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Metabolism
kidney
body weight

basal metabolic rate
glomerular filtration rate
oxygen consumption

growth
body surface area
organ growth

REVIEW

The Relation of Metabolic Rate to Body Weight and Organ Size

A Review

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Introduction

The relation of metabolic rate to body size has been a subject of continuing interest to physicians, especially pediatricians. It has been learned that many quantitative functions vary during growth in relation to metabolic rate, rather than body size. Examples of these are cardiac output, glomerular filtration rate, oxygen consumption and drug dose. This phenomenon may reflect a direct cause and effect relation or may be a fortuitous parallel between the relatively slower increase in metabolic rate compared to body size and the function in question.

The fact that a decrease in metabolism and many other measures of physiological function in relation to a unit of body size is observed in most biological systems. This phenomenon can be demonstrated by interspecies comparisons of mammals and birds, as well as within a species during growth or among matured members of a species that vary in size. Mice, for example, have a basal metabolic rate per kg (BMR/kg) approximately thirteen times that of elephants. In the case of humans during growth, the infant has a BMR/kg more than twice that of the normal adult. A normal adult may have a BMR/kg one and one-half times that of an obese adult.

The purpose of this paper is to review this subject and propose reasons why there is a lower BMR/kg as body size increases. When applied to growing humans, the information developed should allow a greater precision in estimating BMR from body weight during growth. It will be seen that the factors responsible for the decline in BMR/kg during growth differ from the factors operative among different species. The equation describing the relation of BMR to body weight during growth also differs from the equation describing this relation among different species.

Historical Background

The measurement of metabolic rate was first achieved by LAVOISIER in 1780. By 1839 enough measurements had been accumulated among subjects of different sizes that it was suggested in a paper read before the Royal Academy of France (co-authored by a professor of mathematics and a professor of medicine and science) that BMR did not increase as body weight increased but, rather, as surface area increased [42]. In 1889, RICHET [38] observed that BMR/kg in rabbits of varying size decreased as body weight increased; RUBNER [41] made a similar observation in dogs. Both noted that relating BMR to surface area provided results that did not vary significantly with size. These intraspecies observations were then extended to interspecies observations. In 1901, VOIT [48] observed that the BMR of 7 species of varying size ranged from 776 to 1089 calories/m^2 (cal/m^2) while the BMR/kg varied from 11.3 to 75.1 calories/kg (cal/kg). He concluded that BMR varied as surface area varied. This relation came to be known as the 'surface area law'. To some, the 'surface area law' acquired the status of a fundamental biological principle [29]. Nonetheless, as technics improved, data were accumulated which ultimately challenged the 'surface area law'.

Mathematical Models Relating BMR to Body Size

In studying the differences among species, the BMR predicted for small animals from their surface area and the BMR/m^2 of larger animals was not as high as the observed rate. In 1932, KLEIBER [23] compared BMR to body weight of animals of 10 species which ranged from mouse to steer. He plotted the log of BMR as a function of the log of body weight. The relationship was expressed by the equation: $C = 71 \pm 1.8\ W^{\cdot 75}$ where

C = BMR in calories/day (cal/day) and W = weight body in kg.

A similar relationship was described by BRODY and PROCTER [7] in the same year. In 1945, BRODY [8] developed this relationship in great detail and summarized the data which related endogenous nitrogen and sulfur metabolism as well as BMR to the $W^{\cdot 73}$. KLEIBER[1] [24,25] confirmed his previous equation, using new data from animals of 16 species; his newly derived equation was $C = 69 \pm 1.5\ W^{\cdot 75}$, which he simplified to $70 \times W^{\cdot 75}$. The fit was close for all the species studied, except for elephants and whales, where measurements were few and were difficult to obtain (fig. 1). The observed BMR/kg in 5 examples selected from KLEIBER varied from 181 to 14.1 cal/kg/day but in each instance the observed value agreed with that predicted from his equation (table I). BRODY [8] published studies in birds in which the relation between body size and BMR was almost the same as that noted for mammals (cal = $70 \times [\text{kg}]^{\cdot 75}$). The consistency of this relation over so wide a range of sizes and species suggests some unique biological advantage inherent within this relation. As size increases BMR increases less than weight but more than surface area.

In the meantime, an intensive search was being made for the best reference standard for BMR in adult humans, whose range in size was 5 to 10-fold. GEPHART and DUBOIS [14] published standards for males from 20 to 50 years of age, of 'normal' stature, in which 90% fell within ± 15 % of a standard value. HARRIS and BENEDICT [16] published an analysis of their data and derived a separate equation for men and women which took into account their height, weight and age. BOOTHBY and SANDIFORD [4] compared their results calculated from the empirical formulae of HARRIS and BENEDICT and from the surface area formula of DUBOIS [13] and found no greater variability in the data referred to surface area than in the detailed formula of HARRIS and BENEDICT. More recently, MILLER and BLYTH [33] measured oxygen consumption in male college students (weight range 54 to 136 kg) and found least variability when they related it to lean body mass, as opposed to surface area or weight. A still more recent study [50] observed the BMR to show the best degree of correlation with extracellular fluid volume. The difficulty in determining which function of size correlates with BMR among adult humans arises from the narrow range of size and BMR differences within this group, and the interdependence of the various functions of size to each other within the range.

Table I. BMR in adult mammals of various sizes (observed cal/kg/day compared to predictions from Kleiber's formula: cal = $70 \times W^{\cdot 75}$)

Species	Body weight (kg)	BMR (cal/day)	Cal/kg/day Observed	Predicted
Mouse	0.021	3.8	181	171
Rat	0.282	27	96	100
Dog	6.6	288	44	44
Man	55	1400	25	22
Cow	600	8460	15	13

[1] The equation derived by BRODY was $C = 70.5\ W^{\cdot 734}$, which he rounded off to $C = 70.5\ W^{\cdot 7}$, while KLEIBER preferred using $W^{\cdot 75}$.

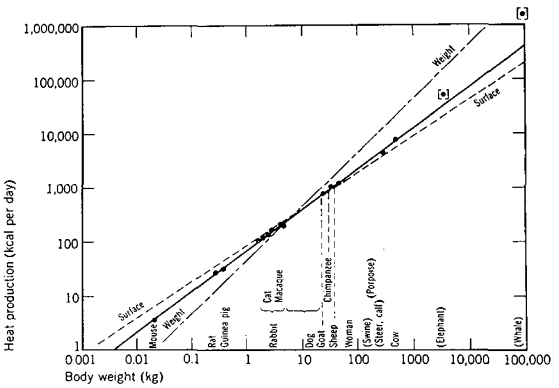

Fig. 1. Solid line (——) calculated regression equation of observed BMR and body weight. *Hashed line* (— — —) theoretical line should BMR increase as a linear function of body weight, i.e. BMR/kg = constant. *Dashed line* (– – –) theoretical line should BMR increase as a function of surface area or $W^{\cdot 67}$ (KLEIBER [24]).

The relation of BMR to body size during growth covers a wider range, so that correlations between BMR and different variables of body size can be tested. Both GEPHART and DUBOIS [14] and BENEDICT and TALBOT [2] noted that BMR/m² during growth differed significantly from that predicted from average adult values/m² (fig. 2). In newborn humans, the observed figures are lower; in the age group from 6 months to 3 to 4 years they are higher than those predicted; thereafter, they tend to approach the adult figure for cal/m²/day. A similar pattern of difference is noted in rats and in cattle during growth [8].

The standard values of BMR found by BENEDICT and TALBOT [2] and more recently by LEWIS *et al.* [32] define an empiric and varying relation between BMR and body weight. An arithmetic plot of this relationship in boys, using the data of BENEDICT and TALBOT, is illustrated in figure 3. The data for girls and the independent data of LEWIS *et al.* [32] are not different in any important respects.

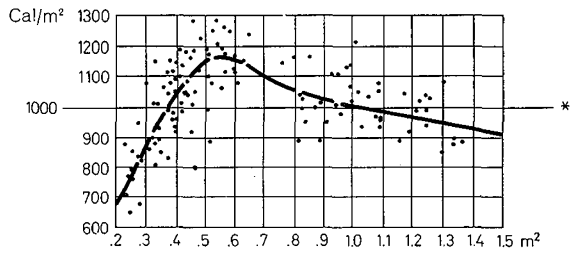

Fig. 2. Plot of cal/m² of observed data from normal children during growth. Below 0.3 m² (3 mo age or 5 kg), the observed figures are less than the adult averages; between 0.3m² and 0.6 m² (6 months to 3–4 years) the observed data are higher than predicted from adult averages (from GEPHART and DUBOIS [14] and BENEDICT and TALBOT [2]).

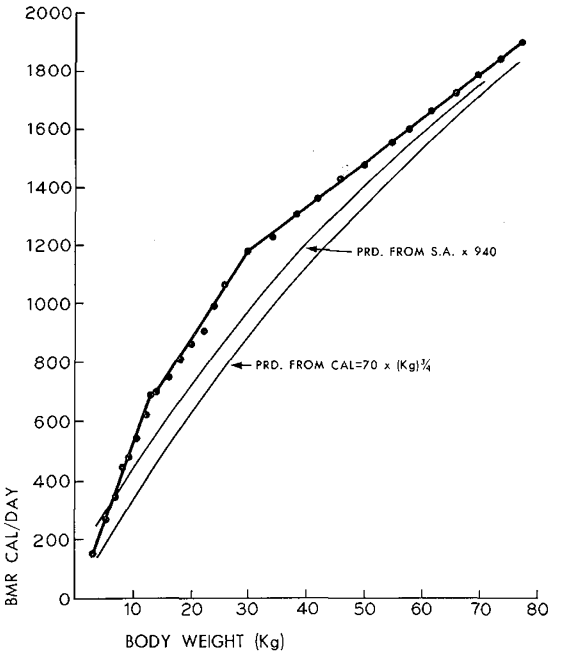

Fig. 3. Heavy line describes observed relation between body weight and BMR (from data of BENEDICT and TALBOT [2]). Upper light line describes relation between body weight and BMR should BMR vary as a linear function of surface area. Lower light line describes this relation should BMR vary as a linear function of $W^{.75}$.

This plot can be described by 3 successive straight lines with changing slopes. From 3 kg (birth) to 10 to 12 kg (approximately 18 months), the slope represents a 55 cal/kg increase. From approximately 12 kg to 28 kg, the average increase is 30 cal/kg. From 28–30 to 80 kg the increase in BMR is 15 cal/kg. For comparison, the predicted BMR from the adult rate/m² surface area, using standard surface area figures for weight, and the BMR predicted from KLEIBER's formula: $C = 70 \times W^{.75}$ are plotted. The predictions, using either theoretical relation, come close to the observed figures at points in infancy and again at maturity, but with considerable differences at other points.

The highest BMR/kg in humans during growth is 56 calories at 6 kg; the lowest is 25.5 calories at 70 kg body weight. The rate of 'increase' of BMR and of body weight are compared in figure 4 by plotting the log of BMR as a function of the log of body weight. Their comparative rates of growth are constant and equal up to 10–12 kg—the plot is linear and the slope is 1.0. Beyond 10–12 kg the rate of 'increase' of BMR is much slower than that of body weight (slope 0.58) but the comparative rate of 'increase' over this range is relatively constant. For comparison, lines are drawn describing the theoretical rate of increase in BMR with growth, assuming it is a linear function of surface area and of body weight to the 0.75 power. Each of these theoretical curves deviates significantly from the curve of the observed values. From the curve of observed data it is evident that the rate of 'increase' of BMR in relation to body weight changes at 10–12 kg. At 30–38 kg a second, less obvious, change can be seen which is more evident in the arithmetic plot (fig. 3). In humans, the comparative rates of increase of weight and BMR do not conform precisely either to the surface area or to any other simple function of body size over the total range.

The difficulty in applying mathematical models to the relation of BMR to body weight is evident from the foregoing discussion. A simple mathematical description of the relation could be found only in interspecies models which encompass an enormous range of sizes. When a model was sought relating BMR to body size in humans, either among different-sized adults or during growth, no simple mathematical model could be found. It then seemed appropriate to formulate a new question: What is the source of BMR? In attempting to answer this question a second question (how BMR might vary in relation to body size) could be reduced to simple alternatives that lent themselves to testing. The rest of this review centers on 3 postulates and the evidence we have adduced in their support.

Postulate 1. Most of the BMR of an organism is derived from the metabolic activity of the principal internal organs; i.e., brain, liver, lungs, heart and kidneys.

It has been observed that the internal organs have an organ metabolic rate per gm (OMR/g) that is much higher than that of the body as a whole and that much of the total BMR is derived from the metabolic rate of

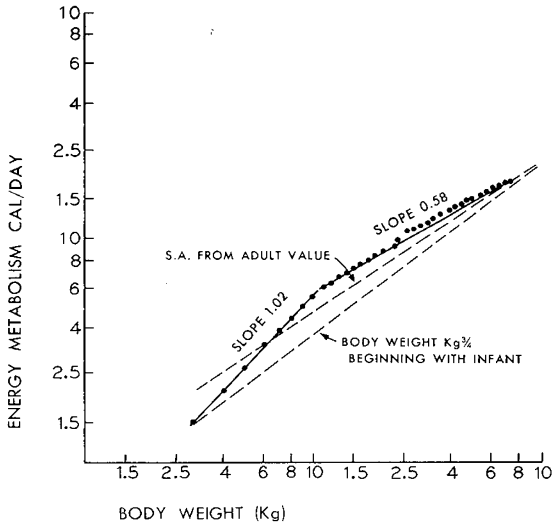

Fig.4. Data used in figure 3 plotted on log-log coordinates compares the rates of growth of BMR to body weight. By definition, both of the theoretical curves are linear in a log-log plot. Slope of S.A. line is 0.67; of $W^{.75}$ is 0.75.

the internal organs. A direct test of this in normal adult humans can be approached from measurements of oxygen consumption and mass of specific organ systems and summating these for comparison with the total BMR. We have estimated the percent of total BMR derived from five organs, four of which have been measured directly and one, the lung, for which a figure had to be calculated indirectly. This has been possible since KETY [21] developed a technic for measuring organ oxygen utilization and organ size in intact living subjects, so that a figure (ml O_2/100 g organ—brain in this case) could be derived. In normal man, the oxygen utilization by brain was found to be 3.7 ml/100 g/min, 260 cal/kg/day or assuming 4.9 cal/L/O_2. Applying the same technic to the kidney, CROSLEY *et al.* [11] reported that renal oxygen consumption in young male adults was 5.5 ml/100 g kidney/min or 400 cal/kg/day. Liver oxygen consumption has had to be derived from splanchnic oxygen consumption. The best figures vary between 3.5–4.8 ml/100 g/min or 350 cal/kg/day [6]. For the heart, oxygen consumption in normal man is 8.6 cal/100 g left ventricle/min or 600 cal/kg/day [39]. For comparison, the BMR of the whole body is 25 cal/kg/day in adults and 56 cal/kg/day in infants. There are no data on oxygen consumption of intact lungs. However, the QO_2 of lung, as measured in a Warburg respirometer, is somewhat less than that of liver.

On the assumption that lung metabolic activity is proportional to its QO_2 *in vitro*, we have calculated (table II) the calorie contributions from these 5 organs, OMR/g and total OMR, in a 70 kg adult and compared them with BMR. Assuming that OMR/g of each organ is the same in childhood (Postulate 3), a similar calculation can be made for a 10 kg infant; 79 % of the BMR can thus be derived from these 5 organs in the adult and 79 % in the 10 kg infant. The balance comes, of course, from muscle and lesser amounts from the smaller organs, the supportive structures and fat. However, it seems likely that with reasonable allowance for error, from 70–80 % of BMR in adults is derived from organs which comprise 7 % of body weight; a similar percent of BMR in children is derived from these organs which comprise 15 % of body weight. ASCHOFF, as cited by SMITH [1], derived the following figures of OMR as percent of BMR: splanchnic and visceral organs 37.3 %; brain 17.8 %; heart 11.9 %; kidney 4.9 %; for a total of 80.5 %.

The precision of these calculations is open to some question until measurements are made of regional oxygen consumption of more organs and of extremities at rest, and until these measurements are extended to children and other species of varying sizes. However, the magnitude of error in the available data would appear to be small. The OMR/kg brain, heart, kidney and liver are all approximately 10–20 times the figure for the body as a whole, 25 cal/kg, so that much of the body must have a correspondingly lower metabolic rate. The figures leave surprisingly little to muscle as a source of metabolic activity in the basal state. Measurement of oxygen consumption in intact resting muscle has not been achieved, although ASCHOFF [1] estimated only 17.4 % of total BMR to be derived from muscle. Muscle is a prime source of extra heat in the event of cold stress, or physical activity. However, its relative unimportance as a source of basal metabolic energy is suggested by the fact that BMR/kg body weight decreases with growth, while muscle mass/kg body weight increases.

Further evidence in support of this view may be adduced from the observation on BMR *during recovery* from starvation [34]. BMR/kg actual body weight is below normal in children with protein depletion (kwashiorkor) and within normal range in children with calorie deprivation as a result of starvation (marasmus). During recovery from malnutrition, the BMR rises to levels substantially above normal within days in both groups, and before there is any major increase in the depleted muscle mass. As muscle mass increases, BMR/kg of whole body begins to decrease toward normal. It has been suggested that the low and normal BMR/kg reflect a depression of tissue metabolic activity due to the effects of starvation and depression of

Table II. Organ metabolic rate, OMR, cal/day compared to whole body BMR for a 10 kg infant and a 70 kg adult

Organ	10 kg infant				70 kg adult			
	OMR/kg (cal/kg/day)	Weight (kg)	OMR cal/organ/day total	%	OMR/kg (cal/kg/day)	Weight (kg)	OMR cal/organ/day total	%
Brain [21]	260	.92	240	45	260	1.4	365	21
Heart [39]	600	.05	30	6	600	.3	180	10
Kidney [11]	400	.07	28	5	400	.3	120	7
Liver (splanchnic) [6]	350	.30	105	19	350	1.6	560	32
Lung (estimated)	(200)	12	24	4	(200)	.8	160	9
Total derived from 5 organs		1.46	427	79		4.4	1385	79
Total BMR			540				1780	

thyroid function. The high BMR/kg during repair has been ascribed to normal tissue metabolic activity and the disproportionate percentage of body weight taken up by the metabolically active brain.

We would suggest that the high BMR was due, in part, to the relatively high proportion of body weight taken up by all the internal organs, including the brain —not that they are large, but that supporting structures are disproportionately small.

To the extent that BMR is predominantly a result of the sum of OMR, the factors which lead to a reduction of BMR/kg as body size increases can be examined from the size and OMR/g of the internal organs during growth. For the reasons already suggested, it is proper to examine the differences separately among species of different sizes and within a species during growth.

Postulate 2. The lower BMR/kg in larger species is due to 2 factors: the source of metabolic energy—the highly active organs—constitutes a smaller percent of total body weight in larger animals; and some of the highly active organs, e.g., liver and kidney, have lower OMR/g as animal size increases.

Neither factor has a systematic influence in determining a combined effect, yet this combined effect is a remarkably consistent function of body size predicted by the equation $C = 70 \times W^{\cdot 75}$. The 5 examples selected from the 16 species in figure 1 illustrate the variations in BMR/kg that exist and the precision of KLEIBER's formula for predicting the BMR of any individual group in the sample (table I). The BMR ranges from 181 to 14 cal/kg, indicating that the mouse has a BMR 13 times that of the steer. The prediction of total metabolic activity from KLEIBER's equation is very close to the observed values. If the decline of BMR/kg during growth is due solely to a decreasing ratio of highly active organs to total body weight, the log-log plot of the weight of the organs against body weight should be linear and have a slope of 0.75. The ratio of the highly active organs to body weight in a steer would then be $^1/_{13}$ that found in the mouse. The OMR/g should not vary among the species. On the other hand, if the ratio of the highly active organs to body weight was constant, irrespective of body size, a log-log plot of the sum of organs' weight against body weight should be linear, with a slope of 1.0 and the OMR/g in the steer would be $^1/_{13}$ that of the mouse. In this case, the decrease in BMR/kg would be due only to a decrease in the OMR/g as the size of the animal increases[2].

The actual relation of organ weight to body weight for 9 species is compared in table III. In figure 5, the data are plotted on a log-log graph together with lines describing the two extreme alternatives. The actual data lie between these lines in random distribution, indicating that differences in relative weight of highly active organs account for some but not all the differences in BMR/kg observed among different species. Organ weight increases at a rate slower than body weight as animals get bigger, but more rapidly than metabolic activity. No consistent pattern of decrease is observed. If the organs are the principal source of metabolic energy, then it is necessary to conclude that OMR/g is less in larger species but not as much less as BMR/kg body weight.

As noted, there are few studies which provide data in the intact state for comparing the OMR/g of animals of various sizes. The renal oxygen consumption for dog kidney is 125 μl/g wet kidney/min [47] and

[2] The decrease which would fit the requirements of this relation is defined by cal/g decreasing to the —0.25 power of unit weight as weight increases.

that for man is 55 μl/g wet kidney/min [11]. An analysis of hepatic oxygen consumption in several species demonstrated that the consumption increased at a rate only slightly greater than metabolic rate, i.e., OMR/g liver decreased in a manner nearly parallel to the BMR/kg [6].

The problem of making comparisons of the BMR of homologous tissue from animals of different species therefore has been approached by measuring the tissue oxygen consumption (QO_2) of these tissues and assuming that QO_2 mirrors the oxygen consumption of the tissues in the intact resting state. TERROINE and ROCHE [46] and GRAFE *et al.* [15] found that the QO_2 of homologous organs declined as animal size increased, but the decline was proportionately less than the BMR/kg. They concluded that change in tissue BMR/g was not responsible for the difference in BMR/kg. KLEIBER [26] on the other hand, noted that the QO_2 of liver was lower in animals of larger size and that these differences, projected to the body as a whole, would account for the lower BMR/kg.

KREBS [27], who studied 5 tissues from animals of 9 different species, found a decrease in QO_2 for homologous organs as the animals increased in size and their BMR/kg decreased. However, the decrease among different species for a given organ was generally less than the decrease in BMR/kg. Among the organs tested, the QO_2 of liver decreased the most as a function of body size, although less than BMR/kg. KREBS concluded from his studies that changes in OMR/g could not account wholly for the decline in BMR/kg and postulated that changes in muscle metabolism must occur concomitantly. He discounted, as unproven, the earlier statements of KESTNER [20] and BLANK [3] that lower BMR/kg in larger animals could be explained altogether by a decrease in the proportions of total body weight as highly active organs. The evidence upon which KESTNER made these statements was considered by KREBS as insufficient to support their claims. It seems to us, however, that their data and the data in table III and figure 5 suggest this to be a factor in the decline, although not the only one.

DAVIES [12] recently reviewed the relation between QO_2 and body metabolism and plotted all of KREBS' data for QO_2 against body weight on log-log coordinates. The slope of decline in QO_2 of the various organs was less than the decrease in BMR/kg, but a significant negative slope was observed for most organs. There were considerable differences in the slopes among the 9 organs studied.

In a study reported previously [18], we demonstrated that glomerular filtration rate (GFR)/g kidney in the rat (1.17 ml/g) was larger than that in dogs (0.65 ml/g) which, in turn, was larger than that in humans (0.45 ml/g). GFR has been shown to vary directly with

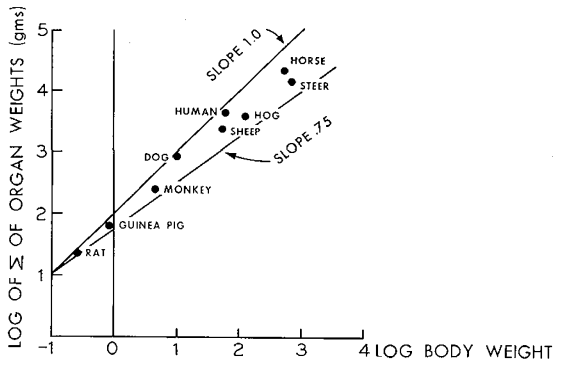

Fig. 5. Log-log plot of the sum of the organs noted in table III plotted against body weight. The line with a slope of 1.0 illustrates the theoretical curve which defines a growth pattern in which internal organs are a constant per cent of total body weight. The line with a slope of 0.75 illustrates the theoretical curve of organ growth if it corresponded to the relation of BMR to body weight among animals of different species. The actual data lie between these 2 curves.

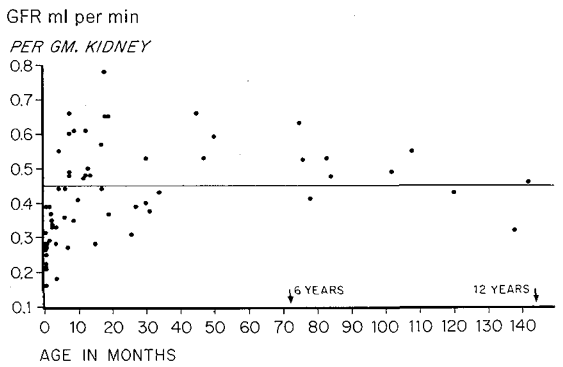

Fig. 6. A plot of GFR/g kidney, using data of GFR and kidney weight derived from body weight to arrive at the value GFR/g kidney (from HOLLIDAY and EGAN [18]).

renal oxygen consumption [31]. These differences correspond to the differences in BMR/kg characteristic of these species (table I—rat 96; dog 44; man 25 cal/kg).

When all the observations are considered together, it seems that OMR/g in the same organs among different species decreases as body size increases although the pattern varies for different organ systems. The sum of the effects of these decreases in OMR/g appears to be less on the average than the observed decrease in the BMR/kg in the body. From these figures and those on organ weight as percent of body weight (table III, figure 5), we have arrived at the conclusion that a relative decrease in weight of the highly active organs as percent of body weight and a decrease in OMR/g are

Table III. Relation of organ weight to body weight in 9 species (Data from BRODY [8])

Organ	Dog	Guinea pig	Hog	Horse	Human	Monkey	Rat	Sheep	Steer
				Organ weight (g)					
Brain	175	4.7	120	670	1300	42	2.00	105	500
Heart	85	2.3	350	4250	320	23	0.94	280	2300
Kidneys	140	11.2	500	3320	500	42	4.20	320	2000
Liver	420	27.0	1600	6700	1700	110	12.00	960	5000
Lung	120	5.0	1300	5400	980	30	1.30	710	3900
Total	940	50.2	3890	20,340	4800	247	20.44	2375	13,700
				Body weight (kg)					
	10	0.8	125	600	60	4.5	0.25	52	700
$\frac{\text{Sum of total organ wt}}{\text{body weight}} \times 100$									
	9.44	6.25	3.12	3.39	8.0	5.49	8.16	4.56	1.95

Table IV. Relation of QO_2 of kidney to body weight and of GFR/g kidney weight to body weight during growth in rats (POTTER *et al.* [37]).

Group A[1]			Group B[2]				
No. of animals	Body weight (g)	QO_2[3]	No. of animals	Body weight (g)	Kidney weight (g)	GFR (ml/min)	GFR/g kidney weight
10	58	12.6	8	60	0.65	0.65	1.03
10	110	13.9	11	115	1.09	1.48	1.36
10	204	14.3	8	198	1.69	2.61	1.54
10	320	16.7	17	338	2.26	3.10	1.37
10	397	14.7	12	389	2.62	3.48	1.33

[1] Group A: Normal growing rats sacrificed at observed weights to obtain QO_2, DNA, protein and water content of kidney.

[2] Group B: Normal growing rats in which GFR was measured as inulin clearance and related to kidney weight obtained following the clearance.

[3] QO_2 measured in a Warburg respirometer as μl of O_2/mg dry wt/hr. in kidney cortical slices incubated in a buffered Ringer solution at 37° C.

responsible for the decline in BMR/kg observed among species as body size increases.

Postulate 3. Decrease in BMR/kg during growth is due to a relatively slower growth of the highly active organs, compared to total body weight; OMR/g organ does not appear to decrease during growth.

Since most of BMR has its source in the internal organs and BMR/kg in humans declines during growth from 56 to 25 cal/kg and in rats from 218 to 87 cal/kg, it is appropriate to examine the role of these organs in this decline. The decline, as seen among different species, may be due either to a decrease in the OMR/g or to a decrease in the relative organ weight in relation to body weight, or both.

OMR/g during growth has been studied in 2 ways: by QO_2 and by indirect measurement of kidney metabolism in the intact organism. In both, the OMR/g did not decrease during growth but remained constant, or increased slightly. The QO_2 of several organs of rats was measured at different intervals of growth by VON BERTALANFFY and PIROZYNSKI [49], who found the QO_2 to be constant. MOUREK [35], who measured the QO_2 of rat brain in newborns and during

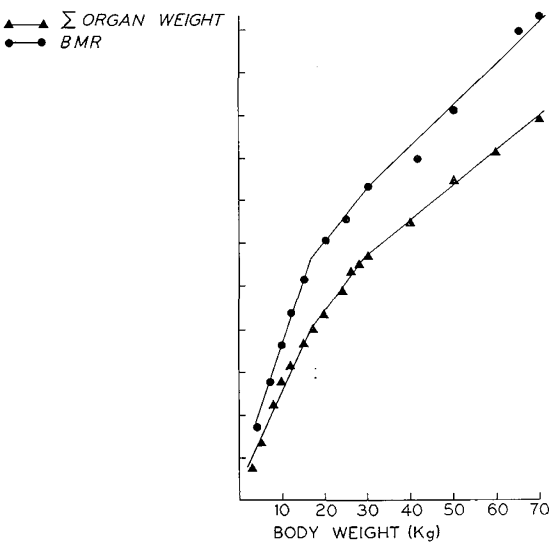

Fig. 7. Plot of BMR against body weight using the same data as in figure 3 and the sum of organs (table III) against body weight (data for organ weight from BOYD [5] and COPPOLETTA and WOHLBACH [10]). Arbitrary units were chosen for the ordinate to permit comparison of curve slopes.

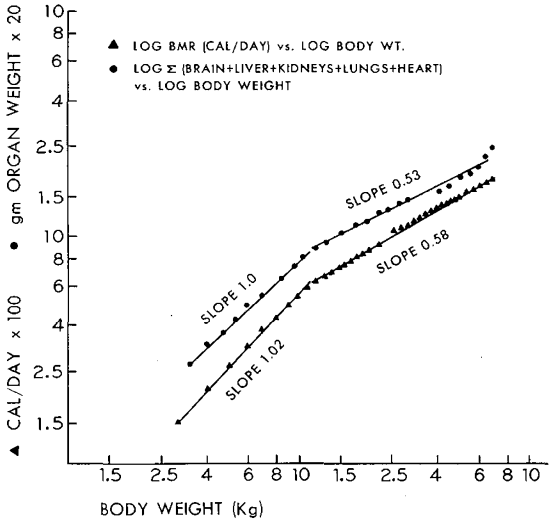

Fig. 8. A log-log plot of the data to allow for a comparison in rate of 'increase'. There is an obvious parallel between the comparative rates of 'increase' of BMR to body weight and of the internal organs to body weight.

growth, found some increase during the neonatal period but no significant change later. NEW *et al.* [36] measured the QO_2 of kidney slices of rabbits and found no increase after the neonatal period. These findings differ from those cited earlier in comparing QO_2 of organs from species of different sizes (Postulate 2).

In a study from our own laboratory, QO_2 of rat kidney was measured at 5 successive periods of growth from 50 to 400 g body weight) and no decrease was noted [37] (table IV, group A). Similarly, we found the QO_2 of liver slices in 60 g rats did not differ from that of 350 g rats. From these data we inferred that OMR/g as measured by QO_2 did not decrease in response to growth as organ size increased. We also measured GFR of rats at successive ages. GFR is a quantitative measure of sodium reabsorption which has been noted to be a direct function of oxygen consumption in the kidney in the intact state [31]. These data are illustrated in table IV, group B. The GFR/g kidney increased as the rat grew from 60 to 115 g but thereafter was stable and did not decrease. The GFR was measured during growth in humans and related to body weight, kidney weight and surface area [40, 22]. The GFR/g kidney did not appear to vary during growth after 6 months of age (fig. 6).

These findings differ from those among different species where GFR/g kidney varied inversely as a function of body size [18]. We infer from these findings and the QO_2 data that OMR/g does not decrease during growth as body size increases in either rats or humans. If this is the case, then the pattern of change in BMR to body weight during growth should be the same as the pattern of change in weight of the internal organs to body weight.

The plots of BMR to body weight and organ weight to body weight in humans during growth are noted in figure 7. The rates of growth using log-log plots are compared in figure 8. The patterns are quite similar: as body weight increases from 3 to 10–12 kg, BMR and weight of internal organs increase at the same rate (slopes 1.02 and 1.0, respectively). Thereafter, both organ weight and BMR increase at a slower rate than body weight (slope averages 0.53 for organ weight and 0.58 for BMR). This indicates that upward from 10–12 kg, BMR/kg declines during growth because its principal source (the internal organs) becomes a smaller proportion of body weight as growth progresses.

These observations thus provide a rational basis for the varying relationship of BMR to body weight during growth. The pattern is similar to that proposed earlier for estimating average metabolic rate of hospitalized patients as a means for determining parenteral fluid requirements [19, 22] and illustrates the reason for the deviation during growth of cal/m² from the average adult value.

Discussion

It has been the purpose of this review to suggest the means by which BMR/kg decreases as body weight increases. This decrease, by whatever means, has the biological advantage of diminishing heat production as the surface to volume ratio decreases. The factors responsible for this in different species vary. During growth within a species the principal factor is the slower rate of growth of high heat-producing organs as compared to supporting structures.

Muscle is generally considered to be the greatest source of heat or metabolic activity in the body. It is certainly the largest heat-producing organ and is the greatest potential source when the animal or human is subjected to cold or work stress. Yet the evidence presented would suggest that muscle is not a principal source of heat production in the resting state. Its relative unimportance as a source for basal metabolic energy is evident in the growth pattern, either in humans [43] or rats [9]. In both, muscle mass is 25 % of body weight shortly after birth, when BMR/kg is high; in adults it is 40 % of body weight or 1.7 times that in infancy. The BMR/kg in the adult is 0.5 that of the human infant and 0.4 that of the young rat.

The growth rate data of the individual organs and surface area, plotted against body weight using log-log coordinates (fig. 7), suggest some of the complexities that face the physician who treats a growing child. The proper reference standard for drug dosage may be related more appropriately to organ size or function rather than to body weight or surface area. Some of the problems have been solved empirically, but this method may be hazardous as medicine begins to deal with anephric patients or increasingly small premature infants with very different body compositions. It is hoped that an extension of these observations will produce a more precise tool for predicting potential metabolic function and for estimating drug dosage as a function of age and size. In the past, part of the difficulty in defining the relations of metabolic rate to body size might have been avoided if the distinction had been made between inter- and intraspecies, mature animals within a species of different size and composition, and growing animals with a characteristic change in composition during growth. Surface area is a better reference standard for BMR than body weight among different species covering a wide range in body size, but an even better reference standard is body weight to the 0.75 power.

It is not surprising that Kleiber's formula (cal = 70 $[W]^{.75}$, which was the best fit for a range of weights from 0.022 to 4000 kg, is not equally precise when applied to humans during the growth from 3.5 to 70 kg. Some of the special reasons for this have been admirably summarized by BRODY [8]. The unknown but evident biological advantage in the specific relation of BMR to body weight, which is defined by Kleiber's formula in animals over a weight range of nearly 200,000-fold, need not apply so rigorously within the 20-fold weight span encompassed by human growth. The mathematics have a different order of magnitude.

The point is perhaps most clearly made from the observations relating oxygen consumption to body size in infants. SINCLAIR and SILVERMAN [44] observed that oxygen consumption/kg increased as body size increased in infants varying in weight from 1 to 3 kg. They further observed that the oxygen consumption/kg was higher in 'small for dates' babies than in premature infants of equal size. They concluded that metabolic mass in this period of growth was increasing more rapidly than body size, probably due to the relative loss of extracellular fluid. SINCLAIR, SCOPES and SILVERMAN [45] more recently demonstrated that 'resting oxygen consumption rate was found to be rather constantly related to body cell mass', which in turn was increasing relatively faster than body size. BMR/kg in this group varied less than BMR/m^2 or BMR/$kg^{.7}$ but BMR/kg active cell mass (including fat) varied least.

The central role of the internal organs as compared to muscle in determining BMR has suggested to us that some purpose may be served by considering cell mass as consisting of two relatively distinct moieties, organs and muscle. These have different growth rates and distinct metabolic rates. The effect of body composition on BMR may be suggested from a recent study [30] in which children with acyanotic congenital heart disease were found to have a high BMR/kg compared to normal children of the same age. These authors described the finding as an example of hypermetabolism. An alternative explanation, suggested from these studies, is that these children had relatively poor growth, particularly of muscle and supporting structures; consequently, the internal organs which have a high OMR comprised a relatively larger percent of body weight. These higher rates would account in part for a higher BMR/kg total body weight. In infants during recovery from growth failure of various causes [28], BMR when related to height or to ideal weight for height was normal, but was high when related to observed weight, i. e., BMR/kg. Since the actual weight, not height or ideal weight, was generating the metabolic rate, its observed high value can be related to a difference in body composition, rather than to a difference in cell metabolism. A similar observation [34] in infants recovering from starvation has been cited (cf. part 2). A much more obvious example is found in obesity [17] in which a measure of the size of internal organs, as a reference standard for BMR, would be an interesting test of the hypothesis that BMRis different in obese people.

In concluding, we feel that BMR during normal growth is best fitted to the empiric curve of observed data in relation to body size than to either surface area or $W^{\cdot 75}$. Perhaps a more important suggestion from these studies, is the need to relate BMR to a measure of internal organ mass when it is abnormal and use this reference as a test of whether basal metabolic rate is altered at the cellular level or simply is a reflection of an altered ratio of internal organ mass to total body size. Such a separation may be valuable in studies of disease states associated with malnutrition and in the study of premature and 'small for dates' infants where assessment of energy metabolism is the central issue.

References and Notes

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