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BODY SIZE AND METABOLIC RATE

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CORRELATION BETWEEN BODY SIZE AND METABOLIC RATE. Günther (1944) introduces a recent review on body weight and metabolic rate with a motto which starts as follows:

“It is believed that far greater progress will be made by discarding all thoughts of a uniformity in heat loss and emphasizing the non-uniformity in heat production. . . .”

The sentence is a citation from Benedict's book, *Vital Energetics* (1938, p. 194).

It is rather difficult to understand how forgetting all thoughts of uniformity and emphasizing non-uniformity can stimulate a comparison of metabolic rates of large and small animals. Any comparison presupposes a common basis, and if I were convinced of the “futility of attempts to discover a unifying principle in metabolism” (Benedict, l.c., p. 178) I should not attempt to write a review on the relation of body size and metabolic rate.

The reader can be expected to spend time on this review only when he can be convinced that body size and metabolic rate are actually related. That these two variables are related is in fact common knowledge.

Does a horse produce more heat per day than a rat or do some rats produce more heat than do some horses? Almost anybody who understands what is meant by “heat production per day” will not hesitate to give the correct answer and will even be convinced that the daily rate of heat production of men or sheep is greater than that of rats, but smaller than that of horses. Thus most people (among those who understand the question) are convinced that in general the bigger homeotherms produce more heat per day than the smaller homeotherms, that, in other words, the metabolic rate of homeotherms is positively correlated to body size.

The answer to the next question: “does a horse produce more heat per day per kilogram of body weight than a rat?” requires some biological training. Most biologists, however, will not hesitate to answer that the rate of heat production per unit body weight of the big animal is less than that of the small animal.

The positive correlation between metabolic rate and body size, and the negative correlation between metabolic rate per unit weight and body size, establish two limits between which we expect to find the rate of heat production of a horse if we know the rate of heat production of a rat. We expect the metabolic rate of the horse to be somewhat between that of the rat, and that of the rat times the ratio of horse weight to rat weight, provided of course that we do not regard these two correlations as simply accidental.

If we are firmly convinced that the metabolic rate of horses, and other homeotherms of similar size, is never outside these two limits, then we admit to recognize a natural law between body size and metabolic rate. The firmness of the

conviction, or the probability of being correct, rather than the range within which we predict a result, justifies the term "law."

For the usefulness of a law, however, the accuracy of prediction is important. We may attempt to formulate the relation between body size and metabolic rate more precisely than "somewhere in the range between rate per animal and rate per unit weight."

Encouraging for such attempts is the fact that the correlation between metabolic rate and body weight is, indeed, rather high. For 26 groups of mammals, dealt with particularly in this review, the coefficient of correlation between the two variables amounts to $+0.98$.

This high correlation involves standardization of conditions under which metabolic rates are measured. The standard metabolic rate should be measured while the animal is in a post absorptive condition, and kept within the range of metabolically indifferent environmental temperature.

The task is to find a metabolic body size which is chosen so that the metabolic rate per unit of this body size is the same for large and small animals.

The square meter of body surface is such a unit which allows a more accurate prediction of metabolic rate than the two limits mentioned above. The surface area of animals is, however, ill defined, and relatively recent results indicate that the metabolic rate per unit surface area tends to be greater the larger the animals (Kleiber, 1932). Among the 26 groups of animals chosen for discussion in this review the metabolic rate per unit of the $2/3$ power of body weight (which roughly represents surface area) has a highly significant correlation to body weight. The correlation coefficient amounts to $+0.71$.

Such correlation disappears when the metabolic rate is divided by the $3/4$ power of body weight. The unit of the $3/4$ power of body weight, $\text{kg}^{3/4}$, is therefore a suitable unit of metabolic body size.

Fasting homeotherms under standard conditions produce daily an average of about 70 kcal. of heat per $\text{kg}^{3/4}$ or 3 kcal. per $\text{kg}^{3/4}$ per hour.

The unit of metabolic body size is of great interest in comparative physiology. It permits an expression of the metabolic level of an animal independent of its body size, and it makes possible the comparison of a particular metabolic level with the interspecific mean of 70 kcal. per $\text{kg}^{3/4}$ per day.

Such a comparison, furthermore, permits for example the statement that the metabolic rate of a 70 ton whale estimated by Irving, Scholander and Grinnell (1941) is high in comparison to that of other mammals (whereas the whale's rate per $\text{kg}^{3/4}$ is only $1/10$ that of a mouse). Such a comparison, made possible by the use of metabolic body size, may stimulate research to establish the conditions producing that high metabolic rate. It may lead, for example, to a comparison with the metabolic rate of Eskimos which also is at a relatively high level (Rabinowitch and Smith, 1936). The unit of metabolic body size is further useful in evaluating levels of food intake in animal production, and in classifying farm animals with regard to their efficiency as food utilizers. Food requirements and dosages of most vitamins and drugs may be expressed in terms of metabolic body size.

This review is limited to mammals. The conclusions are, however, also applicable to birds whose metabolic level was found to be in line with the mammalian metabolic level (Kleiber, 1932). More recent results confirm the metabolic similarity of these two groups of homeotherms. From data published by Dukes (1937) one may calculate that the metabolic rate of hens is 73 kcal. per kg.^{3/4} A rule of body size and metabolic rate, very similar to that for mammals and birds, has also been noted in heterotherms such as the crab by Weymouth and his co-workers (1944).

THE DISCOVERY OF THE SURFACE LAW. The metabolic rate (heat production per unit of time), in particular the basal metabolic rate of humans, is generally expressed in kilocalories per square meter of body surface. This procedure is based on the theory that in animals of different body size the metabolic rate is proportional to their respective surface areas. This theory, called the surface law, is now a little over a century old. It has its roots in the time when a vigorous belief in the power of reason inspired men to explain nature's aims and means. A good deal of a new theology was then evident in teleological scientific discussions. A theology in which Nature, as a bright goddess, revealed her aims and ways to a scientist as a more stern and sombre Lord had revealed His aims and wishes to the nonscientific or antiscientific priests.

Sarrus, a professor of mathematics, and Rameaux, a doctor of medicine and of science, both in Strasbourg, had Thillaye read a thesis to the Royal Academy of France during its meeting of July 23, 1839.

The authors apparently take it for granted that it is nature's aim to make the rate of heat production of large and small animals in proportion to their respective surface areas or the $2/3$ power of their body weights. They then calculate how nature achieves this aim by modulating the frequency of heart beat and the stroke volume, always choosing the middle way between two possibilities. Their basic theory is worth being quoted: (p. 1098) "Lorsque la nature peut atteindre un but par plusieurs moyens, elle n'emploie jamais exclusivement l'un d'eux jusqu'aux limites, elle les fait concourir de manière que chacun de ces moyens tend à produire une part égale de l'effet total."

(When nature can achieve an aim by various means she never uses one of these means exclusively to the limit, she makes these means compete so that each one of them produces an equal part of the total effect.)

Bergmann and Leuckart (1855) concluded from measurements of Regnault and Reiset that the metabolic rate per unit weight was especially great for small animals. In four days sparrows consumed as much oxygen as they weighed. This today would be considered a very high metabolic rate, about four times as high as the rate observed in a sparrow by Benedict (1938). Richet (1889) discovered "après coup," that is empirically, that the metabolic rate per unit weight of rabbits increased consistently as the body weight decreased (p. 220).

The metabolic rate per unit surface area, however, was unaffected by body size, so Richet concluded that, for metabolic rate, surface area was more important than body weight. Simultaneously Rubner (1883 cit. by Krogh 1916, p. 133) noted a systematic decrease of the metabolic rate per unit weight of

fasting dogs as the weight increased from little dogs of 3 kg. to big specimens of 31 kg. body weight.

When the metabolic rate was expressed per square meter of body surface, however, the effect of body size disappeared. From this and similar observations, Rubner deduced his simple rule that fasting homeotherms produce daily 1000 kcal. of heat per square meter of body surface.

Richet's and Rubner's intraspecific observation of the surface law was confirmed by interspecific comparisons. The best known table showing this surface law of metabolic rate is that published by Voit (1901). A 441 kg. horse produces over 948 kcal. daily per square meter of body surface, a 64 kg. man 1042, a 15 kg. dog 1039, and a 2 kg. hen 1008. So well established appeared the surface law that data which did not confirm it were either explained by particular conditions¹ or discarded as results of faulty measurements. Thus Lee (1929) suggests that Mitchell's rat surface is too high because it makes rats disobey the surface law.

THE "TRUE" BODY SURFACE AREA. Large and small bodies of similar shape have surface areas in proportion to the squares of their linear dimensions or the 2/3 power of their volumes. If the two bodies have also the same density, then their surface areas are also in proportion to the 2/3 power of their weights.

In this general way Sarrus and Rameaux understood the surface area of animals. Richet apparently preferred a definite surface that could be visualized. He calculated the surface area of his rabbits from their weights assuming they were spheres with a density of 1 kg. per liter. The surface area of such a sphere is $4.84 W^{2/3}$ square decimeters when W is the weight in kilograms.

Considering that the animals are really not spheres, Meeh (1879), working under Vierordt, substituted in Richet's formula for the factor 4.84 a term, k , which is constant only within a group of similarly shaped animals but differs according to the shape of the animal.

By measuring animal surfaces and weights one may determine the Meeh constant empirically and then calculate the actual surface of similar animals as $S = K \cdot W^{2/3}$, where W is the body weight in kilograms and S the surface area in square decimeters. A set of Meeh constants is given by Lusk (1928, p. 123).

The surface of man averages 12.3 square decimeters per unit of the 2/3 power of body weight ($\text{kg.}^{2/3}$). For slim people the Meeh constant would be higher than this average, for stout people lower. Du Bois and Du Bois (1916) developed a formula which allows calculating the actual surface area of stout and slim human beings more accurately than does the Meeh formula.

Du Bois' formula reads:

$$S = 71.84 W^{0.425} \cdot L^{0.725}$$

S = Surface area in cm.^2
 W = body weight in kg.
 L = body length in cm.

It is probably the best method of estimating the "actual" surface area of man. Du Bois' formula is dimensionally correct and is therefore valid for any size,

¹ Rabbits produced daily only 776 kcal. of heat per square meter; subtraction of their ear surface, however, brought their metabolic rate up to the more legal level of 917 kcal.

as it should be. (Dimensionally correct means that the surface area is expressed in terms of the $2/3$ power of the volume or in the square of the linear dimension.)

Since for similar bodies L is proportional to the mean linear dimension, $W^{1/3}$, Du Bois' formula for comparison of large and small humans of the same relative stature may be written as

$$S = k_1 W^{0.425} \cdot k_2 W^{1/3 \times 0.725} \text{ which amounts to } k_1 \cdot k_2 \cdot W^{(0.425 + 0.242)} \text{ or } k_1 k_2 \cdot W^{2/3}$$

Some later formulas for the calculation of surface area from the weight are dimensionally incorrect, such as the Moulton formula for cattle in which the surface area is proportional to the $5/8$ power of body weight, and particularly the formula used by Ritzman and Benedict (1931) for calculating the surface area of sheep as proportional to the 0.561 power of body weight. The formula may have expressed the surface area of the sheep used for the measurements but it is theoretically incorrect for two animals of similar form which differ in size (but have the same surface per kg.^{2/3}). The Ritzman-Benedict formula would predict too small a surface for the larger of two animals with similar build.

Many methods have been invented for measuring the surface area of animals.

In their eagerness to refine the surface measurements, many workers in this field seem to have overlooked a major question: "What is meant by the surface area?" Unless this question can be answered definitely, how can one decide which of two methods measures the surface more accurately?

One should obviously know whether or not the "true" surface of a rabbit is to include the surface area of the rabbit ears (see Benedict, 1934). As long as this question is open, which means an uncertainty of about 20 per cent, what is gained by refining the surface measurements to an accuracy of one per cent? According to Lee's (1929) (see p. 514) argument, the true body surface is the one that makes an animal's metabolic rate obey the surface law!

Kleiber (1932) pointed out that the various refinements of surface measurements and calculations, instead of clarifying issues, led to a more and more chaotic situation.

A great many published results of good work on metabolic rates are practically lost for comparative physiology because they are expressed only per unit of surface area, and the authors did not furnish the data which would make a comparison with other work possible. It was stated that the surface area was not well enough defined to serve as a basis for measurement, and, following Krogh's (1916) suggestion, and in agreement with Stoeltzner (1928) and Brody, Comfort and Matthews (1928), a power function of body weight was suggested as the basis of metabolic body size. The $3/4$ power was proposed as the best fitting function (Kleiber, 1932).

Since then the situation has not improved. In the Annual Review of Physiology (Kleiber, 1944) alarm is again expressed as follows:

"In 10 papers (from 8 laboratories) studied for this review metabolic rates of rats are expressed per unit of the surface area. Four of the 10 authors did not state how they measured or calculated this area. One multiplied the $2/3$ power of body weight (in kg.) by 7.42, another by 9.1, a third by 10, to calculate the

surface area in square decimeters. One author multiplied the $3/5$ power of body weight by 12.44, and two have calculated a new surface-weight relationship, presumably by an intricate logarithmic interpolation between three older ones $7.42 \times W^{2/3}$, $11.36 W^{2/3}$ and $12.44 W^{3/5}$. That—for rat metabolism only—is this year's result of a century of surface law."

For man, the formula of Du Bois seems to be so generally accepted that the reports do not differ as widely as do those of rats, and clinicians may not have the time to develop new surface formulas for every new paper they publish. But also with human metabolism the valuable fruit of years of tremendous work cannot be used properly for comparative physiology, because the results are reported only in terms of the Du Bois surface without the data (height and weight) which would make a recalculation of the original results at least possible, even if extremely time consuming.

The comparisons of metabolic rates merely on the basis of surface area may be all a clinician wants. For comparative physiology more basic data are necessary.

In the interest of economy in research, physiologists should agree on minimum requirements for publication of metabolic data, and among those should be body weight and either total metabolic rate or metabolic rate per unit weight.

THEORETICAL VALIDITY OF THE SURFACE LAW. *A. The various theories of surface law.* The theories advanced for the interpretation of the surface law of animal metabolism may be classified into 5 major groups:

The metabolic rate of animals must be in proportion to their body surface.

1. Because the rate of *heat transfer* between animal and environment is proportional to the body surface area.

2. Because the intensity of flow of nutrients, in particular oxidizable material and oxygen, is a function of the sum of *internal surfaces* which in turn is proportional to the body surface.

3. Because the rate of supply of oxidizable material and oxygen to the tissues is a function of the mean intensity of the *blood current*, which is proportional to the square area of the blood vessels, which in turn is proportional to the area of body surface.

4. Because the *composition* of the animals is a function of their body size. The composition may be meant either *anatomically*: the larger the animal the lower is the ratio of the mass of metabolically active organs to the mass of metabolically inert organs; or the composition may be meant *chemically*: the larger the animal the lower its percentage of "active protoplasm".

5. Because the cells of the body have an *inherent requirement* of oxygen consumption per unit weight, which is smaller the larger the animal.

B. Critique of the theories of surface law. 1. The *heat transfer theory* is the most convincing of the five interpretations of the surface law. If homeothermism has survival value, and if the rate of heat transfer per unit surface area of large and small bodies is equal, then the surface law may be understood as the result of natural selection.

Accepting for the sake of the present discussion the biological advantages of maintaining a constant body temperature, one may ask: "How accurate is the

postulate that the rate of heat transfer per unit of surface area of large and small bodies is the same?"

The rate of heat flow of a body covered by an insulating layer may be formulated according to Fourier (Mach 1919, p. 84):

$$q = S\lambda \frac{T_i - T_s}{L}$$

where q = rate of heat flow; S = surface area
 L = thickness of the covering layer (skin and fur)
 T_i = internal temperature
 T_s = temperature at the surface
 λ = heat conductivity.

In animals the heat conductivity, λ , of the body covering, and its thermoconductive thickness, L , are rather hard to measure and are, furthermore, variable, since the depth of the layer with a temperature gradient is under vasomotor control. To simplify the problem, one may define the ratio $L/\lambda = r$ as the specific insulation of the animal covering, and write Fourier's law as follows:

$$q = S \frac{T_i - T_s}{r}$$

For a given difference between internal temperature and surface temperature, the rate of heat transfer is proportional to the surface area when the specific insulation for large and small bodies is the same. The specific insulation of animals is, however, variable.

The classical demonstration of this fact is the experiment of Hoesslin (1888). He reared two littermate dogs, one at 32°, the other at 5°C. The latter had to cope with a temperature difference between body and environment six times as great as the corresponding difference for his brother. Yet the metabolic rate of the dog in the cold was only 12 per cent higher. He solved the problem of keeping warm by growing a fur that weighed three times as much as that of his brother.

In the same animal and within a short time, the specific insulation may be reduced to 1/2 when the animal is transferred from a cold to a warm environment (Kleiber, 1932). Instead of maintaining the metabolic rate per unit surface area constant, large and small animals therefore might maintain a constant metabolic rate per unit weight, and with a variable specific insulation adapt the rate of heat loss to that metabolic rate.

The range within which the specific insulation can be changed is, however, limited. One may calculate (i.e., p. 327) that a 60 gram mouse with the same metabolic rate per unit weight as a steer, would need the equivalent of a steer's surface covering in a 20 cm. thick layer to maintain its body temperature in an environment of 3°C. This rather extreme example illustrates why it is advantageous for a small animal to have a higher metabolic rate per unit weight than a large animal. One can similarly show why at a high environmental temperature, for the prevention of overheating, it is advantageous for a large animal to have a lower metabolic rate per unit weight than a small animal.

Considerations of heat transfer thus make the assumption reasonable that natural selection would weed out such representatives of cattle and rats that insisted on having the same metabolic rate per unit body weight. These considerations however do in no way support the hypothesis that the metabolic rate of animals should be strictly proportional to their exact body surface, and that the results of metabolism studies would be more accurate and more reliable the more accurately one measured the "true" surface area of the animals.

2. The theory of *internal surfaces* as interpretation of the surface law would be valid only if the size of cells (or alveoli in the lungs as recently referred to again by Gajja, 1946) were proportional to animal size, if, in other words, elephants were made up of the same number of cells as mice. This logical prerequisite for the theory of internal surfaces does not seem to be supported by histology.

3. Attempts have been made to derive an interpretation of the surface law on the basis of *blood circulation*. The difference in the oxygen content of arterial and venous blood is independent of body size. The rate of oxygen consumption is therefore proportional to the intensity of the blood current, as already postulated by Sarrus and Rameaux (1839). This current intensity is the product of the linear velocity and the cross section area of the duct. Hoesslin (1888) declared that the cross section area of the aorta is proportional to the 2/3 power of body weight and the linear velocity is independent of body size, that consequently the intensity of the blood current is proportional to the 2/3 power of body weight, which is a measure for body surface. That the square area of the aorta should be proportional to the 2/3 power of body weight, appears sound application of the principle of similarity. Why, on the other hand, the same linear velocity of blood flow in the aorta for large and small animals should have particular survival value is not quite clear. (See Kleiber, 1932, p. 332.)

More convincing support of a circulatory interpretation of the surface law is gained by postulating, on the basis of the similarity principle, that heart volume or stroke volume of large and small animals should be approximately in proportion to their body weights.² On mechanical grounds the assumption seems reasonable that the heart of a horse cannot beat with the frequency of the heart of a mouse. The intensity of the blood current (stroke volume times frequency of heart beat), therefore, should increase less than in direct proportion to increase in weight.

$I = f \cdot v$, where I = intensity of blood current, f = frequency of heart beat and v = blood volume per heart beat. If the stroke volume is proportional to body weight, $v = kW$ then, $I = f \cdot kW$, and the Intensity per unit weight $\frac{I}{W} = kf$.

To explain the Surface law, the intensity of the blood current should be proportional to the 2/3 power of body weight, and, therefore, the frequency of heart beat should be inversely proportional to the cube root of body weight. ($f = k_1 \frac{I}{W} = k_2 \frac{W^{2/3}}{W} = k_2 W^{-1/3}$). From data given by Rihl (1927) for normal pulse frequency of various animals ranging from

² The similarity is actually not quite strict. Clark (1927, p. 72) concludes from inter-specific comparison that heart weight varies with the 0.9 power of body weight. The heart weight per unit body weight has thus the tendency to become smaller the larger the animal.

rabbits to elephants, one may deduce the rule that the pulse frequency is inversely proportional to the 4th root of body weight. (The pulse frequency is on the average $186 W^{-1/4}$ if W is given in kg.)

Considering heart volume and pulse frequency, one may therefore be satisfied that, from the point of view of oxygen transport, it is advantageous for large animals to have a lower metabolic rate per unit weight than small animals. Obviously, this consideration does not lend support to the hypothesis that the metabolic rate should be strictly proportional to the "true" body surface.

4. There appears to be very little evidence in support of the idea that the *chemical composition* of animals changes systematically with body size, so that the surface law can be understood on the basis of chemical composition. The concept of "metabolically active protoplasm" seems to be too vague for discussion. It seems that the activity of the protoplasm is determined by the metabolic rate; and what would then be gained by explaining, in turn, the metabolic rate on the basis of active protoplasm? The measurement of the nucleo-protoplasmic mass seems to offer an independent determination of active protoplasm, but Lindeman (1943) failed to find a correlation between nucleo-protoplasmic mass and rate of oxygen consumption of the retina.

The concentration of respiratory enzymes, especially cytochrome *c*, may be related to metabolic rate (Rosenthal and Drabkin, 1943), however this concentration itself, and particularly the activity of the enzymes, probably is under the influence of regulators, especially the endocrine system. (See Barron, 1943.) Enzyme concentration and enzyme activity may thus offer a valid explanation for the metabolic rate of tissues but in regard to body size and metabolic rate, enzyme concentrations and activity call for further explanation on the organismic level.

A good deal of speculation has centered around the anatomical composition as an explanation of the surface law.

Dreyer, Ray, and Walker (1910, p. 158) advanced the theory that the blood volume of animals was proportional to their surface areas. On the basis of the very data from which these authors draw this conclusion, one may demonstrate that, in general, the blood volume is more nearly proportional to body weight than to body surface (Kleiber, 1932, p. 329).

In direct opposition to the conclusion of Dreyer, Ray and Walker, furthermore, is a later observation by Gibson, Kelley and Pijoan (1938), who noted that in a series of dogs the blood volume per kg. body weight increased from 84 cc./kg. in 5 kg. dogs, to 97 cc./kg. in 30 kg. dogs.

Sweeping conclusions, on the basis of measurements on limited material, are often misleading.

Brody, Comfort and Mathews (1928, p. 33) made the following statement: "The weight of the kidney, the weight of the liver and practically the weight of the lung, blood, stomach, and intestine increase directly with the body weight at the same relative rate as does the surface."

This statement presumably led to the following sentence by Benedict (1938, p. 205):

“Our conclusion is, therefore, that if the brain weight is closely related to the heat production among animals other than the primates, this is in large part due simply to the general morphological development in proportion to the two thirds power of the body weight shown by innumerable body structures.”

Before such generalizations are announced, they should be tested rationally by application to extreme cases. This can be done with the allegation that the blood volume is approximately proportional to body surface.

According to Lindhard (1926), the amount of blood in man is about 5 per cent of the body weight. If the statement of Brody et al. or Dreyer et al. were generally correct one would have to conclude from the blood content of a 70 kg. man that 49 per cent of the body of a 70 g. rat would be blood—indeed a bloody rat!

The following calculation similarly illustrates that one should be cautious when one derives a general quantitative rule from the tendency, that large animals have relatively smaller brains than the small animals.

A 5.4 ton elephant had a brain of 7.5 kg. (Benedict, 1936). The brain weight amounted, thus, to 0.14 per cent of the body weight. If the brain weight (in non primates) were proportional to the $2/3$ power of body weight, the brain of a 5.4 gram shrew would amount to 14 per cent of its body weight, or that of a 100 gram rat to 5 per cent of its body weight, which is about 3 times as much as it actually weighs (Donaldson, 1924).

There seems to be a general tendency for the larger animals to economize on brain weights, as J. B. S. Haldane (1946) pointed out in his stimulating essay (“On being the right size”), but what he observes within a group of Felidae from cat to tiger can not be regarded as a general quantitative rule. If generally the weight of the brain were only doubled whenever the body weight is quadrupled, or in other words, if the brain weight were proportional to the square root of body weight, then, starting down from the elephant with a brain weight of 0.14 per cent of its body, one would conclude that one-third of a 100 gram rat should be brain. Similarly, if Dubois’ (cit. by Weber, 1923, p. 151) formula, making brain weight a function of the $5/9$ power of body weight, were generalized, the 100 gram rat would have to have a brain weight of 18 grams. Neither Dubois nor Haldane can be accused of generalizing the brain weight-body weight relationship so much as to include the comparison of rats and elephants. Such generalization is, however, made when this relation of brain weight to body weight is used to explain the surface law of metabolic rate, because that law includes comparisons of rats with elephants.

The idea that the surface law of metabolism can be explained by the anatomical composition of the animal has been advanced especially by Blank (1934), and by Kestner (1934 and 1936) who made the following statement. “Hence I conclude that the relative sizes of the brains and the large glands can give a complete explanation of the different heights of metabolism of different animals.”

In support of this idea Kestner gives the ratios of brain weight to body weight of large and small dogs. A dog of 40 kg, for example, weighs 400 times as much as its brain. A dog of 5 kg, however, weighs only 25 times as much as its brain.

By calculating from these data the absolute weight of the brains we would be led to the somewhat surprising result that the brain of the small dog weighs 200 grams; that of the large dog only 100 grams.

To support his point that higher metabolic rates of the smaller animals are explainable by their greater relative brain size, Kestner states that the brain weight of a 3 kg. dog is about 50–60 grams whereas that of a rabbit of the same body weight is only 10 grams. This comparison, however, far from supporting Kestner's theory that the brain weight dominates the metabolic rate, to the contrary is very good evidence against this theory. Despite the great differences in relative brain weight noted by Kestner, the mean metabolic rate of rabbits is only about 10 per cent lower than that of dogs of the same size (see table 1).

It is generally accepted that primates have exceptionally large brains. If brain weight dominated metabolic level, primates should have a particularly high metabolic rate. Yet a group of college women with an average body weight of 54.8 kg. (and an average brain weight of probably not much less than 1300

TABLE 1

	BODY WEIGHT	DAILY HEAT PRODUCTION PER SQUARE METER	
		1901	1931
	<i>kg.</i>	<i>kcal</i>	<i>kcal</i>
Horse.....	441	>948	
Steer.....	342		1465
Man.....	64	1042	926
Dog.....	15	1039	776
Hen.....	2	1008	676

grams) had an average basal metabolic rate of 1224 kcal. per day, which is slightly less than the corresponding average of 1254 kcal. per day for a group of female sheep with an average weight of 46.4 kg. and a brain weight of, presumably, about 100 grams (Pálsson 1940).

5. *Body size and tissue metabolism* is a problem that is not yet satisfactorily solved. In the paper in which Rubner (1883) demonstrated the surface law in the metabolic rate of dogs he wrote (p. 550):

“Large and small dogs have a different metabolic rate, not because there are definite differences in the organization of their cells, but because the impulses originating in the skin from cooling stimulate the cells to metabolic activity.”

The sum of these impulses, according to Rubner, is in proportion to the body surface.

Later on Rubner accepted just the opposite view, declaring that the metabolic rate of the tissues is a fundamental characteristic of a species (Wels, 1925).

In 1925 Terroine and Roche derived from microrespiration trials with excised animal tissue a hypothesis opposed to Rubner's idea of genetically fixed cell metabolism. They stated: “Homologous tissues of different animals have, in vitro, the same intensity of respiration.” The metabolic differences of tissues

of large and small animals disappear when the tissues are removed from the animal body. These differences, therefore, are not located in the cells themselves, but are imposed on the cells by central systems representing the organism as a whole, the nervous system and the circulatory system.

In the same year Grafe (1925), independent of Terroine and Roche, reached the same conclusion stating: "The living protoplasm of the warm blooded animals and maybe even of many cold blooded animals, shows, as far as respiration is concerned, a certain uniformity, and gets its specificity only by means of the regulating system of the animal!"

The tissues, according to Grafe, respire at a higher rate *in vitro* than *in vivo*, particularly tissues of large animals. *In vivo* the metabolic rate of those tissues is checked by the influence of the central regulators, mainly the nervous and endocrine systems.

There are a number of observations in support of this view. Severance of the spinal cord increased the rate of nitrogen metabolism (Isenschmid, 1920). In line with these ideas is also the observation of Victor (1934) that dystrophic muscles have increased metabolic rate *in vitro*. Recently Houchin (1942) stated that normally tocopheryl phosphate acts as a brake on muscle oxidation, and that vitamin E deficiency lets the oxidation "run riot" so that the muscle is "consumed in its own fire" and muscle dystrophy results.

The discovery of capillary regulation of blood supply to the tissues by Krogh (1929) led to a well rounded theory that the checking of metabolic rate *in vivo* was accomplished by rationing of the oxygen supply. That was in contrast to Pflüger's law (Pflüger, 1872), to be sure, but observations of Thunberg (1905) on lower animals, and of Verzár (1912) on muscles, indicated that Pflüger's law loses its application at low partial oxygen tensions and that oxygen supply may become the limiting factor in the rate of tissue respiration. Recently Gaija (1946) noted that below a given critical partial pressure of oxygen the metabolic rate of homeotherms depends on oxygen supply. Apparently, independent of body size, the limiting partial oxygen pressure amounts to about 90 mm. Hg. This corresponds to a barometric pressure of 450 mm. Hg. or an altitude of 4000 meters.

That the metabolic rate of animals was by no means a genetically fixed constant, but was decidedly affected by somatogenic factors, was demonstrated by Kleiber and Cole (1939) who measured the metabolic rate of giant rats produced by injection of growth hormone. The metabolic rate, either per unit weight or per unit of the $2/3$ power of weight, was lower in the growth hormone rats than in normal litter mate controls. This rate could therefore not be a genetically fixed characteristic of the tissues (being changed by the somatic influence of growth hormone injection). This result was in line with the ideas of Terroine and of Grafe. Kleiber and Cole, however, observed also that the differences in the metabolic rates of giant growth hormone and normal control rats could still be noted in the rate of oxygen consumption of the surviving diaphragm *in vitro*. This observation was in opposition to the results of Terroine and of Grafe.

Field, Belding and Martin (1939) succeeded in summing the metabolic

rates of excised rat tissues *in vitro* to 66 per cent of the actually measured metabolic rate of the rat. Martin and Fuhrman (1941) similarly summated metabolic rates *in vitro* of dog tissues to over 70 per cent of the metabolic rate of the dogs. These results support the idea that the rate of oxygen consumption of the tissues *in vitro* reflects the metabolic rate of these tissues *in vivo* to a considerable extent.

Repeating the investigations of Terroine and of Grafe, Kleiber (1941) measured the *in vitro* rate of oxygen consumption of liver slices from rats, rabbits, and sheep. The metabolic rate per unit weight *in vitro* decreased consistently with increasing size of the animals, almost to the same extent as the metabolic rate of the living animal.

Recent microrespiration trials in our laboratory (Kleiber, 1947, unpublished) with excised liver of rabbits and cows again show that liver slices from cows have a lower rate of oxygen consumption per unit weight than the liver slices from rabbits.

Smyth (1940), on the other hand, reports that "observations by Van Heyningen (1936) indicate a uniformity in the rate of metabolism in the same tissue in different species irrespective of the size of the animal."

This result seems to be in line with the theory of Grafe and of Terroine and in contrast to our findings. A check of Van Heyningen's figures, however, indicates that only anaerobic glycolysis of brain cortex was independent of body size. For respiration, the effect of body size on tissue metabolism was similar to our results.

The following working hypothesis seems justified: The animal as a whole responds to changes in somatic conditions. Reactions to such changes are transmitted to the tissues by centralized metabolic regulators such as the nervous and the endocrine systems. These regulatory influences produce changes in the metabolic conditions of the cells. Among these conditions, which determine cellular metabolic rate, may be structural relations, electrical potentials, ion concentrations, and the concentrations of oxygen, metabolites and enzymes.

The observation that metabolic rates *in vitro* are similar to those *in vivo* suggests that the conditions which determine the rate of cell respiration change but slowly; this would be expected of changes in concentrations of enzymes and metabolites.

Since oxygen supply should not affect the oxidation rate *in vitro*, the similarity between *in vitro* and *in vivo* metabolic rate throws doubt on the theory that tissue metabolism normally is regulated by rationing the oxygen supply.

The observation that the metabolic rate of tissues *in vitro* is similar to the corresponding rate *in vivo*, is sometimes interpreted to indicate an inherent metabolic level of the tissues. If the statement means that the rate of tissue respiration is independent of somatic influences, then it is wrong; if it means that genetic factors are involved in the metabolic levels, then the correctness of the statement is hardly in doubt. One may be able to breed strains of rats with a high, and strains of rats with a low metabolic level under quasi equal environmental conditions. There may be genetically determined limitations

for the extent to which cell metabolism reacts on changes produced in the cells by the metabolic regulators. The demonstration of genetic factors in metabolic level, however, helps but little in the interpretation of the fact that the metabolic rate per unit weight of a 5.3 kg. rabbit is practically the same as that of a 6.6 kg. dog, but differs significantly from that of a 1.5 kg. rabbit; as in turn the metabolic rate per unit weight of a 25 kg. dog differs significantly from that of the 6.6 kg. dog.

The results of Terroine and of Grafe on metabolic rates *in vitro* were not confirmed later, yet an essential part of their theory is sound; namely, the idea that the metabolic rate of the tissues *in vivo* is controlled by central regulators representing the animal as a whole.

Even fetal metabolic rate seems to be under the influence of the maternal metabolic regulators (or perhaps a combination of maternal and fetal regulators).

Kleiber, Cole and Smith (1943) measured the metabolic rate of rat embryos *in vitro*, and obtained good evidence against the theory that a fetus behaves, metabolically, like an independent small homeotherm. The fetal metabolic rate per unit moist weight was of the same order of magnitude as that of normal adult rats, and considerably smaller than that of newly born or 12 day old rats.

This observation, like others mentioned, favors the idea that, to a considerable degree, cellular metabolic rate is adapted to the condition of the animal as a whole. The effect of the metabolic regulators, however, appears to remain in the tissues that are removed from the animal and respire *in vitro*.

The analysis of these factors controlling the metabolic level *in vitro* and *in vivo* appears to be a most fruitful field for future research on tissue metabolism.

C. Integration of valid theories on surface law. Of the five groups of interpretations of the surface law, the one on internal nutritive surfaces has no evidence in its favor. The one on composition of the body has no explanatory value. The same is true for the explanation with a genetically fixed metabolic rate of body cells, even if this postulate as such were acceptable, because the problem would arise: why have those animals been selected for survival whose cells have the inherent metabolic rate such that the metabolic rate follows the surface law?

The theories that relate the surface law to rate of heat transfer, and those that relate it to the hemodynamics, have most value for the interpretation of the surface law. The most promising theory of body size and metabolism integrates the heat exchange and the circulation theory.

In natural selection, those animals probably prove to be the fittest whose cells are adapted to such a level of oxygen consumption that the metabolic rate of the animal is most suitable for the maintenance of a constant body temperature and in line with the most efficient transport of oxygen.

A four ton animal, whose cells insisted on a rate of oxygen consumption per unit weight equal to that of mouse cells, could not survive, because such a metabolic rate could not be supported by the circulatory system and would upset the maintenance of a constant body temperature.

The surface law is unreliable mainly because the definition of an animal's surface is vague. But even if the surface area could be defined and measured

accurately there is no theoretical basis for the hypothesis that the metabolic rate of homeotherms should be exactly proportional to their particular surface area rather than to a more general function of body size.

EMPIRICAL VALIDITY OF SURFACE LAW. Between the efforts of the gadgeteers to design apparatuses for surface measurements, the statisticians to derive formulas for calculating "true" surface areas, and the theoretically inclined biologists who discussed the proper interpretations of the surface law, rather few seemed to have been interested in the question as to just how reliable the surface law itself is.

Among the few that questioned rather early the validity of the surface law was one of the pioneers of vitamin research, F. G. Hopkins, who in 1912 wrote as follows:

"... in the case of very young rats the demand for maintenance is more nearly determined by the live-weight than by the surface area. It becomes of course smaller relatively to body weight as this increases but it falls off more slowly than the surface area would require."

Seven years later, Harris and Benedict (1919) concluded from their extensive measurements on men and women that within the human species there was no evidence for the surface law. Du Bois (1927, p. 202) however, maintained that the data of Harris and Benedict confirmed the surface law.

The differences in size among the material of Harris and Benedict were so small and the influence of factors other than size so relatively large that the two opposing deductions could both be made in good faith (compare pp. 530 and 534).

In an attempt to find the most suitable unit of metabolic body size for estimating maintenance requirements and comparing metabolic rates of animals that differ in weight, Kleiber (1932) compiled results of metabolism measurements from American laboratories, listing 13 groups from 150 gram ring doves to a 679 kg. steer. The surface law was confirmed insofar as the metabolic rate per unit weight decreased systematically as the body weight of the animals increased. The coefficient of variability per unit weight was 80 per cent, and that per unit surface area only 34 per cent. This latter is still quite high, and a comparison of some of the recent results with Voit's table (1901) apparently indicates a trend of the modern American animals to take the surface law less seriously than the European animals in 1901.

There is a considerable positive correlation between body size and metabolic rate per square meter of body surface.

The surface law, that is the theory that the metabolic rate per unit surface area of large and small animals is the same—or at least independent of size—is therefore not strictly confirmed by the recent material.

METABOLIC RATE AS A POWER FUNCTION OF BODY WEIGHT. *A. Linear relation between logarithms of metabolic rate and body weight.* The regularity in the deviations of the empirical results from the surface law justified the search for a function of body size to which metabolic rate might be more nearly proportional than to body surface. Plotting the logarithms of fasting metabolic rate against the logarithms of body weight revealed a linear relation between these two variables

with surprisingly small deviations from the mean trend. For the ten groups of mammals, the standard deviation from the mean regression line amounts to ± 0.03 logarithm unit, which corresponds to a coefficient of variation of metabolic rate from the interspecific mean of 7 per cent.

When the logarithm of metabolic rate is a linear function of the logarithm of body weight, then metabolic rate is proportional to a given power of body weight.³ The metabolic rate was more nearly proportional to the $3/4$ power of body weight than to either the $2/3$ rd power or the surface area of the animals (as derived for each group by a special formula designed for the calculation of its particular surface area).

Soon after the publication of these results, Brody and Procter (1932) extended a similar compilation of metabolic data down to the mouse. They used mostly figures accumulated in their own laboratory and noted that their result was in close agreement with that of Kleiber (i.e., p. 94).

In 1938, F. G. Benedict published an extensive analysis of the great amount of valuable data on metabolic rates of various animals tested in the Carnegie Nutrition Laboratory by reliable methods under rather well standardized conditions.

A chart (p. 171) shows the logarithms of the mean metabolic rates for 28 groups of animals plotted against the logarithms of the corresponding mean body weights. The animals considered ranged in size from 20 gram mice to nearly 4 ton elephants. A regression line indicates the average trend, and Benedict notes "a most gratifying straight line relationship between the total heat production and the body weight." He obviously means the logarithms of these variables. He then continues as follows: "However satisfactory this relationship may be mathematically, this method of presenting the data completely masks metabolic differences within species."

In answer to this remark one may say that any mean of a group of data "masks," that is, does not show, the differences between the single data; that has nothing to do with logarithmic interpolation. If one wants to show the differences within the species one may plot the logarithm of each individual metabolic rate against logarithm of the corresponding individual body weight. In order to supply the reader with an estimate of the variability, as a substitute for presenting every single result, some of the more statistically minded biologists state with a mean also its standard error.

Benedict extends his accusation, stating that logarithmic interpolation "distorts or obscures striking differences between the species." Since, however, a logarithmic chart in a scientific paper is presented to readers who are presumably familiar with logarithms, the accusation of distorting or obscuring can be discarded.

There is nothing obscure about the fact that a logarithmic regression line of a given set of data looks different, in general, from the corresponding arithmetic line, and if this difference in the appearance of the two regression lines be termed

³ If $\log M = \log a + p \cdot \log W$ —(general equation for straight line)
then $M = a \cdot W^p$

distortion, one could call the arithmetic line a distortion of the logarithmic just as well as vice versa.

Benedict further believes (p. 172) that "the seeming similarity between the different species shown by this logarithmic chart is an artificial similarity."

It is true that the conditions under which basal metabolism is measured are somewhat different from those under which animals normally live. The conditions under which the results discussed here are obtained may therefore be classified as artificial, and it might be argued that the metabolic rate of a rat in a sewer, or a cow in a barn, would be different from their metabolic rates measured in the artificial environment of a respiration apparatus; but that possibility has nothing to do with the question, whether or not the linearity of the logarithms of metabolic rates as measured and the corresponding body weights are real. Whether or not such a relationship has physiological significance depends on the physiologist, the same as it depends on the listener whether he hears a symphony or merely a multitude of different sounds.

Benedict concludes his chapter on interspecific comparisons (p. 179) with the following sentence:

"It seems, therefore, unjustifiable to apply mathematics to the pooled end result of the activities of millions of cells each highly differentiated, with different energy potentialities and actuated by different stimuli."

If this is the way Benedict feels, one cannot help but wonder how he ever became interested in conducting a respiration trial and why, furthermore, he even calculated means of groups of several of these pooled end results which indeed is applying mathematics.

Admittedly one may find biological publications in which data seem to be used merely as material for mathematical exercises. Admittedly, furthermore, some biologists learn mathematical tricks and tirelessly apply them, apparently without bothering to understand either the basis and limitations of their methods or the meaning of their results. Publications originating under such circumstances may have developed Benedict's antagonism to the application of mathematics in biology. The answer to such pseudomathematics in biology, however, is not less mathematics, but good mathematics.

For the application of statistical methods the biologist finds an excellent review by H. L. Dunn (1929) with ten "don't's" and two "be sure of's." These twelve commandments ought to be instilled into every student of quantitative biology and physiology.

Benedict's table 4 on p. 175 (1938) contains an error which may lead to some confusion and is therefore mentioned here. The metabolic rates of the animals lighter than 1 kg. seem to have been calculated per unit of the various power functions of body weight: $W^{0.62}$, $W^{2/3}$, $W^{0.72}$ etc., on the basis of the erroneous assumption that generally (weight in g.)^p equals 100 (weight in kg.)^p. For $p = 2/3$ the result happens to come out all right because $1000^{2/3} = 100$ but for all the other powers that calculation is wrong; obviously it would be wrong for $p = 1$, since 1 kg. contains 1000, not 100 grams. The one kcal. of heat produced daily by the 8 gram dwarf mouse amounts to 39.2 kcal. per kg.^{0.76} not 20.6 kcal. as listed in the table mentioned.

The great amount of material on metabolic rates, secured by reliable measurements in Benedict's laboratory, and condensed to a logarithmic chart on the relation of body size and metabolic rate (Benedict (1938) p. 171) is an excellent confirmation of Kleiber's earlier results (1932, p. 321). The two regression lines expressing the mean trends of these two sets of data are practically identical.

B. Check with recent data. To reinvestigate the relation of body size and metabolic rate among mammals, I have compiled 26 groups of metabolic rates measured under apparently comparable conditions. The animals were mature, in postabsorptive condition, measured in the range of metabolically indifferent environmental temperature, and at rest, or at least without abnormal activity. No data were used that were already incorporated in the earlier study (1932).

The basic data and the source of the material are given in table 2.

In figure 1 the logarithms of metabolic rate are plotted against the logarithms of body weight. The results used for calculating the regression line are indicated by dots in circles; those that are not used in the calculation are marked with brackets.

The reasons for not including these data in the calculation are as follows:

The result of only one shrew is so far reported and it is questionable whether the conditions of measurement allow a direct comparison with standard metabolic rate of the other animals. The Swiss mice were not in postabsorptive condition as indicated by a mean respiratory quotient of 0.96. Dwarf mice and growth hormone rats have an abnormal endocrine system. The result for swine was calculated from a mean net energy requirement for maintenance. The steer calves may be regarded as not yet mature and therefore their metabolic rate not strictly comparable with that of the other groups of animals. The conditions of measurement of metabolic rate of elephant, porpoise and whale are not strictly in line with the normal conditions of measuring standard metabolic rates.

Unfortunately, a lot of valuable data on man could not be incorporated in our chart because the results were given only per square meter of body surface. This is particularly true for the material of Boothby and Sandiford (1924), and the more recent findings of Young, Pittman, Donelson, and Kinsman (1943).

For the 26 comparable results, the method of least squares leads to the following linear regression equation:

$$\log M = 1.83 + 0.756 \log W \pm 0.05$$

where M = metabolic rate of animal in kilocalories per day

W = body weight in kilograms.

The regression coefficient of 0.756 ± 0.004 indicates that for the 26 results compiled in our table, the metabolic rate is most nearly proportional to the 0.756 or close to the 3/4 power of body weight.

The same interpolation of the earlier data (Kleiber, 1932) on ten groups of mammals leads to the equation:

$$\log M = 1.87 + 0.739 \log W \pm 0.03$$

TABLE 2

GROUP	ANIMAL	AUTHOR	BODY WT.	METABOL. RATE PER DAY
a. Data used for calculation of regression line				
			<i>kg.</i>	<i>kcal</i>
1	Mouse	Benedict and Lee, 1936	0.021	3.6
2	Rat 230-300 days old	Kleiber, unpubl.	0.282	28.1
3	Guinea pig	Benedict, 1938	0.410	35.1
4	Rabbit	Tomme and Loria, 1936	2.98	167
5	Rabbit	R. Lee, 1939	1.52	83
6	Rabbit		2.46	119
7	Rabbit		3.57	164
8	Rabbit		4.33	191
9	Rabbit		5.33	233
10	Cat	Benedict, 1938	3.00	152
11	Macaque	Benedict, 1938	4.2	207
12	Dog	Galvão, 1942	6.6	288
13	Dog		14.1	534
14	Dog		24.8	875
15	Dog	de Beer and Hjort, 1938	23.6	872
16	Goat	Benedict, 1938	36.0	800
17	Chimpanzee	Bruhn and Benedict, 1936	38.0	1090
18	Sheep ♀	Lines and Peirce, 1931	46.4	1254
19	Sheep ♂		46.8	1330
20	Woman	McKittrick, 1936	57.2	1368
21	Woman	Lewis, Iliff and Duval, 1943	54.8	1224
22	Woman	McCrery, Wolf and Bavoursett, 1940	57.9	1320
23	Cow	Benedict and Ritzman, 1935	300	4221
24	Cow	Kleiber, Regan and Mead, 1945	435	8166
25	Beef heifers	Kleiber, Goss and Guilbert, 1936	482	7754
26	Cow	Benedict and Ritzman, 1935	600	7877
b. Data not used for calculation because conditions not comparable				
	Shrew	Morrison and Pearson, 1946	0.0035	2.9
	Swiss mice	U. S. Navy Res. Unit and Kleiber, 1944	0.0105	3.7
	Dwarf mouse	Benedict, 1938	0.008	1
	Rats (giant)	Benedict, 1938	0.400	33.2
	Rats (growth hormone)	Kleiber and Cole, 1939	0.391	28.6
	Swine	Breirem, 1936	150	2678
	Steer calves	Mitchell et al., 1940	200	3817
	Elephant	Benedict, 1938	3672	49000
	Porpoise	Irving et al., 1941	170	6768
	Whale	Irving, 1941	70000	1.2 × 10 ⁶

The two bands, described by the two regression equations with their standard error of estimate, could be distinguished only by extrapolation to animals weighing less than 4 grams or more than 800 tons.

The figure shows the line by which the results would have to be represented if the metabolic rate were proportional to body weight, and also the line which would summarize the results if the metabolic rate were proportional to the $2/3$ power of body weight (or approximately body surface).

The line expressing proportionality of metabolic rate to body weight stays within the band expressing metabolic rates proportional to the $3/4$ power of

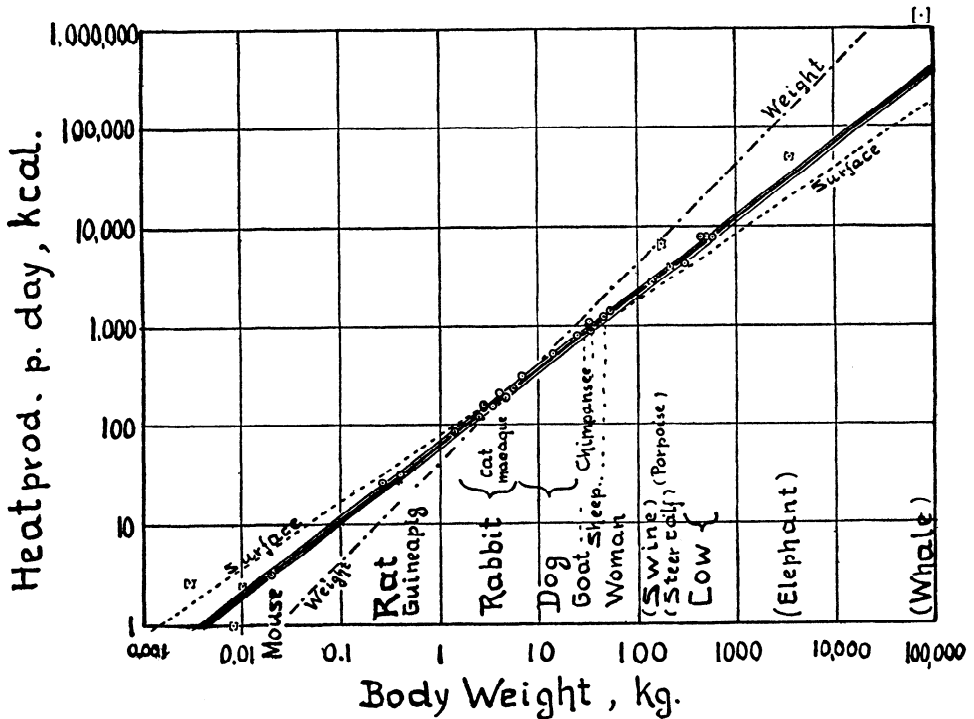


Fig. 1. Log. metabol. rate/log body weight

weight over a ratio of weights of 3.2. That means one would not be able to decide whether metabolic rates are proportional to body weight or proportional to its $3/4$ power, unless the heaviest animals studied would weigh at least three times as much as the lightest animals.

Similarly, one may calculate that a significant difference between proportionality to the $3/4$ power of body weight and proportionality to the $2/3$ power of body weight (representing roughly the surface area), could not be established with groups of animals in which the heaviest animals weighed less than 9 times as much as the lightest animals.

C. Intraspecific comparisons. Since the differences in size have to be so con-

siderable to allow a significant decision of the question, whether the metabolic rate is more nearly proportional to the $2/3$ or the $3/4$ power of body weight, only a few species show great enough differences in mature weight for the establishment of the best fitting power function of body weight as basis for metabolic body size. This is true, even though the variability of metabolic rate for a given size is less within a species than between species.

In three species, namely, mice, rabbits, and dogs, the differences in size are considerable, and an analysis of the relation between body size and metabolic rate within these 3 species seems more promising than in the other species with more uniform size.

The regression line given for metabolic rate of mice (Benedict, 1938, p. 65) as a function of their body weight, would indicate a best fitting power function of body weight for metabolic body size

$$p = \frac{\Delta \log \text{metabol. rate}}{\Delta \log \text{body weight}} = 0.89$$

Benedict's line seems, however, definitely affected by a group of 4 endocrinologically abnormal dwarf mice. If we estimate the line through the other results, the best fitting power function would be 0.76.

The regression line given for rats (l.c. p. 67) would indicate that the rats intraspecifically followed the surface law. Their metabolic rate would be most nearly proportional to the 0.67 power of body weight.

The results of the 5 groups of rabbits reported by Lee (1939) may be represented by the following regression line:

$$\log M = 1.763 + 0.82 \log W \pm 0.09.$$

This indicates that in this population, metabolic rate is most nearly proportional to the 0.82 power of body weight; the range of body size in these rabbits would, however, have to be about 4 times as great as it is, to demonstrate a significant departure of rabbits from the hypothesis that metabolic rate is proportional to the $2/3$ power of body weight. This range would have to be considerably more than four times as large to demonstrate that the intraspecific relation between metabolic rate and body size in these rabbits contradicts the hypothesis that the metabolic rate is proportional to the $3/4$ power of body weight.

The data on the 3 groups of dogs reported by Galvão (1942) indicate proportionality of metabolic rate to the 0.84 power of body weight, and since the variability in this case seems rather small, the deviation from the surface law and even from the $3/4$ power rule appears significant; so does the deviation from the hypothesis that the metabolic rate of these dogs is proportional to their body weight.

The result of Galvão contradicts the one which can be calculated on the basis of the material of Lusk, Kunde, and Steinhaus (see Benedict 1938 p. 79). Selecting from the regression line of this material, given by Benedict, the points for 9 kg. dogs and that for 18 kg. dogs, one may conclude that the metabolic rate of these dogs is most nearly proportional to the 0.55 power of body weight.

It is of interest to note that within the two groups of animals in which an intraspecific investigation of body size and metabolic rate appears most promising, rabbits and dogs, the metabolic rate seems to be most closely related to a power function of body weight higher than the $3/4$. This problem deserves more study. Until there is a great deal more evidence for a difference in the intraspecific and the interspecific relation of body size and metabolic rate, the most rational temporary hypothesis is the one which is the simplest. That is the hypothesis that the intra- and the interspecific relations of body size and metabolic rate are the same. The question is whether the relation found intraspecifically should be assumed to hold also interspecifically, or vice versa. The interspecific derivation of the best suitable unit of metabolic body size seems, at present, the more reliable, because the great difference in size available by interspecific comparison makes size so dominant over other factors.

At present it appears, therefore, reasonable to adopt for intraspecific prediction of the metabolic rate the metabolic unit of body size found most suitable for interspecific prediction, namely, the $3/4$ power of body weight.

METABOLIC BODY SIZE AND PREDICTION OF METABOLIC RATE. The metabolic body size is that function of size of animals to which the metabolic rate is proportional. Once the unit of metabolic body size is established, then the metabolic rate can be predicted by multiplying the metabolic body size with a given factor.

According to the surface law, the metabolic rate is proportional to the surface area. The metabolic body size, consequently, would be expressed in square meters of body surface, and according to Rubner's rule, the daily metabolic rate in kilocalories is 1000 times the number of square meters of body surface.

Since body surface is ill defined, the square meter of body surface is no suitable unit of size, even though it undoubtedly offers the great advantage of being easily visualized. Admittedly, it is easier to talk of heat production per square meter than to talk of heat production per unit of the $3/4$ power of body weight in kilograms.

The Du Bois surface (1916) as calculated from weight and height is well defined within one species, but for comparison between man and rabbit, for example, one would have to rely again on the ill defined concept of "true" body surface.

Attempting to avoid hypotheses, such as the surface law, and ill defined terms, such as the body surface area, Harris and Benedict (1919) derived their empirical prediction equations, namely, (p. 227):

$$\text{for men } h = +66.4730 + 13.7516w + 5.0033s - 6.7550a$$

$$\text{for women } h = +655.0955 + 9.5634w + 1.8496s - 4.6756a$$

h = total heat production in kcal. per day, w = weight in kilograms

s = stature in centimeters and a = age in years.

Krogh (see Boothby and Sandiford, 1924, p. 80) has already criticised these equations.

That they allow an accurate prediction of the metabolic rate of men and

women similar to the material studied by Harris and Benedict is not in doubt, but physiologically the equations are practically meaningless.

Implied in these equations are several rather questionable assumptions; namely, that the metabolic rate of a weightless woman is 10 times that of a weightless man.

Further, it is assumed that metabolic rate is the sum of a linear function of body weight, a linear function of height, and a linear function of age.

Even though the Harris-Benedict equation deals with well defined quantities, such as weight, height, and age, Du Bois' prediction, despite its connection with the ill defined concept of body surface, seems to be more acceptable to clinicians as well as physiologists because it has a rational physiological meaning. Assuming that the metabolic rate is proportional to the 3/4 power of body weight, Kleiber (1932) re-analyzed the data of Harris and Benedict and developed the following prediction equations:

for men: $M = 71.2 \times W^{3/4} (1 + 0.004 (30-A) + 0.010 (S-43.4))$

for women: $M = 65.8 \times W^{3/4} (1 + 0.004 (30-A) + 0.018 (S-42.1))$

M = the metabolic rate in kilocalories per day

W = the body weight in kilograms

A = the age in years

S = the specific stature in $\frac{\text{centimeters height}}{W^{1/3}}$.

The equations have the following meaning: the metabolic rate of a man 30 years of age and with a specific stature of 43.4 cm./kg.^{1/3} has a metabolic rate 71.2 times his body weight in kilograms raised to the 3/4 power. A woman of a standard age of 30 and standard specific stature for women (which is 42.1 or slightly less than that for men) has a metabolic rate of 65.8 per kg.^{3/4}. The ratio of 71.2 to 65.8 for the metabolic rates per unit of the 3/4 power of body weight of standard man and standard woman indicates the effect of sex on human metabolic rate. The second term in the parenthesis indicates that in adult man the metabolic rate decreases about 0.4 per cent of the metabolic rate of standard man for each year above (or increases for each year below) the standard age of 30.

It might have been preferable to express this age effect in relative terms, such as $0.12 \frac{30-A}{30}$. Then the metabolic effect of age, expressed by the coefficient 0.12, would be more comparable with that in other animals with different standard age. (The relation of relative ages in different animals has been extensively studied by Brody (1945, chapter 19). Human metabolic rate would change 12 per cent per unit of relative departure from standard age (that is per 30 years). The last term in the parenthesis indicates that the mean specific stature (in the material of Harris and Benedict) for men is 43.4 cm. per kg.^{1/3} that for women 42.1 cm. per kg.^{1/3}. Each centimeter per kg.^{1/3} increase in specific stature produces, on the average, an increase of 1 per cent of the metabolic rate of men, and of 1.8 per cent of the metabolic rate of women. This suggests that the degree of slender-

ness (specific stature) affects the metabolic rate of women more than it affects the metabolic rate of men. The equations of Kleiber predict the metabolic rate of human beings with about the same accuracy as the empirical multiple regression equations of Harris and Benedict. The major advantage of the newer equations is that all terms have a physiological meaning.

Kleiber (1932) was somewhat vague about choosing a definite power function of body weight as the best basis for metabolic body size, and stated, p. 336, "that further investigation may show that some unit other than $W^{3/4}$ may be preferable."

Brody and Procter (1932) ventured a more definite formulation, namely:

$$M = 70.4 W^{0.734}$$

and Brody, Procter and Ashworth (1934) obtaining exactly the same equation with a wider range of animals, including elephants, were confident that this "equation approaches closely the true relation between basal metabolism and body weight of mature mammals."

This relation was widely accepted (for example, in Höber's book, *The physical chemistry of cells and tissues*, p. 375). The National Research Council conference on energy metabolism (1935) endorsed the power function, after reducing it to two decimals (0.73), as the most suitable unit of metabolic body size. There was some doubt as to whether or not the data available justified the change from the $3/4$ to the more complicated 0.73 power, a change which implied that the second decimal of the exponent was significant.

Taking into account a coefficient of variation in metabolic rate per unit size of 7 per cent, one may calculate that there is no significant difference between Brody's prediction and $72W^{3/4}$ within a group of animals ranging from a 10 gram mouse to a 16 ton super elephant. Within this range, there is thus not much point in discussing the question, whether the 0.734 power or the $3/4$ power of body weight fits the metabolic results more closely.⁴

Recently, Brody (1945, p. 373) dropped also the second decimal from the exponent and suggests that the 0.7 power be used as reference for basal metabolism measurements.

Our recent analysis favors again the $3/4$ power of body weight as the metabolic unit of body size. Aside from its empirical justification, the $3/4$ power is preferable to either of Brody's successive 0.734, 0.73 or 0.7 because it is mathematically simpler since it can be calculated without logarithms.⁵

The daily fasting heat production per kg.^{3/4} was:

in 10 groups of mammals, 1932:	71 ± 1.8 kcal. per kg. ^{3/4}
in 26 groups of mammals, 1947:	69 ± 1.5 kcal. per kg. ^{3/4}
together:	
36 groups of mammals,	69 ± 1.2 kcal. per kg. ^{3/4}

⁴ The classification of the $3/4$ power of body weight as the "Brody-Kleiber unit" (Günther, 1944) nevertheless is confusing. If these units have to be named according to authors at all, then Brody's unit would be the 0.734, 0.73 or 0.7 power, and Kleiber's the $3/4$ power.

⁵ $W^{3/4}$ can be easily obtained on a slide rule (extract the square root of the square root of the cube of the body weight).

For all practical purposes, one may assume that the mean standard metabolic rate of mammals amounts to 70 times the 3/4 power of their body weight (in kg.) per day, or about 3 times the 3/4 power of their body weight (in kg.) per hour.

BODY SIZE, FOOD REQUIREMENT AND DOSAGE OF BIOTICS. Two animals may be regarded as being on the same level of food intake when their rate of intake of metabolizable food energy⁶ is the same multiple, or the same fraction, of their standard metabolic rate. Since the standard metabolic rate is proportional to the metabolic body size, or the 3/4 power of body weight, two animals may also be regarded as being on the same level of food intake, when they consume the same amount of metabolizable food energy per kg.^{3/4}

Not only the requirement of food energy, but also that of protein and of most vitamins, may be expressed per unit of the 3/4 power of body weight, because these dietary requirements are directly related to energy metabolism (see review by Kleiber 1945-46, p. 207).

For the dosage of drugs one should know whether or not the action depends on reaching a certain concentration in the blood stream without regard to its further maintenance. In this case the dosage should be proportional to body weight, since the amount of blood is proportional to body weight. If, however, the action of the biotic depends on the maintenance of a given concentration over a period of time, and if the rate of destruction or excretion of the biotic is proportional to the metabolic rate, then the dosage should be based on the metabolic body size.

The treatment may be so arranged that doses proportional to body weight are given and that the frequency of application depends on body size, so that over a sufficient period of time the rate of intake is proportional to the metabolic body size (the 3/4 power of body weight). In this case the frequency should be inversely proportional to the fourth root of body weight.⁷

If, for example, a 50 gram rat received one unit of a biotic daily, then to establish similar conditions under the assumptions made, a 500 kg. steer should receive a dose of 10,000 units every ten days.

BODY SIZE AND FOOD UTILIZATION. The establishment of a metabolic unit of body size is particularly advantageous for the investigation of food utilization.

$$\text{The quotient: } \frac{\text{energy in animal product}}{\text{total food energy}} = \frac{G}{U}$$

is called the total efficiency of food utilization. It measures (as far as that is possible in terms of energy) the success of animal husbandry.

⁶ Metabolizable energy = heat of combustion of food minus heat of combustion of feces, urine, and methane.

⁷If q = amount given at one time (dosage)

f = frequency of application

W = body weight

then rate of intake = $f \cdot q = k_1 \cdot W^{3/4}$; $q = k_2 \cdot W$

$$f = \frac{k_1}{k_2} \cdot \frac{W^{3/4}}{W} = \text{const.} \cdot W^{-1/4}$$

The quotient $\frac{\Delta G}{\Delta U}$ is the partial efficiency. It is in general dependent on the level of food intake, but the discussion in this chapter may be limited to the simplest special case, that in which the partial efficiency is constant = e .

An animal needs a certain amount of food energy, U_m , to maintain itself without gain or loss of body substance. Only that amount of food energy consumed in excess of this maintenance requirement is available for production. The energy in the animal's production is, thus, the partial efficiency times the food energy available for production:

$$G = e(U - U_m)$$

therefore the total efficiency is:

$$\frac{G}{U} = e \left(1 - \frac{U_m}{U} \right)$$

The maintenance requirement U_m is related to the rate of fasting metabolism, B . The amount, B , of energy in body substance which the fasting animal would lose, is saved from being lost by the food energy U_m . The quotient $\frac{B}{U_m}$ is therefore the partial efficiency of food utilization for maintenance. Assuming for simplicity that this partial efficiency is the same as that for production, then $\frac{B}{U_m} = e$ or $U_m = \frac{B}{e}$.

Introducing this expression in the equation for total efficiency one obtains

$$\frac{G}{U} = e \left(1 - \frac{1B}{eU} \right), \quad \text{or} \quad \frac{G}{U} = e - \frac{B}{U}$$

That means the total efficiency of food utilization is the difference between the partial efficiency (characterizing the nutritive content of the food), and the ratio between the basal metabolic rate and rate of intake of food energy. This ratio characterizes the capacity of the animal to take in food. Partial efficiency of utilization of metabolizable food energy (U) is related directly to the calorigenic (or specific dynamic) effect of food, ΔQ :

$$e = \frac{\Delta G}{\Delta U} = 1 - \frac{\Delta Q}{\Delta U}$$

There is no reason to assume that partial efficiency depends on body size. To the contrary, there is a good deal of evidence against such an assumption. Chambers and Lusk (1930) and Eaton, Cordill, and Gouaux (1936) for example observed that the specific dynamic action of glycine, administered to dogs varying from 5 to 13 kg., was independent of body size. The ratio $\frac{U}{B}$ has been defined as the "relative food level," and if an animal eats to capacity then $\frac{U}{B}$ may be termed the "relative food capacity" in terms of the basal metabolic rate.

Since the basal metabolic rate is proportional to the $3/4$ power of body weight ($W^{3/4}$) the term $\frac{U}{W^{3/4}}$ characterizes the relative food capacity of the animal in terms of metabolic body size. Aside from differences in partial efficiency that animal is the better food utilizer which has the greater relative food capacity. The food intake per kg.^{3/4}, and similarly the gain per kg.^{3/4}, should be important characteristics for selection in breeding farm animals.

Since there is no reason to assume that partial efficiency depends on body size, the question of food utilization and body size is mainly a question of whether or not relative food capacity depends on body size. The simplest hypothesis is that the relative food capacity is independent of body size. Kleiber (1933), based on data obtained by himself and others, produced some empirical evidence in support of this simple hypothesis. By extensive experiments, Brody and his co-workers have confirmed this hypothesis for lactation (Brody and Proctor, 1935; Brody and Cunningham, 1936). Brody and Nesbit (1938) reported that energetic efficiency of rats (for lactation) is within that of cows. The efficiency for mechanical work is the same for large and small horses (Brody and Cunningham 1936) and for large and small men (Robinson, 1942).

A corollary to the hypothesis that total efficiency of food utilization is independent of body size, is the postulate that the relative rate of animal production is independent of body size. The relative rate of animal production may be the rate of gain in body substance per kg.^{3/4}, the rate of mechanical work per kg.^{3/4} or the rate of milk production per kg.^{3/4} (Kleiber and Mead, 1941, 1945).

Kleiber's hypothesis does not, of course, exclude the possibility that there are good and bad food utilizers. The meaning of the hypothesis is that the comparisons of good and large food utilizers with small and bad food utilizers, or vice versa, should not be used to establish a relation of body size and food utilization.

Similarly, one cannot directly compare young small animals with old large animals, even though in some cases age may not affect the relative production level. This is true, for example, for a considerable range in pigs. From figures given by Breirem (1939), one may calculate that the relative rate of gain for a 20 kg. pig is 112 kcal. per kg.^{3/4}; that of a 100 kg. pig, 118 kcal. per kg.^{3/4}.

SUMMARY AND CONCLUSIONS

1. Among homeotherms, from mice to cattle, metabolic rate and body size are correlated. This correlation is especially high when the metabolic rates are measured under standard conditions.

2. The metabolic rate of large and small homeotherms is more nearly proportional to the area of their respective body surfaces than to their body weights. This relationship is known as the surface law.

3. From five types of theories interpreting the surface law three are rejected, namely:

- a. The theory based on the erroneous idea that the summated area of internal surfaces, such as the surfaces of the cells and the pulmonary alveoli, is proportional to the surface area of the body. The similarity in build of large and small animals cannot be extended to the dimensions of cells or alveoli.

b. Rejected also is the theory which bases the surface law on alleged differences in the chemical composition of large and small animals, involving such vague concepts as the "active protoplasmic mass". Neither does the theory which makes metabolic rate a function of anatomical composition stand the test. Uncritical evaluation of empirical data has led to the ill conceived generalization that the weights of the blood, the major glands and other organs are proportional to the $2/3$ power of body weight or to the surface area. Logical application of this generalization can lead to absurd results.

c. The theory relating the surface law to an allegedly genetically fixed constant oxygen requirement of the cells, has rather little value for a physiological interpretation of the surface law. This theory, moreover, is in opposition to the well known fact that the metabolic rate of animals is essentially affected by somatic conditions. Furthermore, the metabolic rates of genetically closely related homeotherms of different size differ more than do the metabolic rates of genetically very different homeotherms but with the same body size. Admittedly, the concepts of "genetically similar or different" may change in the future when the biochemistry of the gene is further developed.

4. Two of the five types of theories on surface law are basically sound, namely, the theory connecting metabolic rate with rate of heat transfer and the theory relating metabolic rate to blood circulation. These theories may be integrated into one as follows: *In natural selection, those animals prove to be better fit whose rate of oxygen consumption is regulated so as to permit the more efficient temperature regulation as well as the more efficient transport of oxygen and nutrients.*

5. This theory does not postulate a strict proportionality between the area of a "true" body surface and metabolic rate. Body surface area has been used in very valuable work on animal heat exchange (Rubner, 1902; Deighton, 1933; Winslow et al., 1934-39; Burton, 1934; DuBois, 1937; Hardy and DuBois, 1938). As a basis for comparing metabolic rates of large and small animals, however, body surface area is not well enough defined. The use of an ever increasing variety of surface areas, even for the same species of animals, has led to an unnecessary and deplorable state of vagueness in comparative physiology of metabolism.

6. Relatively recent results on homeotherms, ranging from mice to cattle, indicate that the metabolic rate per unit of the surface area is greater the larger the animal. A linear correlation between the logarithm of metabolic rate and the logarithm of body weight shows that metabolic rate is proportional to a given power function of body weight. The metabolic rate divided by the $3/4$ power of body weight is independent of body size.

7. The $3/4$ power of body weight is therefore recommended as representative of metabolic body size, and "kg.^{3/4}" chosen as the symbol for the unit. The body weight in kilograms, raised to the $3/4$ power, measures the metabolic body size of an animal in kg.^{3/4}.

8. The metabolic level of an animal may be characterized as the metabolic rate per kg.^{3/4}. Under standard conditions the metabolic level of adult homeotherms, from mice to cattle, averages 70 kcal. per kg.^{3/4} per day or about 3 kcal per kg.^{3/4} per hour.

9. At present there seems to be no sufficient reason against the intraspecific application of the $3/4$ power rule of metabolic rate. Modulating factors for age and specific stature may be incorporated into prediction equations for human metabolic rate based on the $3/4$ power rule. Such equations are preferable to the irrational regression formulas of Harris and Benedict, and they avoid the connection with the ill defined body surface involved in the Du Bois prediction.

10. The unit of metabolic body size is useful for expressing levels of food intake and of animal production, it is a sound basis for comparing food capacity and production capacity of animals that differ in body size. Relative food capacity (maximum rate of food intake per $\text{kg}^{3/4}$) and relative production capacity (maximum rate of production per $\text{kg}^{3/4}$) should be among the most important criteria for selecting efficient food utilizers. The metabolic body size may also be useful in estimating dosage of biotics.

11. When the concepts concerned with the relationship of body size and metabolic rate are clarified, and when not only the methods of measurement, but also those of reporting the data are sufficiently standardized, then comparative physiology of metabolism will be of great help in the efforts to solve one of the most interesting and intricate problems of biology, the regulation of the rate of cell metabolism.

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