Ann. Rev. Nutr. 1985. 5:267–93

BODY SIZE AND ENERGY METABOLISM

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INTRODUCTION

The experimental work concerning the relationship between body size and energy metabolism is the topic of many excellent reviews (2, 3, 11, 12, 20–22, 26, 27, 36, 38, 48, 51, 57–60, 70, 71, 76, 77, 79, 80). The aim of the present review is to discuss the conceptual development of this relationship and to reexamine its theoretical foundation in order to define a rational mass-

0199-9885/85/0715-0267$02.00

independent expression for intraspecific and interspecific energy metabolism. In addition, I develop a rational basis for choosing appropriate statistical methods to analyze metabolic data.

COMPARATIVE ENERGY METABOLISM

Variations in energy metabolism in an animal are due to the effect and interaction of innumerable environmental and biological factors. Changes in energy metabolism have no absolute meaning in themselves, they can only be interpreted with respect to a standardized configuration of significant metabolic factors. This has led to the concepts of basal metabolism in homeotherms (5) and standard metabolism in poikilotherms (4). Further standardization for body mass was achieved with the Brody–Kleiber metabolic equation (8, 42). In particular, Kleiber (41) proposed that in the power function,

$$P = aM^b, \qquad 1.$$

where P = basal metabolism, a = mass coefficient, M = body mass, and b = mass exponent, b be set equal to 0.75 and a to 70 kcal/$M^{3/4}$ (mass in kg) for mammals.

The 0.75 mass exponent was subsequently adopted by the Third Symposium on Energy Metabolism (43) without a critical analysis of (*a*) the statistical method by which this exponent was derived; (*b*) the theoretical implications for comparative physiology, particularly with regard to the concept of biological similitude; and (*c*) the practical consequences for intraspecific comparisons of energy metabolism.

The interspecific metabolic power function has been empirically derived by simple regression analysis in which the mass coefficient a is held constant. However, covariance analysis shows that the mass coefficient is actually not constant from mice to cattle (28). Moreover, the mean values of basal metabolism for different mammalian species *do not lie on a regression line*. Consequently, the computed least-squares line for the mean values is not an accurate description of the physiological relationship and cannot be used for extrapolation.

The conventional use of the Brody–Kleiber empirical equation as a mathematical model is based on the implicit assumptions that (*a*) it is theoretically possible to define a mammal of unit mass from which basal metabolism of all mammals can be derived by a similitude transformation, and (*b*) a change in body mass has the same energetic effect regardless of intraspecific or interspecific differences in structure or body composition. The theoretical analysis and the experimental confirmation presented in this paper question the validity of these assumptions.

CONCEPTUAL DEVELOPMENT OF THE RELATIONSHIP BETWEEN BODY MASS AND ENERGY METABOLISM

Biologists have studied the problem of body size and function for at least three centuries. Their questions stemmed both from pure theoretical speculations concerning the similitude of structure and function in animals (18, 51, 74), and from practical considerations, such as how to quantitatively determine food rations for humans and animals, taking into account differences in size.

Galileo (18) appears to be the first modern investigator concerned with the problem of similitude in animals. He demonstrated the dichotomy between morphological and functional similarities by arguing that animals cannot maintain the same form and structure or be made of the same material and remain functionally similar over a large range of body mass. Proportionate function necessitates a change in the physical properties of the material (density, mechanical resistivity), or a change in structure and form. Galileo's proposition leads to a central question in the conceptual development of biological similitude: are animals biologically similar when they are morphologically similar or functionally similar?

In 1684, Redi (64) observed that during starvation large animals survived longer than small ones. This was probably the first evidence that a biological duration, survival time during starvation, was mass dependent. Redi's observations were confirmed in 1820 by Naumann (54), in 1828 by Collard de Martigny (14), and in 1843 by Chossat (13).

The fact that heat produced per unit weight was greater in small than in large animals was well established by 1843, i.e. 140 years ago there was evidence that mass-specific metabolism cannot be used to compare the metabolism of animals of different size.

In 1838, Sarrus & Rameaux (69) applied the concepts of geometrical similitude to physiology for establishing functional relationships in animals of the *same species*. Their paper, which has never been published, is summarized in a report to the Royal Academy of Medicine in Paris by Robiquet & Thillaye (see 69). Sarrus and Rameaux's ideas were discussed in detail in a later paper by Rameaux (62), and they used these considerations to establish the food ration for the workers of the state tobacco plant in Strasbourg, France (37).

Sarrus and Rameaux established ideal intraspecific relationships between size, respiratory frequency, and cardiac frequency in animals of the same species. The derivation of these relationships was based on the assumption that heat loss in a mammal is proportional to its body surface area. This remarkable work has been largely ignored by physiologists.

In contrast, Bergmann's speculation that an animal's heat loss is proportional to its surface area (6) drew much more attention. Subsequently, Meeh (52) determined the numerical values of the constant in the relationship between

surface area and body weight in various species, and body surface area was used as a reference in metabolic studies.

In 1883 and apparently without knowledge of Sarrus and Rameaux's work, Rubner (67) experimentally established that the heat produced per unit surface area is mass independent in fasting dogs. Rubner interpreted the constancy of this ratio as a relation of causation: nerve impulses originating in the skin under the influence of cooling stimulate cell metabolism, and the animal's surface area is the determining factor of its heat production. Rubner formulated the Surface Law by stating that the amount of heat produced per square meter of body surface is constant in mammals.

In 1885 Richet (65) compared the heat produced per unit surface area in ten homeotherms ranging from 0.020 to 10 kg (sparrow to dog) and observed differences due to species, size of species, and the nature of the animal's integument.

In 1888 von Hoesslin (33) published a theoretical paper "On the Cause of the Apparent Dependence of Metabolism on the Body Surface Area," in which he reported that in two dogs, one kept at 5°C and the other at 31.5–32°C, the difference in heat production was only 12% instead of the 400–500% required by the Surface Law. He concluded from this experiment that, contrary to Rubner's Surface Law, animal heat production is not proportional to the difference between body temperature and ambient temperature.

Moreover, von Hoesslin rejected Rubner's explanation of the Surface Law by pointing out that since heat loss is a consequence of heat production, heat loss cannot determine heat production. He established that oxygen transport by the cardiovascular system is related to body weight to the power 2/3, because at constant blood flow velocity, oxygen transport is proportional to the cross-sectional area of the blood vessels. In a 64-kg man with the same heat production per unit weight as a 64-g rat, the cardiovascular system capable of transporting the necessary oxygen would have to weigh 50 kg! Therefore, the relation between body weight and energy metabolism cannot be linear over a large weight range. The relative proportions between organ weights as well as the ratio of organ weight to total body weight can only be maintained if energy metabolism varies with weight to the power 2/3. He predicted that according to his reasoning energy metabolism of poikilotherms should also vary with their body weight to the power 2/3.

In 1911, Putter (61) argued that homeothermy cannot explain Rubner's Surface Law, since in poikilotherms the same relationship holds between body mass and energy metabolism.

In 1916, Pfaundler (55) also questioned Rubner's interpretation of the Surface Law in pointing out that mass to the power 2/3 does not specifically define the body surface area, since this power bears the same relationship to any surface area (alveolar, intestinal, etc). In addition, he claimed that an objective

measure of body surface area is theoretically impossible, because it depends on the level of observation and the chosen units. Pfaundler's claim was confirmed by Mandelbrot's (49) fractal geometry published in 1982. In 1928, Stoeltzner (73) proposed weight to the power 2/3 as the reference for energy metabolism.

In 1927, Lambert & Teissier (47) extended von Hoesslin's speculation on geometric similitude to include the dimension of time. They elegantly derived the 2/3 mass exponent for animal heat production independently of any consideration of heat loss.

These theoretical papers were largely ignored and Rubner's Surface Law became an example of Cantor's Law of Conservation of Ignorance: "A false conclusion once arrived at and widely accepted is not easily dislodged and the less it is understood the more tenaciously it is held" (44).

With the introduction of statistical analysis in physiology, in particular with the application by Brody (9) of regression analysis to the relationship between body mass and basal metabolism, it became clear that the actual interspecific mass exponent in mammals was between 0.73 and 0.75 (40). During the ensuing polemic between Brody and Kleiber (8, 42), emphasis was shifted from finding a theoretically meaningful expression of energy metabolism to the search for a statistical mass exponent that yielded the most constant expression of basal metabolism in mammals. The difference between 0.75 and 2/3 was attributed to the effect of gravity (42). The Brody–Kleiber exponent became a criterion of biological similitude (21–23) and elastic similarity (51). The validity of the statistical derivation was never questioned. Blind faith in statistical quantification and the temptation to make this statistical relationship a Physiological Law led to a dead-end empirical approach that has confined research to confirming or justifying the 0.75 mass exponent.

In this paper, I resume the theoretical endeavor of Lambert & Teissier (47) by placing the metabolic power function into its physical and dimensional framework. This approach gives new insights into the physiological meaning of the mass coefficient and mass exponent, and offers new avenues for research and speculation.

MASS-INDEPENDENT COMPARISONS OF METABOLIC RATES

It has been well established that there is a positive correlation between energy metabolism and body mass, the relation between these variables being a power function. Studies that demonstrate a significant metabolic effect due to some treatment must be very carefully examined when that effect is also associated with a change in body mass. The important question to address in such studies is whether the metabolic effect would still be significant if the treated animals were of the same mass as the control animals. In other words, is there a

significant mass-independent metabolic effect in the treated animals? This question leads to a conditional comparison based on the relationship that is assumed to hold between body mass and energy metabolism. Irrespective of how accurate the experimental data are, the outcome of this comparison will be physiologically valid only if a truly mass-independent expression for basal metabolism is used.

A mammal may change its body mass in different ways. During neonatal growth a *quantitative* increase in mass is associated with *qualitative* changes in body composition and form (56, 77). At a later phase, body composition and form tend to remain constant while mass continues to increase (8, 77). Body mass can also increase by accumulation of fat and retention of water, both metabolically inactive components (24). These examples show that we can differentiate quantitative from qualitative changes in mass. More importantly, we can formalize this differentiation and develop a rational method, based on the same theoretical foundations used in thermodynamics, for the analysis of metabolic data in nutritional studies or comparative physiology. The first step is to distinguish extensive (or quantitative) properties that necessarily change with mass from intensive (or qualitative) properties that cannot be altered by mass alone (32).

An understanding of intensive properties is crucial for differentiating the statistical relationship between body mass and energy metabolism from the underlying physical relationship between these two variables. An intensive property is by definition mass independent; i.e. it cannot be physically determined by mass. For example, temperature is an intensive property, as opposed to heat, which is an extensive property. Stating that temperature is an intensive property simply means that the temperature of a system cannot be altered by changing the mass of that system. Intensive properties are nonadditive; e.g. the temperature of a system is not equal to the sum of the temperatures of the components of that system. Being mass independent does not mean that systems of different mass must have the same temperature. Mass independence, in its thermodynamic meaning, cannot be tested by statistical tests, since correlation does not establish causation.

When expressing energy metabolism as a function of mass alone (Equation 1), we implicitly assume that the mass coefficient is constant and represents the metabolic effect of all significant metabolic factors other than mass. However, this may not be true. The mass coefficient may take different numerical values depending upon whether quantitative changes in mass are associated with (*a*) qualitative changes in mass (chemical composition, density, relative proportions of organs) and/or (*b*) qualitative changes in function, (body temperature, circadian rhythm, thermal adaptation, etc) (32).

How can the metabolic power function (Equation 1) and the concepts of extensive and intensive properties be used to recognize the various ways in

which mass affects energy metabolism? To answer this question, I first demonstrate that specific biological relationships between mass and energy metabolism in a single animal correspond to particular mathematical forms of the power function. In order to relate this conceptual development to nutritional studies, the analysis of the relationship between body mass and energy metabolism in obesity is emphasized.

PHYSIOLOGICAL INTERPRETATION OF THE POWER FUNCTION

Assume the power function (Equation 1) accurately describes the relationship between body mass (M) and basal metabolism (P): $P = aM^b$ (Equation 1). Here a is the mass coefficient and b is the mass exponent.

Equation 1 corresponds to the following physical relationship:

$$[\text{energy/time}] = [\text{energy}/(\text{time} \times \text{mass}^b)]\ [\text{mass}^b]. \qquad 2.$$

This physical relationship can be expressed in terms of the primary quantities of mass M, length L, and time T (28):

$$[ML^2T^{-3}] = [M^{1-b}L^2T^{-3}][M^b]. \qquad 3.$$

Careful examination of Equations 2 and 3 leads to the following observations and conclusions:

1. The mathematical form of Equation 1 (i.e. power function) is a consequence of the dimensional structure of energy metabolism [energy/time] and has no biological significance in itself. Equation 1 could just as well describe the relationship between mass and energy consumption in airplanes or any other physical system.
2. The mass coefficient a is the sole parameter with dimensions; the mass exponent b is a pure number. The mass coefficient can therefore represent a physical quantity with physiological meaning, whereas b is without counterpart in the physical or biological world.
3. The dimensions of a are determined by the numerical value of b (28–32). I shall determine what value b must take so that the mass coefficient becomes a dimensionally meaningful, mass-independent parameter.

Taking into account the dimensional and numerical interrelationships between a and b, the metabolic power function becomes more than a convenient algorithm for computing energy metabolism in animals of different mass. The distinction between extensive and intensive properties provides insight into the physiological meaning of the parameters and allows us to define the appropriate conditions for mass-independent comparisons of energy metabolism.

Individual Metabolic Power Function

What does the power function tell us about the nature of the relationship between mass and energy metabolism in a single animal? Consider the logarithmic form of Equation 1:

$$\log(P) = \log(a) + b[\log(M)]. \quad 4.$$

Equation 4 consists of three terms, each of which may remain constant (C) in a particular physiological situation to give the following cases:

1. $b[\log(M)] = C$: $\log(P) = \log(a) + C$
2. $\log(P) = C$: $C = \log(a) + b[\log(M)]$
3. $\log(a) = C$: $\log(P) = C + b[\log(M)]$.

Figure 1 graphically represents the three cases in an animal of mass M.

First case: $\log(P) = \log(a) + C$. 5.

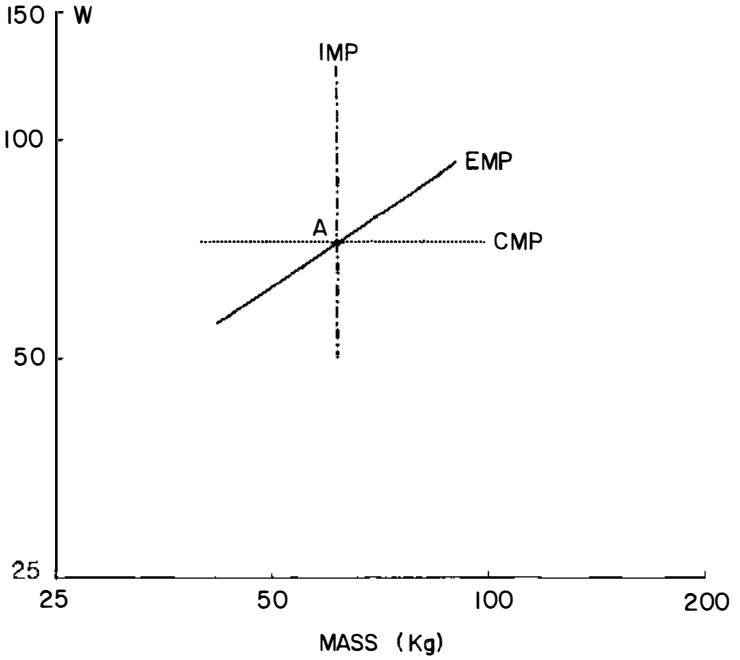

Figure 1 Metabolic paths of a single animal: intensive metabolic path (IMP), extensive metabolic path (EMP), and constant metabolic path (CMP). W = watts.

The mass remains constant and energy metabolism changes under the influence of factors such as circadian rhythmicity, ambient temperature, body temperature, locomotor activity, stress, thermal adaptation, etc. The metabolic values fall on the line parallel to the metabolic axis and going through point *A*. This line represents the intensive metabolic path (IMP). The ordinates of all points on the IMP can be algebraically expressed by assigning the appropriate values to a in Equation 5. Mass being constant, the changes in a represent intensive metabolic changes (28–32) and Equation 5 expresses qualitative functional or structural changes.

Second case: $$C = \log(a) + b[\log(M)]. \quad 6.$$

The energy metabolism of this animal remains constant despite changes in body mass. The metabolic values fall on the line parallel to the mass axis and going through point *A* (constant metabolic path or CMP). In this case, mass increases by accumulation of metabolically inactive mass (water or fat, for example); the result is no change in energy metabolism. The metabolic effect of the quantitative change in mass (the increase in $b[\log(M)]$) has been compensated for by that of the qualitative change in mass (i.e. a decreases during the increase in mass).

Third case: $$\log(P) = C + b[\log(M)]. \quad 7.$$

This is by far the most important case. A change in energy metabolism is solely due to a change in mass. Mathematically, Equation 7 could be solved for any value of b. However, since this equation involves dimensional quantities (M, P), a is constant only for a particular value of b, i.e. when the animal remains qualitatively the same (same intensive properties) during its change in mass. For which value of b does Equation 7 hold?

The constancy of the mass coefficient can also be expressed by the following relation:

$$[a_2]/[a_1] = [m_2/m_1]^0 = 1, \quad 8.$$

where a_1 = initial mass coefficient, a_2 = final mass coefficient, m_1 = initial mass, and m_2 = final mass. The dimensional form of Equation 8,

$$[M_2^{1-b}L_2^{2}T_2^{-3}]/[M_1^{1-b}L_1^{2}T_1^{-3}] = [M_2]^0/[M_1]^0, \quad 9.$$

shows that the mass ratio depends on the value of b, which is contained in a. Equation 9 holds when all the intensive properties are constant. In this case,

body composition is constant, and therefore the density and the mass-specific enthalpy are constant. Under these conditions $b = 2/3$ (32).

The condition stated by Equations 8 and 9 is therefore satisfied if and only if $b = 2/3$. Under these conditions, any new value for energy metabolism would fall on the extensive metabolic path (EMP) passing through point *A* and having a slope of 2/3. Metabolic changes that take place along this path are due only to mass, since the animal remains qualitatively the same. Conversely, any new value of *P* not falling within the confidence interval of the EMP would reveal a mass-independent or intensive metabolic change associated with the change in mass. Any treatment producing this situation must be interpreted as having a mass-independent metabolic effect.

From this discussion we see that the mass exponent *b*, which as shown by Equation 3 has no physical representation, is a *criterion* for the constancy of *a* during the change in mass. That is, a value of *b* different from 2/3 reveals the existence of qualitative (intensive) changes associated with mass (form, structure, composition), metabolism, or both.

When $b = 2/3$ the mass coefficient is

$$a = P/M^{2/3}. \qquad 10.$$

The value of 2/3 has been theoretically derived under the assumption that *a* is mass independent: the ratio $P/M^{2/3}$ is therefore an intensive metabolic property and a mass-independent expression of energy metabolism. This derivation does not preclude a statistical correlation between this ratio and body mass. The reasoning we used to obtain this ratio is valid for any animal, whether homeotherm or poikilotherm, and is not based on any physical law governing heat loss.

So far, we have focused on a single animal whose energy metabolism may evolve along different ideal paths (IMP, CMP, EMP) that reveal changes in this animal with respect to its initial state, but do not tell us anything about the initial state itself. The power function is not specific to any particular function or structure: it only detects changes in function, structure, composition, and form when mass changes. This particular feature explains the ubiquity of the power function in the animal kingdom.

The actual metabolic path of an animal is a dynamic combination of the three ideal paths. It reflects the various functional and structural transformations an animal undergoes during its lifetime. This metabolic path is continuous because of the continuity in function, mass, and composition of an animal. For each state there is a specific EMP, along which the animal would evolve if it were to remain qualitatively the same. This path is virtual during growth or senescence, but may be approximated during maturity. A corollary is that two individuals of

different body composition or in a different physiological state have different EMPs.

Statistical Analysis of the Power Function

Thermodynamic considerations show that body mass and energy metabolism must be related. Dimensional analysis reveals that this necessary physical relationship is a power function that, according to the foregoing reasoning, takes specific forms under particular physiological conditions. Therefore, the question arising in the analysis of metabolic data is not whether there *is* a relationship, but what are the best estimates of the parameters of the power function?

The a priori theoretical information about the data must be integrated with any statistical analysis. In particular, the theoretical assumptions under which regression analysis is valid must be consistent with the physical nature of the data. We cannot expect to describe accurately a relationship by simple regression analysis when we have compelling theoretical reasons indicating that the mass coefficient is not mass independent. The aim of regression analysis is to establish the mean metabolic path of a population of virtual, individual metabolic paths. However, in plotting body mass and energy metabolism we establish a correspondence between the respective properties in individuals whose metabolic paths may be different.

Assuming the regression line is representative of the individual paths, then the individual points are scattered about this mean path, and the residual variance of energy metabolism is a quantitative measure of this scattering. However, the variance of energy metabolism that is statistically correlated with mass represents the actual metabolic effect of mass only if the mass exponent is equal to 2/3. When b is different from 2/3, part of this statistical variance is actually due to the effect of intensive metabolic factors that are correlated with, but not due to, mass.

When the ratio $P/M^{2/3}$ (or mass-independent metabolism, MIM) is the same in two animals of the same species but of different size, we can conclude that their EMPs coincide, i.e. they would have the same energy metabolism if they had the same mass. The converse is also true: if their MIM is different, the two animals have different EMPs and they would not have the same energy metabolism even if they had the same mass.

The following example is an application of these concepts to the comparison of body mass and basal oxygen consumption in lean and obese mice. The data are from Mayer et al (50). The mean values of body mass and basal oxygen consumption in lean mice are $M = 28.2 \pm 0.72$ g (standard error), $\dot{V}_{O_2} = 100 \pm 6$ ml O_2/h, $N = 7$, where N is number of mice. In obese mice, $M = 53.7 \pm 3.71$ g, $\dot{V}_{O_2} = 84 \pm 7$ ml O_2/h, $N = 6$. In obese mice the MIM (5.9 ± 0.8 ml

$O_2/M^{2/3}$) is significantly less than that in lean mice (10.8 ± 0.8 ml $O_2/M^{2/3}$, t-value = 4.33, degrees of freedom *(df)* = 11, $p < 0.005$). If the lower MIM is due not solely to the accumulation of adipose tissue but also to a metabolic effect per se of obesity, then oxygen consumption in the obese mice should be significantly less than that of the lean mice. A one-tailed t-test shows that oxygen consumption of the obese mice is indeed significantly less than that of the lean mice ($t = 2.46$, $df = 11$, $p < 0.025$), so we conclude that in addition to the reduction due to the accumulation of adipose tissue, there is a reduction in metabolism in obesity. This result suggests that a normal level of energy metabolism could not be restored in an obese mouse through weight loss. In other words, lean and obese mice are qualitatively different.

The data of Koong et al (45, 46) also illustrate the physiological meaning of the $P/M^{2/3}$ ratio. In 22-week-old pigs of about 40 kg the fasting heat production may differ by as much as 40% depending on the nutritional history of the growing animals. These animals of the same mass have significantly different relative organ masses, i.e. they have different intensive properties. Their metabolism expressed per mass to the power 2/3 is not the same.

In summary, the power function reveals whether or not metabolic changes are simply due to changes in mass. The values of both the mass coefficient and the mass exponent are important sources of information about the energy metabolism of the compared animals. There is no theoretical justification for the generally accepted assumption that basal metabolism expressed per mass to the power 0.75 is mass independent. The $P/M^{0.75}$ ratio fails to standardize energy metabolism with respect to mass.

INTRASPECIFIC REGRESSION BETWEEN BODY MASS AND ENERGY METABOLISM

The following examples are practical applications of the theoretically derived concepts using various data from the literature. Data presented in graphical form were digitized (GTCO digi-pad 5), and then replotted by computer (IBM PC and Bausch & Lomb Hiplot DMP-40). An interactive digitizing and plotting subsystem (Vishnu) developed by MOMS Computing (Sausalito, CA) was used. Graphs obtained in this manner were carefully checked against the originals. Individual values were reproduced within a maximum error of 0.2%. Mass exponents and other population statistics were reproduced within 0.1%. Errors introduced by digitizing were therefore negligible with regard to possible plotting errors in the original graph.

Sex Differences

The first example is a regression between body mass and basal metabolism. The data were obtained from Harris & Benedict's biometrical study of basal

metabolism in humans (25). Figure 2 shows the scatter diagram of body mass (kg) and basal metabolism (watts) of 135 males and 103 females; the data are plotted on a double logarithmic scale. The equal probability ellipses, which summarize the data and their dispersion, were computed for each sex using Hotelling's T^2 statistic (10, 15, 72). Each ellipse circumscribes a region in which a new measurement made on an individual, randomly chosen from the same population and under the same experimental conditions, would fall with a

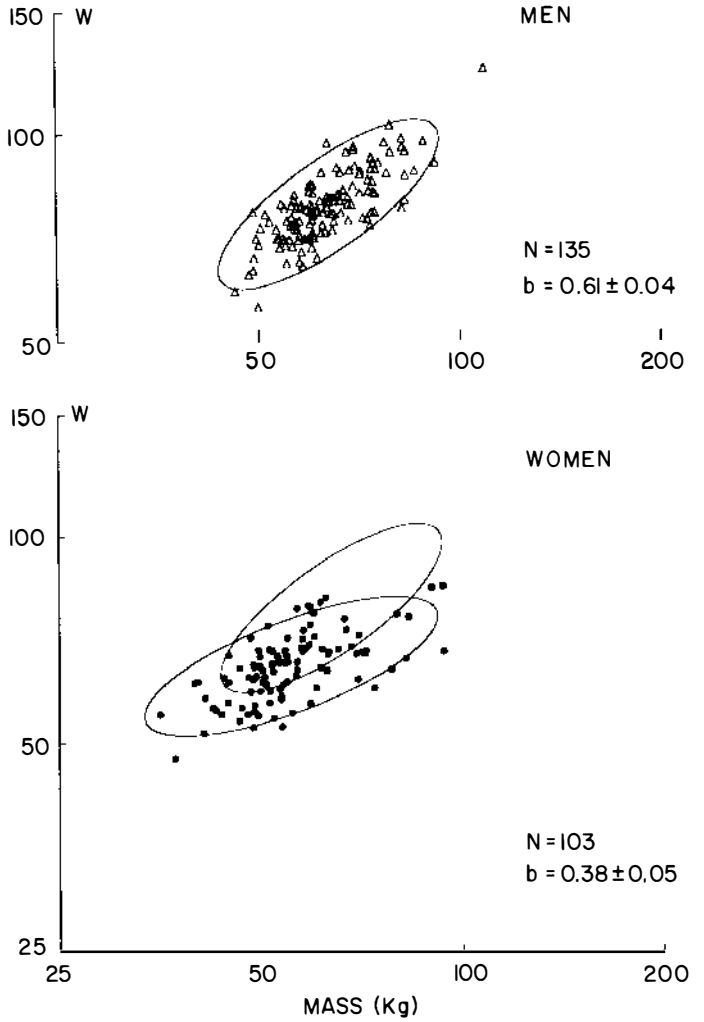

Figure 2 Scatter diagrams of body mass and basal metabolism in men and women with 95% equal-probability ellipses. In the lower diagram, the ellipse for men is superimposed on that for women for comparison. The data are from Harris & Benedict (25).

probability of 95% (34). The ellipse is a graphical representation of the intensive metabolic effects; i.e. in the absence of these effects (residual variance = 0), the ellipse would reduce to the regression line. Ellipses established with large samples of carefully measured data drawn from a specified population (healthy, normal, adult men or women of known ethnic origin) can serve as simple criteria or standards for basal metabolism.

The top of Figure 2 shows the ellipse for Caucasian men. The ellipse closely fits the data: as would be expected, seven data points (5%) fall outside. The regression is highly significant ($F = 198$, where F is the variance ratio; $df = 1, 133$; $p < 0.001$). The square of the correlation coefficient ($r^2 = 0.59$) indicates that about 60% of the variance in basal metabolism is *statistically correlated* with body mass; the remaining 40% (or residual variance) is mass independent. The mass exponent of 0.61 ± 0.04, being not significantly different from 2/3 ($t = 1.3$, $df = 133$, $p > 0.1$) reveals that the observed mean metabolic path is not significantly different from the EMP of the mean data point. That is, body composition tends to remain constant in males as mass increases, and the metabolic effect of age is too small for this sample size to make the difference between 0.61 and 2/3 statistically significant.

The bottom of Figure 2 shows the scatter diagram and the corresponding ellipse of basal metabolism in Caucasian women, the male ellipse being superimposed for comparison. There are some interesting differences between the two ellipses: (*a*) the female ellipse does not fit the data as closely (11 data points or 11% fall outside); (*b*) residual variance of the female data is higher (60% of total variance versus 40% in males); and (*c*) the mass exponent for females is significantly lower ($b = 0.38 \pm 0.05$; $t = 4.62$, $df = 234$, $p < 0.001$) and significantly different from 2/3 ($t = 6.16$; $df = 101$; $p < 0.001$). The lower mass exponent in women and the weaker correlation between body mass and basal metabolism suggest that, contrary to men, body composition of women does not remain constant as mass increases.

If body composition in women were mass independent, their basal metabolic values would be randomly distributed about the extensive metabolic path (EMP) of the average 40-kg woman. This EMP is computed in the following way. Basal metabolism of the average 40-kg woman is 57.32 W, her MIM is $57.32/40^{2/3}$ or 4.90. This MIM is not different from that of men (4.95 ± 0.03). The EMP for women is then given by the following equation:

$$P = 4.90\, M^{2/3}. \qquad 11.$$

Figure 3 shows this EMP (solid line) and the experimental regression line (dotted line) on a linear scale.

The right shift of the observed curve with respect to the EMP may be due to:

1. an increase in body mass from *A* to *B*, due to accumulation of metabolically inert mass (fat and water), which causes a change in body composition that in effect dilutes the metabolically active mass;
2. a reduction of basal metabolism taking place at constant mass and constant composition from *A* to *C*;
3. a combination of both mechanisms, such as the effect of a change in body composition and a concomitant reduction in basal metabolism due to age, nutritional state, etc.

Assume, as a first approximation, that the right shift is mainly due to an increase in adipose tissue (*A* to *B*). Knowing the chemical composition of this tissue [2–2.3% protein, 13.6–15% water, 83% fat (19, 20)], we can estimate the relative change in body composition with mass with respect to a 40-kg woman of known body composition. The estimated values for the percentage of fat at various masses are well within the limits of those reported in the literature (7, 16, 35, 39, 78).

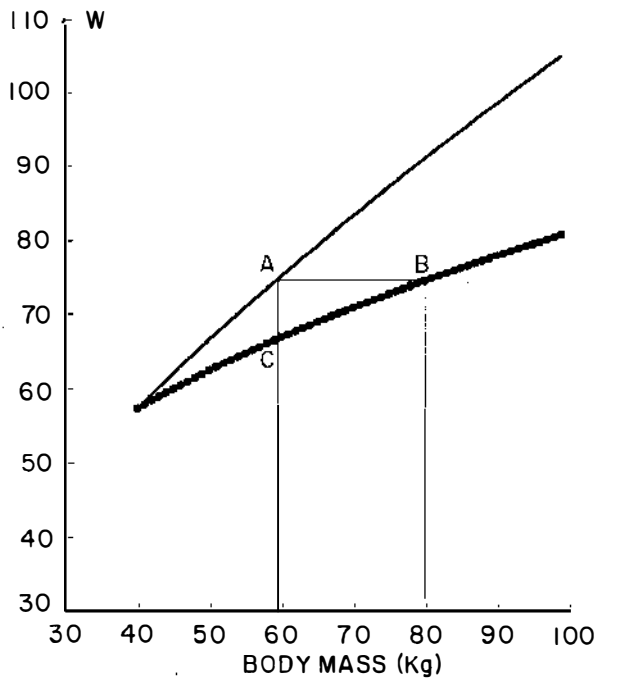

Figure 3 Extensive metabolic path and actual mean metabolic path of women. The right shift of the actual mean metabolic path may be due an increase in body mass without metabolic effect (*AB*) or an intensive metabolic effect (*AC*) or a combination of the two.

Is this change in body composition with increased mass characteristic of females? Using the data of Miller & Blyth (53) for basal metabolism in men of larger mass, one can calculate a mass exponent of 0.57 ± 0.05 that is not significantly different from 2/3 ($t = 1.93$, $df = 46$, $p > 0.05$). According to Miller & Blyth the mass exponent for the same metabolic data with respect to lean body mass is 0.64. I could not confirm this result by reanalyzing their data. Regression analysis of the logarithms of the digitized data yields a b value of 0.77 ± 0.04. Is this discrepancy due to digitizing, plotting, or computational errors? We can rule out digitizing errors, since we could reproduce the linear regression equation for basal oxygen consumption and lean body mass reported by Miller & Blyth in an earlier paper [$\text{LBM} = -6.8 + 0.29(\dot{V}_{O_2})$].

If Harris & Benedict's data (25) are pooled with those of Miller & Blyth, the mass exponent is significantly lower than 2/3 ($b = 0.55 \pm 0.03$, $t = 4.19$, $df = 180$, $p < 0.0005$), i.e. in a large sample with a wide range of body mass, significant but small changes in body composition can be detected in men (it is unlikely that the 0.55 mass exponent is due to the effect of age, since heavier than average normal men are not necessarily also older). The theoretical interpretation of the mass exponents of the power function between body mass and basal metabolism in men and women reveal more important qualitative changes in mass in women than in men, a fact that has been confirmed by analysis of body composition (7, 19, 20, 39).

A similar sex difference exists between female and male rats. Figure 4 shows the ellipse for body mass and basal metabolism for 515 rats (for source of data see figure caption). The mass exponent is significantly different from 2/3 ($b = 0.53 \pm 0.01$, $t = 13.6$, $df = 513$, $p < 0.0005$).

In order to prevent masking or exaggerating the sex difference by extraneous factors, the ellipses for female (F) and male (M) rats (Figure 4, bottom) were computed using only data measured in the same laboratory, Benedict's Nutrition Laboratory (5). Regression analysis yields the following statistics: for male rats, $b = 0.66 \pm 0.04$, $N = 52$; for female rats, $b = 0.47 \pm 0.06$, $N = 42$; $t = 2.48$, $df = 90$, $p < 0.01$.

Obesity and the Metabolic Power Function

The comparison of energy metabolism in normal and obese women and men provides an ideal example for illustrating the effect of body composition on basal metabolism. Figure 5 shows the ellipses for individuals of normal weight [Harris & Benedict's data (25)] and for obese men and women [White & Alexander's data (75)].

The ellipse for obese men has the same orientation as that for normal men, but is shifted to the upper right of the graph. The mass exponent of $b = 0.64 \pm 0.09$, $N = 39$ (not different from that in normal men or from 2/3) reveals that obese men as a group tend to maintain a constant body composition.

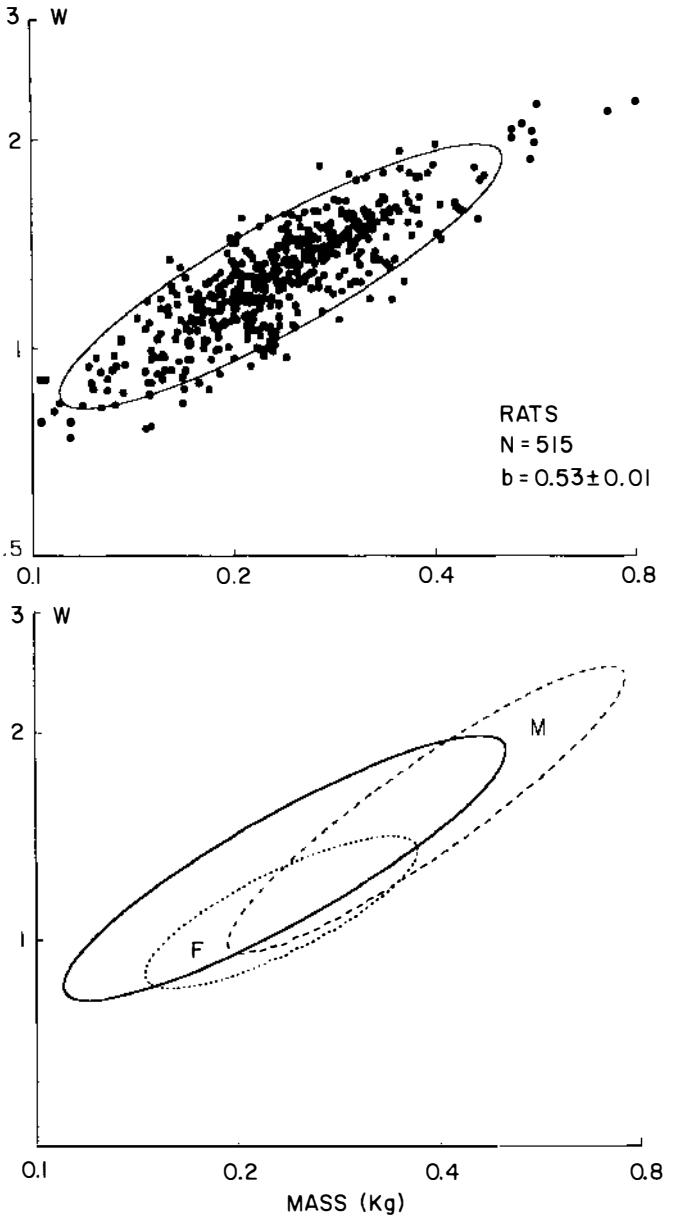

Figure 4 The 95% equal-probability ellipses of body mass and basal metabolism in rats. The data sources are given in Reference (34). In addition there are 220 data points from Rufeger [personal communication and Ref. (68)]. The bottom figure shows the overall ellipse *(heavy line)* and the ellipses for female rats (*F*) and males rats (*M*). These values were determined in Benedict's Nutrition Laboratory (5).

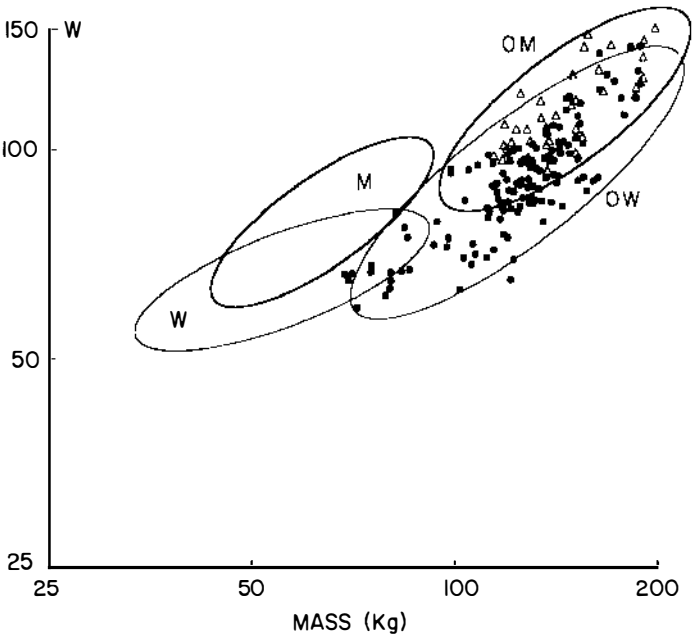

Figure 5 The 95% equal-probability ellipses of body mass and basal metabolism in normal men (*M*) and women (*W*) and in obese men (*OM*) and obese women (*OW*). The data for normal humans are from Harris & Benedict (25); those for obese individuals are from White & Alexander (75).

However, the obese body composition is not the same as the normal body composition, since the ellipses for normal and obese men are not aligned, a fact confirmed by analysis of covariance ($F = 16$, $df = 1, 172$, $p < 0.001$).

The ellipse for obese women differs significantly in position and orientation from that of the normal women. Contrary to normal women, obese women tend to maintain a constant body composition: $b = 0.68 \pm 0.04$, $N = 130$ (not significantly different from that of normal and obese men or from 2/3). The relative positions of the four ellipses show that small samples drawn within different mass ranges or from different areas of these ellipses may lead to conflicting conclusions as to the effect of obesity on energy metabolism.

When comparing energy metabolism in normal and obese subjects, our aim is to determine whether energy metabolism would be the same in an obese and a lean individual if both had the same body mass and the same respective body composition. Figure 6 shows the MIM of normal and obese individuals of both sexes.

In normal men (pooled data of Harris & Benedict and Miller & Blyth) the MIM declines slowly with mass, from 5.11 to $4.13 W/M^{2/3}$ (regression coefficient is $b = -0.0076 \pm 0.0018$, $df = 1, 180$, $F = 17.95$, $p < 0.001$). However, 91% of the variance of the MIM is uncorrelated with body mass ($r = -0.3$).

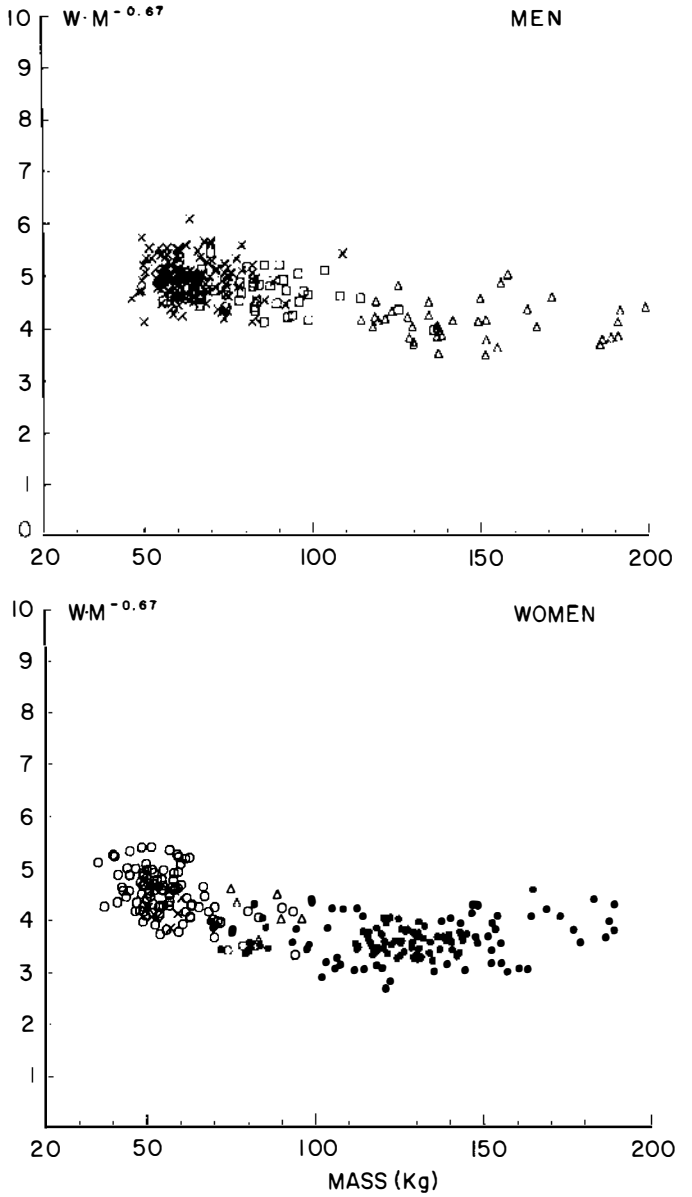

Figure 6 Scatter diagram of body mass and the $P/M^{2/3}$ ratio (MIM) in normal and obese humans. Top figure shows the data for normal males (*X*) from Harris & Benedict (25) and Miller & Blyth *(squares)* (53). The data for obese males *(triangles)* are from White & Alexander (75). Bottom figure shows the data for normal females *(open circles)* from Harris & Benedict (25). The data for obese females *(closed circles)* are from White & Alexander (75). Also are shown data from Bessard et al (7): normal (*X*) obese *(triangles)* (63).

There is no correlation between body mass and the MIM in obese men ($r = -0.05$, $df = 37$, $p > 0.05$). These results suggest that adipose tissue increases slightly in normal men, but remains at a constant percentage of body mass in obese men.

In normal women (bottom graph in Figure 6) the MIM declines more with mass than in normal men from 4.83 to $4.00 W/M^{2/3}$ (regression coefficient is $b = -0.021 \pm 0.003$, $df = 1, 101$, $F = 37$, $p < 0.001$). 73% of the variance of the MIM is uncorrelated with mass ($r = 0.52$). In obese women the MIM is constant (no correlation with mass: $r = 0.087$, $df = 128$, $p > 0.05$). Its level is significantly lower (12%) than that in obese men (women: 3.63 ± 0.03; men: 4.13 ± 0.06, $df = 167$, $t = 12.8$, $p < 0.01$). If this difference in the MIM is solely due to body composition, then these results suggest that adipose tissue reaches a higher concentration in obese women than in obese men. At equal mass, basal metabolism is on the average lower in obese women than in men. For a given mass and within both sexes, basal metabolism is higher in the normal than in the obese person.

These conclusions are necessarily speculative at present. They are based on new theoretical considerations and were derived by integrating experimental data recorded in different laboratories and at very different times. In particular, the experimental and control data have not been obtained in the same laboratory. These conclusions should therefore be considered as hypotheses to be tested, rather than as definitive statements about the effect of obesity on energy metabolism. They also suggest that conclusions obtained with small samples, regardless of how carefully the experiments have been planned and conducted, may not be as general as the investigators wish them to be and may be the source of disagreement among investigators.

INTERSPECIFIC COMPARISON OF ENERGY METABOLISM

Energy metabolism is mathematically a multivariate function whose geometrical representation is difficult to visualize because for each variable there is a coordinate axis. We have seen that when $b = 2/3$, the effect of all the other variables is expressed by the mass coefficient a. In this case energy metabolism can be expressed as a function of mass (X-axis) and a (Y-axis) and can be geometrically represented by a three-dimensional XYZ-graph. Each value of a defines a mass-power plane (MP-plane), which is perpendicular to the a-axis. Metabolic data for which a is significantly different are in different MP-planes. In practice the MP-plane is a "slice" whose thickness depends on the confidence interval of a. This slice contains the statistically estimated confidence region of the data points.

Covariance analysis of interspecific metabolic data has shown that the values of a for various mammalian species are significantly different (17, 28). There-

fore interspecific data points do not lie in the same *MP*-plane. In theory there is a particular *MP*-plane for each species. In practice however, there is an *MP*-slice for each species, the thickness of which depends on the confidence interval of *a*. Interspecific comparisons of basal metabolism based on extrapolation of the Brody–Kleiber line are physiologically meaningless because this line does not lie in the same *MP*-plane and the mean data points do not lie on this line. Benedict (5) recognized the practical consequences of this fact when he stated: "However satisfactory this relationship may be mathematically, this method of representing the data completely masks metabolic differences within the species and distorts or obscures striking differences between the species. . . . It is obvious that this apparent straight-line relationship is of no physiological significance, whatever its mathematical significance may be thought to be." This is a case where "we cannot extrapolate data arbitrarily, even within a similarity class: we must respect the fact that such data can be transformed only to the corresponding situation in another species. Failure to take account of the limitations of similarity can lead, and has led, to terrible mistakes" (66). How are we then to compare basal metabolism in animals of different mass and species?

Figure 7 illustrates the comparison of basal metabolism in mice and rats. The EMPs for mice ($P = 2.32M^{2/3}$) and rats ($P = 3.4M^{2/3}$) and their respective 95% confidence regions are shown. Even though represented in the same *MP*-plane, one has to keep in mind that the mouse EMP is in the "mouse slice" and the rat EMP is in the "rat slice." These slices do not coincide because mice and rats are qualitatively different (different $P/M^{2/3}$ ratios).

The solid line *AB* going through the origin O in Figure 7 would indicate that there are a mouse and a rat with the same mass-specific basal metabolism. However, we cannot infer from this that both animals would have the same basal metabolism if they had the same mass. Basal metabolism of the theoretical 175-g mouse would be *A'*, not *B*. Conversely, basal metabolism of the theoretical 52-g rat would be *B'*, not *A*. This comparison shows that while it is true that two animals having the same mass and basal metabolism also have the same mass-specific basal metabolism, the converse is not true. Two animals of different size having the same mass-specific basal metabolism cannot have the same basal metabolism if they have the same mass. Mass-specific basal metabolism is not suitable for interspecific comparisons. Contrary to common belief, expressing energy metabolism per unit mass does not correct for the difference in mass, but introduces a definite bias into the data. A metabolic difference that was not significant for the whole animal may become significant when mass-specific basal metabolism is used, but this is no proof that the treatment had a significant effect.

When comparing basal metabolism of rats and mice, we are asking whether both animals would have the same basal metabolism had they the same mass. Comparing their $P/M^{2/3}$ ratios shows that at the same mass, the mouse would

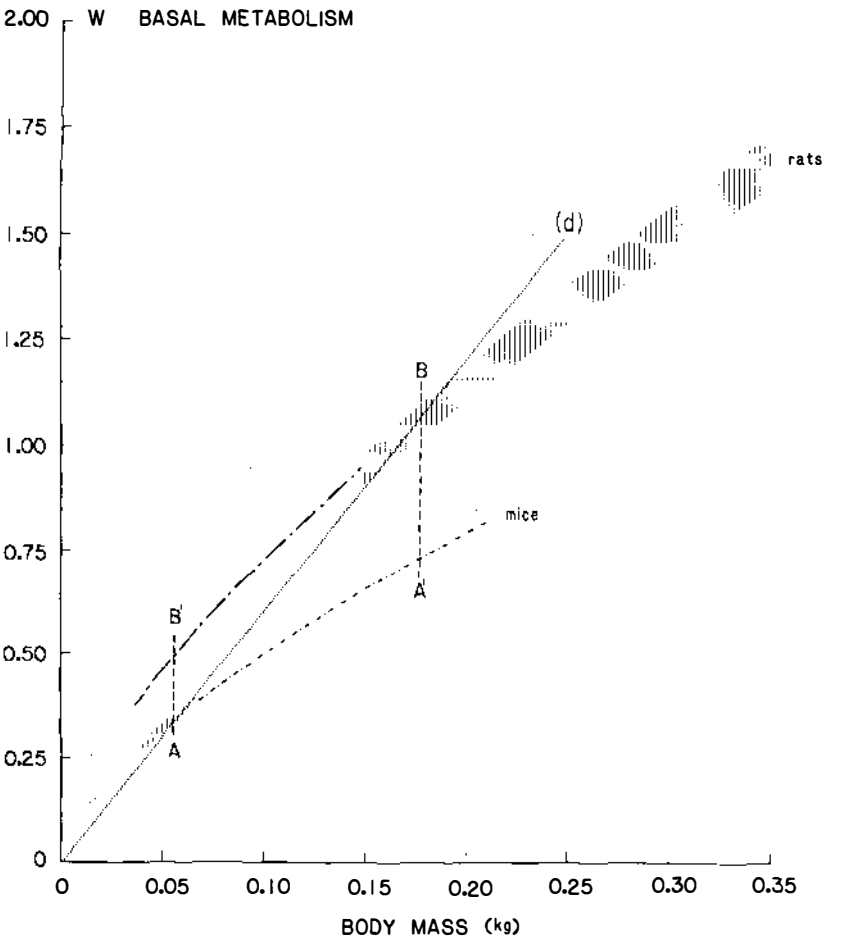

Figure 7 Body mass and basal metabolism in mice and rats. The EMPs and their confidence regions were computed from the statistics given in Heusner (28). The x and y scales are linear.

have a 32% lower basal metabolism than the rat. This relative difference is constant and mass independent. In this biologically meaningful comparison we take into account the qualitative differences between rats and mice. If we were to predict the basal metabolism of either animal based on the Brody–Kleiber line we would have masked these physiologically important differences between the two species.

PHYSIOLOGICAL MEANING OF THE $P/M^{2/3}$ RATIO

Dimensional interpretation of the metabolic power function and the distinction between extensive and intensive properties show that this function enables us to

detect (*a*) qualitative changes over time in an organism and (*b*) qualitative differences between individuals. It does not identify or characterize these changes or differences. Their true nature must be experimentally established. Changes in this ratio are energetic measures of the qualitative changes. The variability of this ratio reflects the diversity of function, form, structure, and body composition in the animal kingdom: It is an expression of the almost infinite number of combinations of qualitative properties. Figure 8 shows the variability of this ratio from shrews to the largest mammals.

There is a statistically significant ($r = 0.35$, $N = 178$, $p < 0.01$) but physiologically weak correlation (only 12% of the variance of this ratio is correlated with mass) between body mass and this ratio. This ratio is not evenly distributed over the whole mass range in mammals, a fact expressed by the Brody–Kleiber mass exponent. However, within the mass range from 2.5 to 10,000 g, which includes 83% of the data, the correlation is no longer significant ($r = 0.13$, $N = 148$, $p > 0.05$). Assuming that all the values are basal

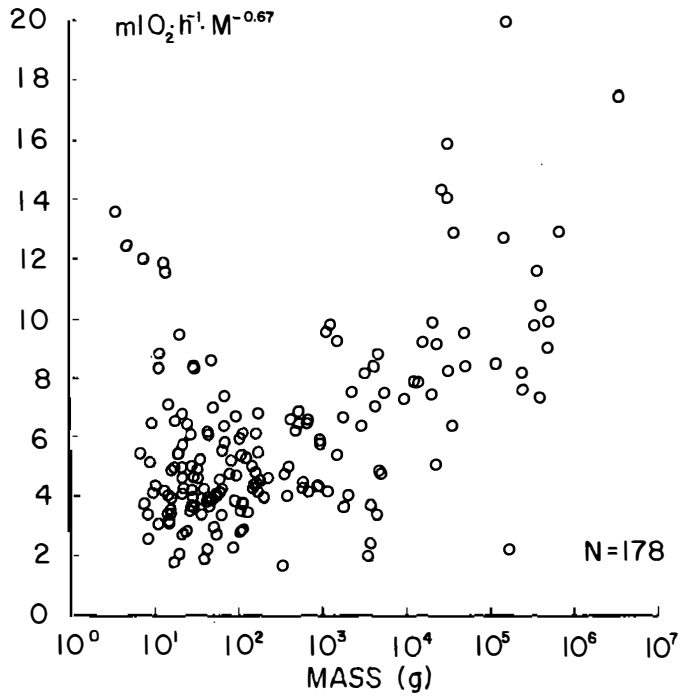

Figure 8 Scatter diagram of body mass and the $P/M^{2/3}$ ratio in 178 mammalian species. The data are from the *Biological Handbook* (1). The large variability may partly reflect the fact that all values may not be strictly basal.

metabolism, the distribution of this ratio suggests that the statistical correlation may reflect the sampling of the animal species.

In this paper I designated the $P/M^{2/3}$ ratio as "mass-independent metabolism" and the "mass coefficient." In intraspecific regression analysis pertaining to animals whose intensive properties are the same (homomorphic animals), this ratio is constant and equal to the mass coefficient of the EMP. In general, it is the dimensionally defined mass-independent measure of basal metabolism (MIM) that is valid regardless of the observed value of the mass exponent.

The constancy of this ratio is a criterion for biological similitude or homomorphism. The $P/M^{2/3}$ ratio represents the energy spent per unit mass and physiological unit of time, or mass-specific physiological power (29). In homomorphic animals the energy spent per unit mass and unit of physiological timescale is constant (29).

CONCLUDING REMARKS

The physiological relationship between body mass and energy metabolism is a complex multivariate function that can be mathematically expressed by a simple power function. By taking into account the qualitative or quantitative nature of the involved variables and parameters and their dimensional constraints, this simple mathematical formulation becomes a conceptual model. From a practical point of view, this model provides a rational basis for choosing the appropriate statistical methods for analyzing metabolic data and for physiologically interpreting the results. From a theoretical point of view, this model provides a unifying principle for comparative physiology from which the concepts of biological similitude and homeostasis can be logically derived. In the light of this model, the 2/3 mass exponent, which has intrigued and misled physiologists for more than a century, is a general expression, at the level of the species, of Claude Bernard's principle of the constancy of the "milieu interieur."

ACKNOWLEDGMENTS

I owe special gratitude to Dr. M. L. Tracy for her encouragement and for the many hours spent in critically reviewing and editing the manuscript. I gratefully acknowledge the suggestions and criticisms offered by Drs. E. Bernauer, B. Horwitz, P. Mole, B. Moore, and J. Stern. My special thanks to Eric Semanne for his expert assistance in the computer analysis of data and to Mr. J. Munshi for implementing the Vishnu software.

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