which the author was to present it, experts and those with varying degrees of knowledge could master the main points of the thesis. They would thus be prepared to join in, or to listen to, a debate which would certainly be a real contribution to the progress of knowledge.—The London *Times*.

SPECIAL ARTICLES

ON THE LAW OF SURFACE AREA IN ENERGY METABOLISM[1]

THE generalization that heat production in animals is proportional to the surface of the animal body rather than the weight of the body was first hinted at by French writers before the middle of the last century. It was formulated rather definitely by Bergmann in 1848 and was first placed on a definite footing of fact almost simultaneously by Rubner in Germany and by Richet in France in 1885. This so-called law of surface area has been quite generally accepted and has contributed much to the understanding of metabolism which we now have.

Recently this law has been submitted to severe criticism by F. G. Benedict and his colleagues[2] and the conclusion has been reached that surface area is little or no better as a measure of metabolism than is body weight. The purpose of the present communication is to direct attention to some natural limitations of the law of surface area which seem to have been overlooked by these critics. Harris and Benedict have rendered a service to the science of metabolism and nutrition by calling attention to the fact that since surface is usually expressed as a quantity in which two thirds power of the weight enters as a factor it must of necessity be less variable than the weight. As a matter of fact the mathematical relationship does not stop here; for in many instances the constant employed in the formula, for example, of Meeh or of Lissauer, by which the two thirds power of the weight is multiplied, equalizes the proportions between surfaces and weights. A few illustrations will make this clear. Suppose, for example, we have two infants weighing 7 and 8 kilograms respectively. Expressing their weights in grams and their surfaces in sq. cm. by the Meeh and Lissauer formulæ, we have the proportions shown in the first line of the following table. The ratio of weights is .88 : 1 and of surfaces .91 : 1. Now it is obvious that if the metabolism of these two children is proportional to their weights it must of necessity also be nearly proportional to surface. With two youths weighing 40 and 41 kilos the surfaces bear to each other exactly the same ratio as the weights, whether the Meeh or Lissauer formula be employed. Both, therefore, will be equally good measures of metabolism for the two individuals. The "discovery" that surface is no better as a measure of metabolism, than weight *as between individuals of nearly the same weight* could, therefore, have been made with paper and pencil.

TABLE I.

Relation of Body Weights and Surfaces to Each Other

Weight Gm.	Ratio	Meeh-Rubner $11.9\sqrt[3]{(w)^2}$		Lissauer $10.3\sqrt[3]{(w)^2}$	
		Surface sq. cm.	Ratio	Surface sq. cm.	Ratio
7,000		4,354		3,769	
8,000	0.88	4,760	0.91	4,120	0.91
20 kgm...		0.8768 sq. m.		0.7589 sq. m.	
21 kgm...	0.95	0.9058	0.97	0.7840	0.97
40 kgm...		1.3920 sq. m.		1.205	
41 kgm...	0.98	1.4150	0.98 +	1.225	0.98 +
4 kgm...		0.299		0.259	
40 kgm...	0.10	1.3920	0.210	1.205	0.21
3.5 kgm...		0.274		0.237	
70 kgm...	0.05	2.021	0.135	1.750	0.136

[1] Abridged from an address delivered before the Yorkville Medical Society, New York City, March 21, 1921.

[2] Harris, J. A., and Benedict, F. G., "A Biometric Study of Basal Metabolism in Man," Carnegie Inst. of Washington, Publ. No. 279, Washington, 1919; Benedict, F. G., and Talbot, F. B., "Metabolism and Growth from Birth to Puberty," Carnegie Inst. of Washington, Publ. No. 302, Washington, 1921.

Contrast with this the relationship between individuals weighing 4 and 40 kilograms, or still better, an infant weighing $3\frac{1}{2}$ kilograms and a man weighing 70 kilograms. The weights are to each other as .05 to 1, and the surfaces as .135 to 1. In other words, the weight of the larger individual is twenty times that of the smaller, while the surface is a little over seven times that of the smaller. In this case the weight and surface can not possibly be of equal value as measures of the metabolism. One is nearly three times as good (or as bad) as the other. As a matter of fact it is now well known that surface is about two and one half times as good a measure as weight between two such individuals.

In the judgment of the writer it is incorrect to suppose that physiologists have believed the metabolism to be absolutely proportional to surface, regardless of circumstances. Rubner for the German literature and Richet for the French are responsible for the first demonstrations of the applicability of the law. Rubner worked with dogs of adult stature but widely different size, estimating their metabolism by the indirect method. Richet worked first with rabbits ranging from 2,000 to 3,500 grams in weight but he determined only the heat of radiation and conduction, neglecting, as nearly all subsequent French observers have done, the heat given off by evaporation. Naturally his quantities would be more nearly proportional to surface than the total. However, in the estimation of surfaces he says,

If one supposes that animals of different size are like spheres of different volumes, then the respective volumes are related among themselves as the cubes of their radii; while the respective surfaces are related among themselves as the squares of their radii. These considerations apply to living animals, and, since their form is so irregular compared with that of a perfect sphere, one can only apply the geometrical facts to them approximately.[2]

Further in summing up the factors which determine heat production Richet notes that one of these is "the nature of the integument." In two important respects, therefore, Richet made saving clauses regarding the application of the law of surface, one concerning the measurement of surface and the other concerning the nature of the skin, meaning, of course, its conducting properties. Rubner in the beginning considered that he had demonstrated the law only for adult animals and later in applying it to children made this very emphatic reservation:

The law of surface area holds under all physiological conditions of life, but for its proof it is a reasonable presumption that only organisms of similar physiological capacities, as regards nutrition, climatic influences, temperament,[3] and functional power, should be compared.[4]

Other students of metabolism have made similar reservations. Thus Schlossman says,

The presumption is on the one hand that the environment is relatively normal, on the other that the child has a relatively normal surface, that is, a functioning and good conducting skin with the normal amount of subcutaneous fat.[5]

Otherwise, he thinks, the law could not be expected to apply.

One other point of some importance may be mentioned in this connection. There has been much discussion regarding the formula which should be used to express the body surface of infants. Rubner and Huebner modified the old formula of Meeh changing the constant from 12.3 to 11.9. Later Lissauer, from the measurements of a group of infants most of whom were distinctly undernourished, found the constant 10.3 to be more exact. Then came the formula of Howland and Dana of the $y = mx + b$ form, and still more recently the height-weight formula and the linear formula of DuBois, the latter similar to one previously devised by Roussy and first applied to infants

[2] Richet, Ch., "Recherches de Calorimetrie," *Arch. de Physiol. norm. et path.*, 1885, 3d ser., VI., 237.

[3] Misquoted as "temperature" by Harris and Benedict, loc. cit., p. 196.

[4] Rubner, M., "Ernährungsvorgänge beim Wachstum des Kindes," *Arch. f. Hyg.*, 1908, LXVI., 89.

[5] Schlossmann, A., "Atrophie und respiratorischer Stoffwechsel," *Zeitschr. f. Kinderheilk.*, Orig., 1912–13, V., 227.

by Variot and Lavialle. Benedict and Talbot have recently shown that the linear formula of DuBois gives results very nearly the same as the formula of Lissauer with a somewhat variable constant. Which of these formulæ is most nearly correct for body surface can only be determined by a statistical study of a large number of cases. However, if one of them is clearly superior to the others as a measure of heat production it should appear in the coefficients of correlation between heat production and surface as measured by the several formulæ. Harris and Benedict include in their statistical studies the basal metabolism of a series of 94 newborn infants, previously published by Benedict and Talbot. They did not, however, carry the analyses so far as to determine which formula gives the closer correlation with heat production. I have taken the trouble to work out the coefficients of variability and of correlation for the Boston series of 94 newborns using four different formulæ. They are given below.

TABLE II

Coefficients for the Minimal Metabolism of Newborn Infants (According to the data of Benedict and Talbot)

Coefficients of Variability	Coefficients of Correlation
$Vh = 15.37 \pm 0.79$	
$Vw = 14.68 \pm 0.72$	$Phw = 0.7530 \pm 0.0205$
$Vs_M = 9.92 \pm 0.48$	$Phs_M = 0.7672 \pm 0.0202$
$Vs_L = 10.08 \pm 0.49$	$Phs_L = 0.7762 \pm 0.0195$
$Vs_H = 10.25 \pm 0.50$	$Phs_H = 0.7677 \pm 0.0202$
$Vs_D = 8.84 \pm 0.43$	$Phs_D = 0.7682 \pm 0.0202$

$V_h =$ Coefficient of variability of heat production, V_w of weight; etc. $s_M =$ Surface by Meeh-Rubner formula ($s = 11.9 \sqrt[3]{(w)^2}$); $s_L =$ Surface by Lissauer's formula, ($s = 10.3 \sqrt[3]{(w)^2}$); $S_H =$ Surface by Howland and Dana formula ($y = mx + b$, where x is body weight, m represents a constant 0.483 and b represents 730 sq. cm.); $S_D =$ Surface by weight-height formula of DuBois and DuBois ($s = \text{wt.}^{0.425} \times \text{ht.}^{0.725} \times 71.84$).

There are two surprises in this table: one, that heat production as determined by Benedict and Talbot is more variable than either body weight or body surface, no matter by which formula it is measured; and the other, that it makes very little difference which formula is used for body surface so far as correlation with heat production is concerned. The formula of Howland and Dana gives the most variable body surface; the height-weight formula of DuBois, which has never been confirmed for infants, gives the least variable. But the formula of Lissauer gives a body surface which parallels the metabolism *slightly* better than the others, the difference, however, being altogether negligible. Taking the entire group of newborns in this series we may conclude that the sleeping metabolism, which is practically the whole of metabolism in the newborn, is as well measured by one formula as another; also that surface by any formula is but slightly better than body weight as a measure.

We must distinguish clearly the arguments against the law of surface as of two classes: (1) on the basis of fact and (2) on the basis of explanation. The arguments against the law, so far as they rest upon facts, seem, as we have just seen, to have been misconceived. It never was supposed by its chief proponents that the law would apply to all physiological and pathological conditions but only to similar physiological (normal) conditions. Also, a very superficial understanding of the necessary mathematical relations shows that the law has natural limitations which must be recognized if one is to avoid compromising it with impossible conditions.

There is no doubt that Rubner, following Bergmann, first conceived of the law as casually related to Newton's law of cooling. This dependence as commonly accepted may be phrased in this way. Solid bodies when warmed lose heat in proportion to the difference between the temperature of the body and the temperature of the surrounding medium. Since this heat must all pass through the surface it follows, other things equal, that they will lose heat for any particular gradient of temperature in proportion to surface. As applied to the animal body it is observed that the body temperature is *nearly* constant. Hence, if heat is lost in proportion to surface, it must also be produced in proportion to surface. This implies a causal relationship between surface loss and interior production of heat. It is this causal relationship to which Benedict and Talbot in their latest publication make objection. They say,

> As the result of the critique of the body surface law presented by Harris and Benedict, we believe that the accurate measurements of body surface made possible by DuBois may legitimately be used in a manner heretofore never practicable in metabolism experiments, provided that they are considered as physical measurements and with no erroneous conception as to the existence of a causal relationship between surface area and heat elimination.[6]

Nevertheless they compute many of their measurements by the Lissauer formula and find that many others as given by the DuBois linear measurements agree with the Lissauer formula provided a "constant" varying from 10.0 for infants up to 6 kgm. to 11.5 for youths between 25 and 40 kgm. is used. How the use of a physical measurement instead of a formula which agrees with the physical measurement improves matters it is difficult to see. The elaborate biometric analysis of Harris and Benedict has proved nothing more regarding the causal relationship than is proved by the simple mathematical analysis shown in Table I. Whatever the physical measurement of surface, if it can be expressed even approximately by a formula such as Lissauer's, it will follow that the ratio of body weights for certain ranges will be the same as the ratio of body surfaces *provided the weights are not far apart,* and for subjects of a continuous series in which weights differ by small increments it will follow that surface will be only a little, if any, better as a measure of metabolism than weight.

The question of causal relationship stands just where it always has stood. If the possession of a large surface in proportion to weight, as in a mouse, is accompanied by a vastly higher heat production per unit of weight as compared with a horse, but the heat production is found to be proportional to the surfaces of two such animals with approximately the same body temperature, it seems to follow that surface loss of heat is at least a more probable *cause* of heat production than body mass. The same is true as between a baby and a man. How else are such facts to be explained?

[6] Benedict and Talbot, *loc. cit.*, p. 159.

A word as to the teleological aspect of the case. Since heat production of animals seems to be proportional to surface area, it would seem to follow that heat is produced *in order to* replace that which is lost, or *to maintain* body temperature. This view some say, denotes an all too naïve conception of nature. Blood does not coagulate in order to prevent hemorrhage, but because certain chemical agents are present and certain properties. The fact that it does stop hemorrhage is quite incidental. It may have selective value, so that a species whose blood did not clot would have the worst of it in the struggle for existence, but it will never do to say that this chemical-physiological function originated for the purpose of preventing hemorrhage; for that would imply a mind at work in anticipation of the result. So also with heat production. These critics, of whom Kassowitz has been chief, prefer to account for heat production in a perfectly causal manner.

> Small animals maintain a higher rate of oxidation, it is true, than large ones, but this is not because they lose heat more rapidly in consequence of greater (relative) surface, but because their alternating movements (later phases caused reflexly by earlier phases) follow one another more rapidly on account of shorter nerve paths.[7]

Kassowitz indeed finds that the higher rate of oxidation in small, warm-blooded animals has even for them "dysteleological consequences; for because of the more extensive muscular contractions more food and reserve substances are placed in requisition and by this means the deposit of reserve fat in the whole body, and especially in the subcutaneous tissues, is made more difficult, so that the protection against cooling—which a thick layer of fat prevents—fails in part amongst the very animals which need it most."[8] Even

[7] Kassowitz, M., "Allgemeine Biologie," 1904, Chap. XXV., par. 40.

[8] Kassowitz, M., "Der grossere Stoffverbrauch der Kinder," *Zeitschr. f. Kinderheilk.*, 1913, VI., 247.

Kassowitz is obliged to admit, however, that "in warm-blooded animals which are in a position to maintain their own body temperature under the most diverse conditions, one can claim the appearance of some justification that their living parts produce heat in order to protect the body against loss by radiation, etc."[9]

Whether this is a real justification or only the appearance of one will not trouble the practical physiologist so long as the generalization that human beings of different size produce heat in proportion to surface rather than weight, and therefore, require food energy in this proportion, helps him to understand his feeding problems; and there is no doubt that the law of surface area has been immensely useful in this connection. It explains the much higher basal metabolism per unit of weight of the small individual in comparison with the large better than the so-called causal explanation cited by Kassowitz. It explains also much better the need for conservation of heat in the infant, and the role which subcutaneous fat plays in this connection.

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[9] Kassowitz, M., *ibid.*, p. 240.

ON THE SIGNIFICNACE OF AN EXPERIMENTAL DIFFERENCE, WITH A PROBABILITY TABLE FOR LARGE DEVIATIONS

THE results of experiments from which scientific conclusions are drawn always constitute a sample, limited in number, of a potentially unlimited universe. The argument is always from the limited number to the infinite number, and assumes that the sample is representative of the universe. This is a priori not necessarily true, which is proven in the fact that two sets of measurements of supposedly the same quantity never agree in any absolute sense, that they may disagree widely, and that they therefore have to be qualified by a measure of their precision, which is derived from the magnitude of the mutual disagreement of the individual measurements of the same set.

This fact becomes of trying significance in many biological measurements. We may make two sets of measurements, A and B, under conditions alike except for one experimentally varied factor, and find that although their means show an apparently definite difference, many of the measurements A lie beyond the mean of B, and vice versa. It may be that a plot of the aggregate of the two distributions shows little or no bimodality corresponding to the difference in the respective conditions of A and B.

The usual mode of procedure in such a case is, first, to compute the measure of precision of the difference of the two means, according to the formula:

$$\sigma_\Delta = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}},$$

where Δ is the difference between the arithmetic means $(M_1 - M_2)$, σ_Δ its standard deviation, σ_1 and σ_2 are the standard deviations[1] of the two distributions A and B, respectively, and N_1 and N_2 are the respective numbers of measurements.

Then the probability, P, of a deviation lying within the limits $\pm\Delta$, in a normal distribution of standard deviation σ_Δ, is found from the table.[2] The complement of this, $1 - P$, is the probability of such a deviation lying outside the limits $\pm\Delta$.

The accompanying probability table was computed by the writer for deviations higher than those included within the range of most such tables extant, with a view to giving values of P much nearer to unity than usual. An approximate method of computation was used. While the computation of values of

$$\int_0^x e^{-x^2} dx$$

[1] This assumes that

$$\sigma_1 = \sqrt{\frac{\Sigma\delta_1^2}{N_1 - 1}}.$$

Where N_1 is large the error due to the use of N_1 instead of $(N_1 - 1)$ tends to become negligible.

[2] Such as Table IV., pp. 119–125, Davenport, "Statistical Methods," third edition, New York; or Table 24 or Table 25, Smithsonian Physical Tables, Seventh Edition, Washington, 1920.