of the average Lilliputian. This value is almost identical to his 1724-times food ration. In other words, Gulliver was provided food in direct proportion to his mass and not the ¾ power of his mass. Although presented as a light-hearted contribution this distortion does Kleiber's argument no favour. His strong selling of the simple ¾ power of body mass for most things metabolic likely contributed to the relationship becoming a "law" or "rule".

One of the important consequences of the discovery that mass-specific BMR of mammals and birds decreases with increasing body size was that it stimulated investigations into what determined metabolic rate. From the earliest studies, it became apparent that resting metabolic rate was not likely limited by supply constraints. As pointed out earlier, Regnault and Reiset [7] showed that the rate of oxygen consumption did not change when mammals were placed in highly oxygen-enriched environments. It also became apparent that BMR was not determined by the need to produce heat. Indeed, at environmental temperatures above the lower end of the thermoneutral zone for an endotherm (the critical temperature), BMR produces heat in excess to that needed to maintain body temperature. This excess heat must be lost by vasomotor control of blood circulation to the body surface. The fact that, under resting conditions, blood leaving tissues (*i.e.*, venous blood) still contains substantial oxygen and nutrients also argues against BMR being determined by supply limitations. BMR represents the minimum "cost of living" while doing nothing but maintaining the thermodynamic non-equilibrium living state.

It also became obvious that parts of the body did not contribute equally to BMR. Furthermore, the relative size of metabolically-active tissues and organs differed in different-sized animals. For example, measurement of heat production in resting humans showed that internal organs (including the brain) represented only 8% of total body mass but were responsible for 72% of heat production [28] (p. 298). Measurement of tissue mass in mammals differing in body size produces allometric equations with scaling exponents of 0.7, 0.85, 0.87, 0.98, 1.0, and 1.1 respectively for brain, kidney, liver, heart, muscle, and skeleton mass (see [17]). This means that for each 100% increase (doubling) in total body mass of mammals, the mass of the brain increases only 62%, kidney mass increases 80%, liver by 83%, while heart and muscle mass increase by 97% and 100% respectively and the mass of the skeleton increases by 114%.

Similar scaling exponents apply to relative tissue size in birds. A series of studies examining eight bird species ranging in size from 13 g zebra finches to 35 kg emus provides data on the size of brain, kidney, liver and heart of these different-sized birds [29–32]. Using these data, the respective scaling exponents for the size of these tissues are 0.46, 0.83, 0.84 and 0.93. These scaling exponents mean that for each 100% increase in body size of these bird species, there is only a 38% increase in brain size, a 78% increase in kidney mass, a 79% increase in liver mass, and a 91% increase in the size of the heart. The tissue order of these exponents is the same in birds as in mammals and, apart from the brain, the scaling exponents for each tissue are similar in birds and mammals.

Two conclusions emerge from these and other studies; (i) that different-sized mammals and birds are constructed differently, and (ii) that the relative size of tissues/organs might explain a large part of the allometric variation in mammalian and avian BMR. The combination of the active internal organs can be thought of as Benedict's "*active protoplasmic mass*". Body composition (*i.e.*, relative size of body tissues/organs) has also been found to be important in determining metabolic rates of mice [33] and sparrows [34].

Mass-specific tissue metabolic rates also vary allometrically with body size of mammals and this has structural correlates at the tissue level. For example in one study of a specific mixture of mammal species, where BMR varied with the 0.62 power of body mass, mitochondrial membrane surface area per cm^3 of brain, liver, kidney and heart all significantly decreased with increased body size. When these membrane surface densities are combined with the respective tissue size and summed, the combined total mitochondrial membrane surface area calculated for these metabolically-active organs varied with the 0.59 power of body mass [35]. For a more detailed discussion of the processes that constitute BMR and how they vary with body size, the reader is referred elsewhere [36,37].

4. Metabolic Rate and Body Size: Ectotherm SMR Compared to Endotherm BMR

Because "cold-blooded" species have body temperatures that vary with environmental temperature they are also called *poikilotherms* while "warm-blooded" species are *homeotherms* because of their relatively constant body temperature. It was early observed that *homeotherms* increased their metabolic rate in cold environments (in order to maintain a relatively constant body temperature), but the metabolic rates of *poikilotherms* decreased in cold environments because of a decreased body temperature. This resulted in the concept of *Standard Metabolic Rate* (SMR) for metabolic rate comparisons between cold-blooded animals. The conditions of SMR are similar to those of BMR with the additional requirement that the temperature at which measurement is made (and thus the animal's body temperature) must be specified. While the very early studies [7] showed exceptionally large differences in MR between "cold-blooded" and "warm-blooded" animals, these comparisons involved very different body temperatures. August Krogh developed very accurate respirometers suited for the measurement of metabolic rate of small cold-blooded species and accumulated much information regarding the effect of physical factors on the metabolic rates of cold-blooded species. In his 1916 monograph, *The Respiratory Exchange of Animals and Man* [11], he showed that: (i) the SMR of cold-blooded animals (measured at the same temperature as each other) and expressed relative to body mass increased with decreasing body size; and (ii) even when compared at the same temperature that the "*oxidative energy of the tissues is greater in the warm-blooded than in the cold-blooded organism*" (see p. 146).

Likely because of their agricultural interests, neither Brody [14] nor Kleiber [19] considered the relationship between body size and SMR of cold-blooded animals. Benedict [18], however, compared the metabolic rates of cold-blooded and warm-blooded animals of the same size and at the same body temperature. He concluded that mice and canaries have BMR that is approximately 5–8 times the SMR of similar-sized (~20 g) frogs and fish with the same body temperature. In another comparison, he demonstrated that the measured BMR of marmots and rabbits are about 4–6 times the SMR of similar-sized (~2.5 kg) snakes at the same body temperature. These comparisons suggest that cold-blooded species have a similar relationship between metabolic rate and body size but at a

lower absolute level of metabolism. The labelling of "warm-blooded" animals as *endotherms* and "cold-blooded" animals as *ectotherms* is compatible with the large difference in their level of energy metabolism.

Since these early comparisons, many studies of the allometry of SMR have been carried out for a variety of ectothermic animals, both vertebrate and invertebrate. One compilation of such studies [17] provides exponents ranging 0.60 to 0.91 for ectothermic vertebrates, and ranging from 0.15 to 0.86 for invertebrates. Another compilation [22] provides exponents for interspecific comparisons that range from 0.56 to 0.98 for ectothermic vertebrates, and from 0.50 to 0.91 for invertebrates. For intraspecific comparisons the exponents range from 0.63 to 1.08 for ectothermic vertebrates and from 0.32 to 1.00 for invertebrates. A recent study of vertebrate SMR and BMR values provides exponents of 0.88, 0.88 and 0.76 respectively for fish, amphibians and reptiles compared to 0.64 and 0.68 for birds and mammals respectively [38]. In all cases, the actual level of metabolic activity (compared at the same body temperature) is many times less in the ectotherms than in endotherms.

As for BMR, the SMR of ectotherms represents the minimal metabolism necessary to maintain the living state and internal organs (such as liver, kidney, heart and brain) likely contribute disproportionally to SMR. In this respect, it is interesting that in a study of reptiles, the relative size of these tissues decreases as body size increases and that the mitochondrial membrane surface area (m^2 per total tissue) of liver, kidney, heart and brain have scaling exponents of 0.74, 0.56, 0.65 and 0.45 respectively [39]. Tissue size is also part of the explanation for the large ectotherm-endotherm metabolism difference. A comparison of reptiles and mammals of the same size and body temperature showed that mammals have: (i) much larger livers, kidneys, hearts and brains than reptiles; (ii) the mammalian tissues have a greater volume density of mitochondria in compared to those of reptiles; (iii) the mammalian mitochondria have a greater membrane density than the reptilian mitochondria; and (iv) that the difference in total mitochondrial membrane surface mirrors the difference in metabolic rate [40].

5. Metabolic Rate and Body Size: Metabolic Rates other than BMR or SMR

It is understandable, for technical reasons, that it was the conditions of BMR (and SMR) that were used for the early comparisons of the metabolic rates of different species. However, animals in nature will only occasionally operate at the minimal state implicit with BMR or SMR conditions. More relevant to the natural state and, importantly, relevant to evolution by natural selection will be: (i) an animal's maximal sustained rate of metabolism; and (ii) its daily average energy expenditure, also called the field metabolic rate.

Both endotherms and ectotherms can dramatically increase their aerobic metabolism in response to sustained exercise and the maximum oxygen consumption rate achieved is called the animal's maximal metabolic rate (MMR). Endotherms also increase their heat production in response to cold environments and the maximum rate achieved is called their summit metabolic rate. The use of treadmills, enclosed running wheels, air tunnels and water flues as well as open flow respirometry systems has resulted in a large number of MMR values for different-sized animals. The most recent analysis of MMR and body size of mammals [41] has shown that there is no significant difference between values obtained using treadmills or running wheels and found 0.84 to be the scaling exponent. The 95% confidence intervals (0.80–0.88) include values reported for mammals by two earlier studies; 0.81 by [42] and 0.87 by [43]. For birds, McKechnie and Swanson [44] report exponents of 0.80 and

0.96 respectively for studies of MMR of flying birds and MMR of running birds. The MMR of reptiles (at a body temperature of 30 ℃) is reported to have a scaling exponent of 0.82 [45] while the MMR for swimming salmon (at 15 ℃ environmental temperature) has an exponent of 0.97 [46].

As mentioned above, because both mammals and birds increase their heat production in cold environments, it is possible to measure their maximum metabolic rates in response to cold exposure. This is known as summit metabolism and, for both mammals and birds, the rates of oxygen consumption during summit metabolism are less than those measured during maximal sustained exercise. For example the calculated summit metabolism of a 1 kg mammal is 47 $mL{\cdot}O_2{\cdot}min^{-1}$ compared to 113 $mL{\cdot}O_2{\cdot}min^{-1}$ for exercise MMR [39], while a 1kg bird is predicted to have a summit metabolism of 67 $mL{\cdot}O_2{\cdot}min^{-1}$ compared to a flying MMR of 164 $mL{\cdot}O_2{\cdot}min^{-1}$ [44]. Interestingly, the scaling exponents are also less for summit metabolism compared to those for exercise-induced MMR. For example, in mammals summit metabolism has an exponent of 0.65 compared to 0.87 for exercise MMR [43] while for birds, summit metabolism scales with an exponent of 0.68 compared to 0.80 for flying MMR [44]. This difference may be due to body surface area influences on thermally-induced maximal metabolism.

In their natural environment, generally animals have a metabolic rate that is between their BMR and MMR. While both BMR and MMR are generally measured as oxygen consumption rate under laboratory conditions, the discovery that water, where both H and O atoms were isotopically-labelled, could be used to measure the rate of CO_2 excretion by animals [47] has enabled determination of the field metabolic rates (FMR) of a large number of different-sized endothermic and ectothermic vertebrates. One compilation of FMR data found the scaling exponent for the FMR of mammals to be 0.73, for birds to be 0.68 and for reptiles to be 0.89 [48]. A more recent compilation reports exponents of 0.64 for mammals and 0.71 for birds [49]. The actual level of FMR of mammals and birds is 12–20 times that of similar-sized reptiles and while some of this difference will be due to the endotherm-ectotherm BMR difference, a large amount of the difference will be due to the fact that reptiles will spend substantial amount of time in the field at a lower body temperatures [48]. Interestingly, while much of the variation in FMR can be explained by body mass, there is still considerable variation in mass-adjusted FMR values between species, with the range of residual variation in FMR being more than six-fold [48].

6. Metabolic Rate and Body Size: The Relationship during Growth

So far, I have considered the relationship between body size and various rates of metabolism for adult animals. Of course, individual animals also experience a wide range of body size during growth and development and that is the subject of this section (which will be restricted to considering development of metabolic rate in mammals). The resting metabolic rate of a growing mammal is by definition not BMR (the animal is not an adult) and for this reason I will refer to it as MR. Use of allometric scaling in the study of relative growth precedes its use in the analysis of metabolic rates by many years [2].

Adolph reports that rat zygotes and adult rats have similar mass-specific metabolic rates but that the mass-specific MR of the newborn rat is about 3-times the zygote and adult mass-specific values [50]. Similarly, the mass-specific MR of the newborn mouse and rabbit is several times that of both the zygote and adults of the same species [50]. This means the ontogeny of metabolic rate and body size for these species cannot be described by a single allometric relationship.

Studies on humans, cattle, and rats show multi-phasic developmental patterns of MR change with size. During early growth and development (up to approximately 20–30% of adult mass), allometric exponents relating MR to body size are much higher than ¾ (in some cases >1) while after this period (*i.e.*, above 20–30% of adult mass) scaling exponents relating MR to body mass are much less than the ¾ value. For example, the scaling exponent for MR of humans up to ~10 kg is 1.02 while above this size it is 0.58 [51]. For cattle, from 28–100 kg, MR scales with the 0.84 power of body mass, while from 100–400 kg, the scaling exponent is 0.56 [14]. For rats, Kleiber and colleagues measured the MR of rats ranging in age from 1 d to ~3 y post-natal, and ranging in mass from 6.5 g to 345 g [52]. These data were not presented in a log-log plot (but were presented in units per $kg^{3/4}$) but when a log-log plot is done, the scaling exponent is 0.87 up to ~100 g body mass and thereafter it is 0.31 [53]. When the MR values for rat zygotes and fetuses [50] are added to the same log-log plot, the pre-natal scaling exponent is 1.23 [53].

These ontogenetic changes in MR of mammals are likely related to the relative growth rate of the internal organs that contribute disproportionately to resting metabolic rate. For example in humans, five internal organs (brain, heart, kidney, liver and lungs) are responsible for 14.6% of total body mass in a 10 kg child but only 6.3% of total body mass in a 70 kg adult [51]. Even though they constitute a relatively smaller proportion of the total body mass in the adult, they are estimated to be responsible for a combined 79% of MR in both cases [51]. However, the relative contributions of different tissues to MR vary with growth. For example, the brain is 9.2% of body mass and responsible for 45% of total MR in 10 kg humans, compared to 2% of body mass and 21% of total MR in 70 kg humans, while the liver is 3% of body mass and responsible for 19% of total MR in 10 kg humans compared to 2.3% of body mass and 32% of MR in 70 kg humans. Interestingly, when the growth in the combined mass of these five organs is allometrically plotted, the scaling exponent is 1.0 up until 10kg mass and 0.53 above 10 kg body mass, thus demonstrating a similar trajectory of allometric tissue growth as observed for the MR [51]. This supports the importance of body composition in determining an animal's resting MR.

7. Synthesis and Conclusions

There is no universal metabolic scaling exponent. There is no single allometric "law" that describes the relationship between body size and metabolism. Allometry has always had an empirical basis, being, initially, a mathematical technique to analyse relative growth and only later being applied to the comparison of metabolic rates of animals. It was largely because the "surface law" proved to be inadequate (both conceptually and mathematically) in comparison of metabolism of different-sized animal species, that the method of allometric analysis was adopted from relative growth studies.

It was recognised early that the metabolic rate of an animal was variable and this led to the development of standard conditions for the measurement and comparison of metabolic rates. Thus the conditions for BMR were defined and used for such comparisons as well as BMR being used as an important clinical diagnostic (especially for thyroid diseases). Likely for two reasons, the first allometric analyses of metabolism were of the BMR of endotherms. First, the conditions and techniques for measuring metabolic rates other than BMR were not well developed. Secondly, measurements were primarily carried out on animals of agricultural and domestic interest. Although, some zoologists were measuring the metabolic rates of ectotherms (e.g., August Krogh), early metabolic comparisons were of different-sized mammals and birds by agricultural scientists (e.g., Brody and Kleiber). These studies

produced allometric exponents of 0.73 [20] and 0.74 [21]. For purposes of comparison the concept of a unit of *metabolic body size* was developed and while one of these investigators suggested mass$^{0.7}$ be used [14], the other suggested mass$^{3/4}$ be the unit of metabolic body size [21]. One of the suggested advantages of using the ¾ exponent value was that it could be easily calculated using a slide rule. The value of ¾ was suggested as an approximation of the empirically determined value. Thus the "3/4 Rule" was born. "Kleiber's Law" replaced the "surface law".

Since these initial studies, there have been numerous other studies of mammalian and avian BMR using an increasing number of species. Scaling exponents have been influenced by the particular species combination examined in each study. Although BMR scaling exponents vary quite a lot between studies (and such variation is real, *i.e.*, exponents are often statistically significantly different), many of these exponents are less than the "3/4" value. Scaling exponents calculated from studies comparing maximal metabolic rate of different-sized animals are very different to those from BMR comparisons. Similarly, the scaling exponents, calculated from studies of changes in MR during the growth and development of mammals, do not agree with those from BMR comparisons. Indeed, these ontogenetic studies show that there is no single allometric relationship during the development and growth of mammalian MR, instead they show that different periods during the ontogeny of the MR-body size relationship are best described by different allometric relationships. They emphasise that allometry is not a law but a mathematical technique to describe proportional change in a structure or function with change in total size of an animal.

Allometry is an empirical mathematical technique applied to a set of data (from different sized subjects) that assumes a "power equation" can describe the data. Such a relationship is "linear" on a log-log plot with the slope of the relationship representing the value of the exponent. However, the vast majority of allometric relationships are "curvilinear" relationships, and only in the case of isometry (*i.e.*, when the exponent = 1) are they linear relationships. It has been suggested by others that the assumption of a simple power law is not an appropriate mathematical model to describe the relationship between BMR and body mass of mammals and these authors suggest more complex mathematical relationships are required [54,55].

Why does mass-specific metabolic rate decrease as animals get bigger? Explanations of metabolic scaling are essentially explanations of how metabolic rate might be limited or determined as animals increase in size. An interesting aspect is that while the scaling exponents for BMR of endotherms and for the SMR of ectotherms are similar, the actual levels of BMR and SMR are very different in these two types of animal (about 4–8 fold when considered at the same body mass and body temperature). Yet, to my understanding, none of the theories put forward to explain metabolic scaling include an attempt to explain the endotherm-ectotherm metabolism difference. Although allometric scaling of metabolism was described (in the scientific literature) for endotherms prior to being described for ectotherms, of course metabolic scaling presumably existed in ectotherms long before it existed in endotherms (mammals and birds have only existed for the last ~200 million years). Thus, in my opinion, such theories should concentrate first on explanation of scaling in ectotherms (both invertebrate and vertebrate) and theories that emphasise factors that might limit the rate of metabolism in animals would thus need to also explain how such limitations were circumvented when there was the dramatic (and, in evolutionary terms, likely relatively sudden) increase in the rate of metabolism when mammals and birds evolved from their reptilian ancestors.

The original formulation of the "surface law" emphasised heat loss from the body surface of warm-blooded animals as the reason why metabolic rate of different-sized mammals was expected to be proportional to surface area. While this theory proved unsuccessful as an explanation for the empirically observed relationship between BMR and body size of warm-blooded animals, consideration of the geometry of organisms still has important implications for the scaling of metabolic activity. For example, while there has been a general tendency for increase in the size of organisms during the evolution of life, simple calculations show that energy metabolism could not have evolved in direct proportion to body mass because the increase in the internal and external surfaces responsible for food and gas uptake as well as for loss of wastes (including heat) could not keep pace. As Hemmingsen [56] points out if a mammal grew from the size of a rat to that of a rhinoceros with metabolism increasing in direct proportion to mass, then the latter would have to maintain a surface temperature of that of boiling water to get rid of the heat produced. Consequently, it can be deduced that it is the similarity of regulated body temperature in different-sized mammals, combined with geometric considerations (regarding surface) that necessitated and selected for a decrease in the mass-specific MR as larger mammals evolved from smaller mammals. Similar calculations for food uptake and waste excretion also support the contention that metabolism cannot increase isometrically with body size. From this perspective, the various scaling exponents (for different types of metabolic rates, as well as, for different groups of animals) are the result of a variety of evolutionary tendencies and pressures.

In appreciating the role of geometry in animal metabolism, it is important to also appreciate how animals of different size are constructed. Statements that the scaling of surface functions requires proportionality to $mass^{2/3}$ are often too simplistic and do not take relative growth into account. For example, it is important to realise that, compared to small species, larger animals are not made up of the same number of bigger cells but instead larger species generally consist of a greater number of cells that are roughly the same size as those making up the smaller species [4]. Consideration of the allometry of mammalian lungs [57] illustrates this point well. Large mammals have bigger lungs than small mammals, and during growth, lungs increase in size by the addition of more alveoli. If geometric similarity applied, mammals of different size would have the same number of alveoli and the linear dimensions of the lungs (such as the diffusion distance from alveoli to blood vessels) would scale with $mass^{1/3}$. However, this is not the situation. The lungs of large mammals consist of more alveoli, have more lung cells than smaller mammals and because cell size varies relatively little with body size, there are only very small changes in the diffusion barrier with increasing body size. For mammals, the scaling exponent for lung volume is 1.05, for mean barrier thickness (*i.e.*, diffusion distance) it is 0.05, while alveolar surface area scales with an exponent of 0.98 and lung diffusion capacity has a scaling exponent of 0.96 [57]. These mean that for every 100% increase in body mass of the mammals that there is, on average, a 107% increase in total lung volume, a 4% increase in diffusion distance, a 97% increase in alveolar surface area, all resulting in a 95% increase in the calculated lung diffusion capacity. If geometric similarity applied (*i.e.*, proportionality to $mass^{2/3}$), alveolar surface area would have increased by only 59% for every 100% in body mass. This example illustrates the importance of understanding animal structure and avoiding simplistic assumptions of geometric similarity when attempting to understand allometric scaling of metabolism.

Many exponents have been found for the allometric scaling of metabolic activity. The values vary depending on the mixture of species examined and the type of metabolic activity measured. These do

not represent deviations from some universal allometric relationship but can be best understood by considering body composition, especially the relative sizes of tissues and organs relevant for the activity being measured, as well as their relative growth, the area of science where the empirical art of allometric analysis began.

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Conflicts of Interest

The author declares no conflict of interest.

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