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Scaling of respiratory variables in mammals[1, 2]

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Stahl, Walter R. *Scaling of respiratory variables in mammals.* J. Appl. Physiol. 22(3): 453–460. 1967.—Data have been collected from the literature on respiratory variables and correlated against body weight on the assumption of log-log relationships (allometry) with the use of computer regression analysis. Statistically validated power law formulas, with correlation coefficients of 0.99–0.90, are presented for lung weight, VC, TLC, FRC, V_T, V_D, $\dot{V}_{O_2}$, $\dot{V}_E$, f, C_L, $D_{L_{CO}}$, $D_{L_{O_2}}$, total respiratory flow resistance, work per breath, and several nonrespiratory parameters. The study deals principally with the rat-human size range, but the prediction formulas probably cover mice to steer and possibly all mammals. Predicted and observed values are compared for the rat, cat, dog, and man; good agreement is demonstrated. Size-independent dimensionless and dimensional respiratory invariants or "design parameters" may be obtained by forming simple and complex quotients from the individual power laws that have net residual mass exponents (dependency on body weight) approaching zero.

respiratory scaling laws; respiratory allometry; body size and respiratory variables; respiratory dimensional constants

Mammals occur in the size range of 2.5-g shrews to 150-metric-ton blue whales, which represents a weight increase of roughly 70 million. In spite of this enormous variation in weight the heart, lungs, kidneys and other major organs of mammals show much similarity in morphology and function. The 1- to 2-g heart of a rat and 100-kg heart of a medium-sized whale look surprisingly alike except for size. Integrated scaling of physical variables is a necessity for function of the mammalian system over any substantial changes in body weight. This study deals with the scaling laws or power law prediction formulas for basic respiratory variables.

In a series of previous reports the author (54, 57) explored the application of engineering dimensional analysis or physical analogue theory in physiology. By canceling statistically fitted power law prediction formulas for various physiological parameters it is possible to obtain dimensional constants and dimensionless "design criteria" which characterize integrated mammalian physiology. It follows that lungs in small and large mammals are physically similar systems or physical analogues of each other, as this concept is used in dimensional analysis theory. The reduction of data to size-independent form also makes possible the systematic comparison of respiratory function in different sizes and species of mammals.

METHODS

Data were collected from standard physiological journals, handbooks, etc., checked for units consistency and general validity, and key punched for computer processing. Handbooks examined include those edited by Spector (27), Dittmer and Grebe (3), Altman and Dittmer (7, 8), and Fenn and Rahn (22, 23). Major sets of comparative respiratory data are provided by Crosfill and Widdicombe (17), Agostoni, Thimm, and Fenn (2), and Radford (50). Power law formulas for respiratory parameters have been discussed previously by Brody (10), Adolph (1), Guyton (25), Gunther and Guerra (24), Drorbaugh (18), Bartels (5), Kleinman and Radford (34), and Tenney and Remmers (59). Specific reports were also used, containing data on the rat (38, 39, 43), cat (6, 11, 19, 22, 31, 37, 44–46, 52), dog (3, 12, 13, 16, 29, 33, 36, 40, 41, 49, 53, 58), goats and sheep (3, 4, 26), and steer and horses (10, 23). Normal human values are given by Comroe et al. (14). The majority of data points are from a comparatively small number of reports by experienced respiratory physiologists who did repeated determinations on groups of animals.

Statistical analysis was performed on a SDS-920 computer (with the assistance of D. L. Lindgren and D. Williams). The data were transformed to base 10 logs and then fitted by a conventional least-squares regression analysis, to yield the parameters in the "allometric" formula $x = aM^b$, with x = any variable and M = mass or body weight in kilograms. The parameter a is the actual value of the variable for a 1-kg "standard animal" while b is the slope on a log-log graph. The most informative statistical measures were taken to be the correlation coefficient (r), 95% confidence limits for

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TABLE 1. *Power law prediction parameters for respiratory variables in mammals**

Variable, Units	*a*	*b*	*r*	N	s_a	S_a	s_b
Total lung wt, g†	11.3	0.99	0.96	>100	~15	50	0.02
Total lung cap, ml	53.5	1.06	0.98	333	14	40	0.02
Vital cap, ml	56.7	1.03	0.99	315	11	19	0.01
Funct resid cap, ml	24.1	1.13	0.97	261	24	45	0.03
Tidal vol, ml	7.69	1.04	0.99	688	7	45	0.01
Dead space, ml	2.76	0.96	0.95	52	59	42	0.09
Resp rate, min^{-1}	53.5	−0.26	−0.91	692	6	40	0.01
Minute vol ml/min	379	0.80	0.98	691	7	45	0.01
Oxygen uptake, ml/min	11.6	0.76	0.98	349	11	30	0.01
Lung compliance, ml/cm H_2O	2.10	1.08	0.98	286	15	32	0.02
Thoracic compliance, ml/cm H_2O	4.52	0.86	0.98	60	31	38	0.05
Total compliance, ml/cm H_2O	1.56	1.04	0.99	114	21	36	0.03
Total airway resist, cm H_2O/(liter/sec)	24.4	−0.70	−0.96	137	25	38	0.04
Work/breath, g-cm	17.1	1.08	0.99	68	25	47	0.04
Power of breathing, g-cm/min	962	0.78	0.98	89	22	40	0.03
Diffusing cap-CO, ml/min per mm Hg	0.22	1.14	0.96	258	29	44	0.04
Diffusing cap O_2, ml/min per mm Hg	0.16	1.18	0.98	58	39	21	0.05
Total blood vol, ml	65.6	1.02	0.995	840	5	34	0.01
Heart wt, g‡	5.8	0.98	0.99	>200	10–15	41	0.01
Cardiac output, ml/min	187	0.81	0.98	568	7	31	0.01
Cardiac rate, min^{-1}	241	−0.25	−0.88	447	9	34	0.02
Body area, m^2	0.11	0.65	>0.95	>100	10–20	~30	0.04

* Statistical fit of $x = aM^b$, M in kg; r = correlation coefficient; N = total data points; s_a = 95% confidence limits of a in percent; S_a = mean (±) standard error of the estimate of a in percent; s_b = 95% confidence limits on b in slope units from mean slope value. † Modified from Brody (10). ‡ From Stahl (56).

repeated lines fits (s_a and s_b), and the standard error of the estimate (S_a), which has much the same significance for a regression line as a standard deviation for a mean, i.e., 2 S_a limits should include 95% of cases. With log-log analysis $+S_a$ and $-S_a$ differ slightly (see figures); a mean of the two values is shown in the tables for purposes of simplicity.

As seen from Table 1, over 250 data points were found for many variables, with greater than 600 for tidal volume, minute volume, and blood volume. In order to prevent excessive bias towards human values the generally accepted means for humans were weighted as 20–50 data points, depending on the total number of nonhuman values. The number of data points, N, shown in Table 1 is the summation of individual measurements plus one-half of the number of determinations entering mean values used in the correlation. This is an arbitrary but conservative means for summing means and single data values; more complex statistical techniques were not attempted because necessary statistics are not given with most published means. A computer program was also written for predicting expected ranges of variables from the values and standard errors of the *a* and *b* coefficients.

RESULTS

Table 1 presents the power law (allometric) coefficients for respiratory variables. Figs. 1–4 are representative graphs of the data which demonstrate that the line fits are generally satisfactory. The data in Table 1 are notable for high *r* values and narrow 95% confidence limits (s_a and s_b), even in the case of variables on which there is limited data, e.g., $D_{L_{O_2}}$.

Table 2 contains systematic predictions of 10 respiratory variables for the rat, cat, dog, and man. The value shown is a range based on simultaneous 1 standard error limits of the *a* and *b* coefficients. This table reveals surprisingly good agreement of predicted and observed values; even better results can be obtained if the specific weights of animals are used in the formulas rather than an over-all mean species figure. It should be noted that for an individual species such as the cat or dog the experimental results often differ among themselves by 100% or more because of experimental error or animal variations. The formulas also give reasonable order of magnitude estimates for basic respiratory variables in kangaroos (42) and giraffes (51), although these animals are probably too specialized to fit precisely on the "normal mammalian" prediction lines. Good results have also been obtained in prediction of values in the rhesus monkey. Studies on smaller groups of animals and during growth of individual species often give less satisfactory correlations; the power laws arising in maturation are usually not the same as, but comparable to, those found in adult size-change comparisons.

The validity of the computed power law formulas is also confirmed by comparisons with previously published estimates of respiratory allometric coefficients, such as those of Guyton (25), Drorbaugh (18), and Tenney and Remmers (59). For example, in a report from 1947 Guyton found V_T (ml) = 7.4 $M^{1.00}$, while the new value is V_T (ml) = 7.69 $M^{1.04}$; Drorbaugh (18) obtained VC (ml) = 63 $M^{1.00}$, with the new formula: VC (ml) = 56.7 $M^{1.03}$. This author also reported a formula for compliance (ml/cm H_2O) = 1.21 $M^{1.00}$; Table 1 yields the formula, compliance (ml/cm H_2O) = 1.56 $M^{1.04}$. The prior allometric estimates were given without necessary statistical limits, but the old and new regression formulas agree within ± 10% in several cases.

Tables 3 and 4 illustrate what the author (54–56) has called the "allometric cancellation" technique and applied to a wide variety of physiological and somatic allometric prediction formulas. Consider, for example, the power laws VC (ml) = 56.7 $M^{1.03}$ and blood volume (ml) = 65.6 $M^{1.02}$ (M in kg), which were computed independently using 315 and 840 data points, respectively. The quotient:

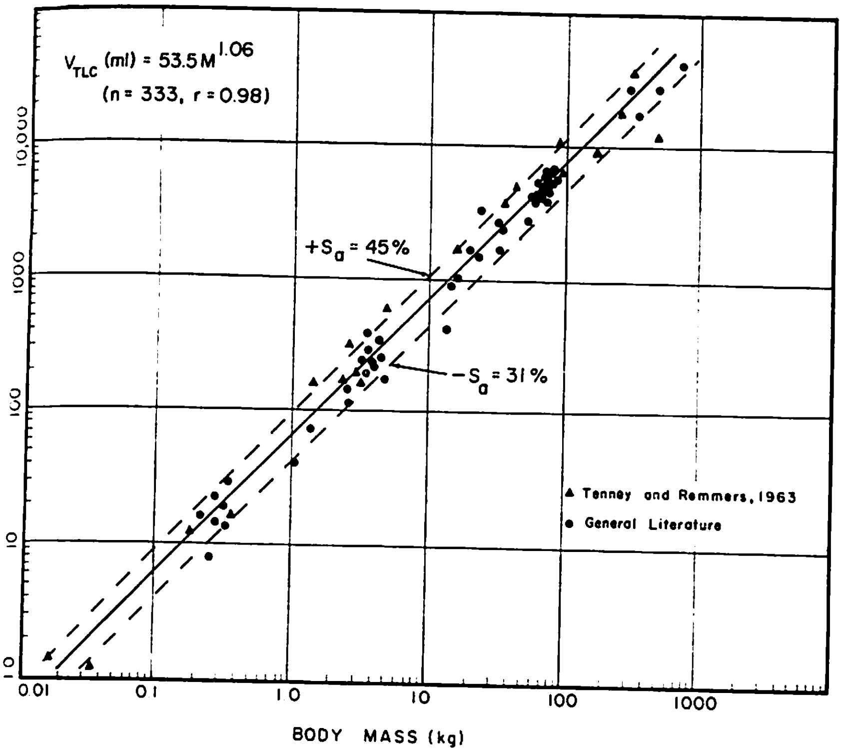

FIG. 1. Allometry of total lung capacity in mammals from the mouse to cattle and steer. Most of the points are mean values. Dashed lines indicate 1 standard error of the estimate.

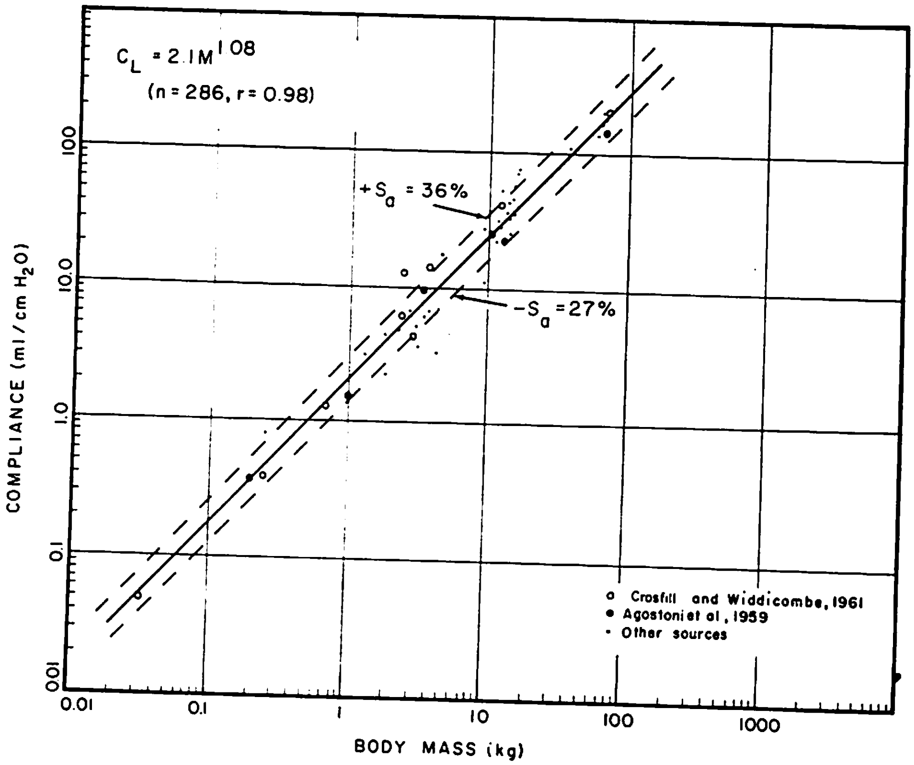

FIG. 2. Allometry of lung com- ance The larger points are often an values, with smaller ones in- dual measurements from a variety eports. The dashed lines indicate 1 dard error of the estimate.

$$\frac{\text{vital capacity}}{\text{blood volume}} = \frac{56.7\,M^{1.03}}{65.6\,M^{1.02}} = 0.85\,M^{0.01}$$

is a residual mass index (RMI) of only 0.01 slope units, hich is not different from zero on the basis of the statistical slope limits for VC and BV given in Table 1. Any number to the zero power equals unity, so for all values of M in kilograms the VC/BV ratio is invariant of size on the basis of available data. The expected accuracy of the quotients in Tables 3 and 4 depends on

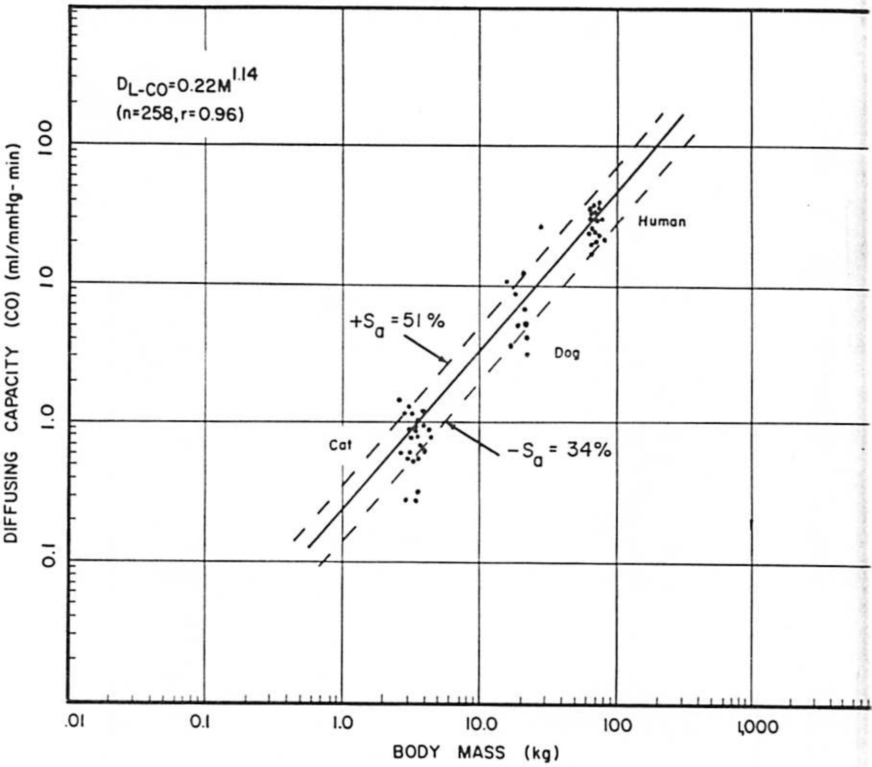

FIG. 3. Allometry of carbon monoxide diffusing capacity. Most of the points are individual determinations for the cat, dog, and man, from sources cited in the text. The dashed lines indicate 1 standard error of the estimate.

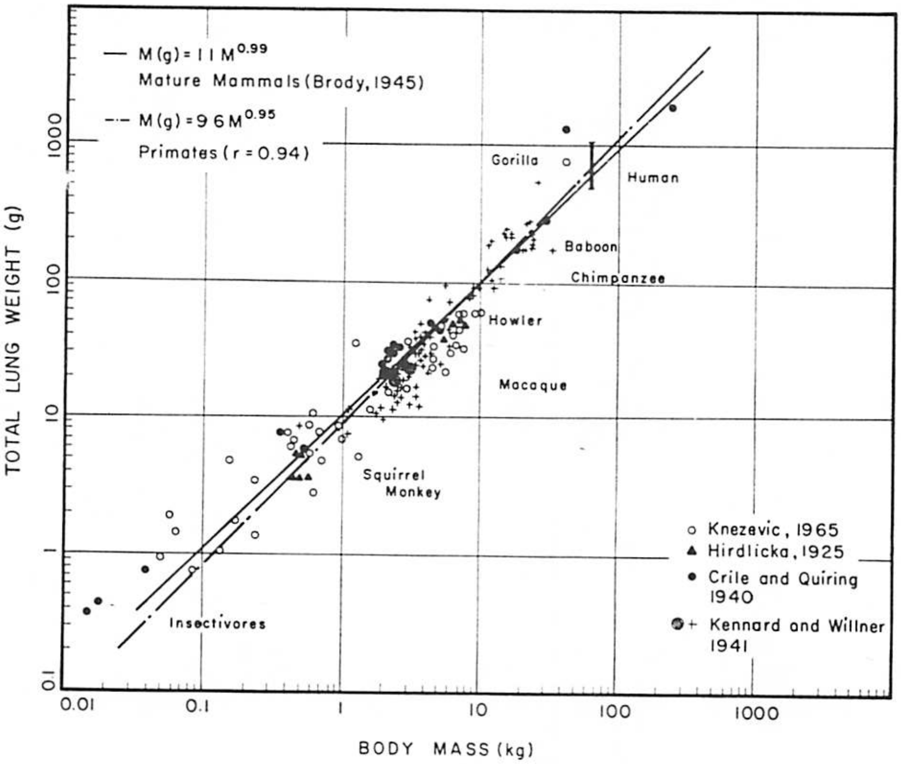

FIG. 4. Allometry of lung weigh The data points are for primates rangin in size from about 0.2 to 100 kg, wit some data also on the tree shrew, whic is an insectivore related to primates. line previously computed for mamma in the mouse-elephant range nearl overlaps the new one for primate From Stahl (56), which gives citatio for additional sources shown on figure.

the standard errors of their components and is approximately ±15 to ±50 for various constants. The last two entries in Table 4 are composed of three variables, yielding dimensionless group with RMI's of −0.02 and 0.08, respectively, both within statistical limits of zero.

For respiratory variables RMI values below 0.08 ar probably not significant but several values above 0.1 in Tables 3 and 4 suggest a systematic small "size effect" on the dimensional constant or dimensionless proportio in question. For example, $D_{L_{CO}}$ per unit of lung weigh

TABLE 2. *Predicted and observed basal values of respiratory variables in common mammals**

Animal	TLC	FRC	V_T	V_D	f	$\dot{V}_E$	C_L	R	$D_{L_{CO}}$	W_{BR}
Predicted	7–17	3–7	1.0–2.7	0.38–1.2	45–105	0.07–0.18	0.31–0.64	38–93	0.02–0.07	217–470
Reported	8–11	1–2	1.5–1.8		97–115	0.16–0.24	0.3–0.6	71–119		250–1,000
References	2, 43	17	27, 39		17, 39	17, 39	17, 50	17		17
Predicted	130–300	58–160	16–44	5–15	22–52	0.6–1.6	5–12	6–14	0.5–1.5	1,500–3,900
Reported	130–260	66–145	25–34	5–16	26–30	0.3–1.0	5–15	8–20	0.7–1.2	1,300–2,900
References	2, 37	6, 17	17, 45	31, 46	2, 7	17, 31	45, 50	19	31, 37	17
Predicted	550–1,400	270–800	69–192	17–67	15–37	1,800–4,900	25–54	2.1–5.6	2.4–7.7	4,500–12,000
Reported	900–1,000	250–600	140–260	70–100	18–26	2,000–6,000	30–75	0.6–3.7	1.7–10	2,200–9,500
References	2	16, 50	16, 17	2, 40	7, 16	40, 58	40, 50	17, 40	49, 58	17
Predicted	2,700–7,300	1,500–4,700	330–970	67–330	10–25	6,000–17,000	130–290	0.7–2.0	13–47	15,000–44,000
Reported	5,000–6,000	2,400–3,700	400–500	150	11–22	6,000–7,000	125–200	0.9–1.9	17–50	30,000–50,000
References	2, 14	14, 50	14, 17	14	7, 14	14, 17	14, 50	14, 17	14, 21	14, 17

The reported range is usually the total range from one or more references. * Predicted values for 0.25-kg rat, 3.7-kg cat, 15.0-kg dog, 70.0-kg man, shown with estimated 1 standard error limits based both on slope and intercept values. TLC = total lung capacity (ml): FRC = functional residual capacity (ml); V_T = tidal volume (ml); V_D = dead space (ml); f = frequency of respiration (min^{-1}); $\dot{V}_E$ = minute volume (ml/min); C_L = lung compliance (ml/cm H_2O); R = flow resistance (cm H_2O/(liters/sec); $D_{L_{CO}}$ = diffusing capacity CO (ml/mm Hg per min); W_{BR} = power of breathing (g-cm/min).

creases slowly with size, which is not unexpected because of probable changes in proportions of the airways and lung parenchyma during adult size increase. The general applicability of the respiratory constants, which presumably apply to any "typical" mammals, can also be verified by comparison with specific animal findings. The over-all mammalian value of VC/body wt is 57 ml/kg and does not differ in a statistically significant manner from the TLC figure of 53.5 ml/kg on the basis of data in Table 1. Agostoni, Thimm, and Fenn (2) studied VC in a variety of animals, finding values of [illegible] ml/kg in the guinea pig or rabbit and 80–100 ml/kg in the cat and dog, but with an over-all mean in the 50–60 ml/kg range. Cook et al. (16), working with dogs, found FRC/body wt = 32.9 ml/kg, while the predicted range using 1 standard error and the RMI of 0.13 shown in Table 1 is 27–43 ml/kg. The nominal value of V_T/body wt is 7.7 ml/kg, which agrees with animal data. The power law ratio FRC/TLC is 0.45, with a 0.07 RMI of borderline statistical significance. For human beings, Comroe et al. (14) and Briscoe (9) list FRC as 40–50% of TLC. A dead space-to-tidal volume (V_D/V_T) ratio of 0.3–0.4 is usually cited as normal for human beings or laboratory mammals (34), while the allometric quotient value is 0.36 with a RMI of −0.08 which is probably not significant.

The ratio $\dot{V}_E/\dot{V}_{O_2}$ is sometimes called the "ventilation index" and has a normal value for humans (14) of about 2. The power law quotient for this variable is 32.7 with a very low RMI. Proportions may also be formed among $\dot{Q}$, $\dot{V}_E$ and $\dot{V}_{O_2}$. The value of $\dot{V}_{O_2}/\dot{Q}$ from Table 1 is 0.062 (RMI = −0.05), which defines a mean whole-body arteriovenous oxygen extraction of 6.2 vol %, in reasonable agreement with reported data. The value of $\dot{V}_E/\dot{Q}$ is 2.03 (RMI = −0.01); figures of 1.0–2.0 are typical for human beings.

The same technique may be applied to more complex variables. The ratio of lung compliance over VC has a mean value of 0.037 (cm H_2O)$^{-1}$ or 37 ml/cm H_2O per liter (RMI = 0.06). Agostoni, Thimm, and Fenn (2) found 28–39 ml/cm H_2O per liter in a rat, cat, dog, and man series. Table 3 shows lung compliance per gram lung to be 0.18 ml/cm H_2O per g (RMI = 0.99). Crosfill and Widdicombe (17) report figures of 0.2–0.7 ml/cm H_2O per g in a mouse-man series. Cook, Helliesen, and Agathon (15) found quite similar values in growing children, though ordinarily it cannot be assumed that the scaling laws and constants obtained from adult mammalian comparisons will apply precisely to maturation data. In studies on dogs, Collier and Mead (13) normalized total compliance by body weight, obtaining figures of 1.6 ml/cm H_2O per kg. The predicted value is 1.56 ml/cm H_2O per kg (RMI = 0.04). However, other studies on dogs by Cook et al. (16) yielded 4.6 ml/cm H_2O per kg.

There are no known prior estimates of the scaling laws for diffusing capacity. The observed somatic indices of 1.14 for $D_{L_{CO}}$ and 1.18 for $D_{L_{O_2}}$ are in good agreement, suggesting that the somatic index of D_L is distinctly above unity; predictions for specific animals in Table 2 are in reasonable agreement with measurements. Table 3 shows $D_{L_{CO}}$/TLC to be 0.0041 ml/mm Hg per min per ml with a RMI of 0.08, which implies that D_L scales more closely as TLC than lung weight. In a study of cats, Lawson et al. (37) include data that makes $D_{L_{CO}}$/TLC equal 0.0039 ml/mm Hg per min per ml, while figures

TABLE 3. *Size-independent respiratory dimensional constants**

Quotient	Numerical Value	Residual Mass Index
Vital cap/Body wt	56.7 ml/kg	0.02
Tidal vol/Body wt	7.69 ml/kg	0.04
Vital cap/Lung wt	5.02 ml/g	0.03
Funct resid cap/Body wt	24.1 ml/kg	0.13
Minute vol/Body area	3.45 liters/m² per min	0.15
Oxygen consump/Body area	105 ml/m² per min	0.11
Lung compliance/Lung wt	0.18 ml/g-cm H_2O	0.09
Lung compliance/Vital cap	0.037 (cm H_2O)$^{-1}$	0.06
Lung compliance/Funct resid cap	0.087 (cm H_2O)$^{-1}$	−0.05
Minute vol × airway resist†	0.15 cm H_2O	0.10
Diffusing cap (CO)/Lung wt	0.019 ml/g per mm Hg per min	0.15
Diffusing cap (CO)/Total lung cap	0.0041 (mm Hg per min)$^{-1}$	0.08
Work per breath/Lung wt	1.51 g-cm/g	0.09
Power of breathing/Minute vol	2.54 g-cm/ml	−0.02

* Obtained by cancellation of power law formulas. The numerical value is an over-all normal mammalian mean; individual species may deviate by 50% or more, depending on physiological specialization or other factors. † In consistent liters/sec units.

TABLE 4. *Size-independent dimensionless respiratory variables**

Quotient	Numerical Value	Residual Mass Index
Lung wt/Heart wt	1.95	−0.02
Vital cap/Blood vol	0.87	0.01
Tidal vol/Total lung cap	0.14	−0.02
Dead space/Tidal vol	0.36	−0.08
Funct resid cap/Total lung cap	0.45	0.07
Heart rate/Resp rate	4.5	−0.01
Minute vol/Oxygen consump	32.7	0.04
Thoracic compliance/Lung compliance	2.16	−0.20
Tidal vol × resp freq/Minute vol	1.08	−0.02
Total compliance × resist†/Resp period	0.034	0.08

* Obtained by cancellation of power law formulas. The numerical value is an over-all normal mammalian mean; individual species may deviate by 50% or more, depending on physiological specialization or other factors. † In consistent ml/sec units.

for dogs from Burrows and Niden (12) are 0.004–0.014 ml/mm Hg per min per ml. In his thorough analysis of diffusing capacity in human beings, Forster (21) finds $D_{L_{CO}}$/TLC values of 0.0035 ml/mm Hg per min per ml. Rosenberg and Forster (52) normalized $D_{L_{CO}}$ by lung weight; their data (converted from dry to wet lung weight) are equivalent to 0.015–0.027 ml/mm Hg per min per g, while the predicted value of this parameter from Table 3 is 0.019 ml/mm Hg per min per g.

The final two entries in Table 4 each contain three component power formulas, but nonetheless have RMI's of −0.02 and 0.08, respectively, which is a rather impressive reduction of complex data. The first of these simply confirms the tautology $\dot{V}_E = \dot{V}_T \times f$ and should be unity by definition; the deduced value of the quotient is 1.06, within statistical limits of 1.00. This relationship was also shown in 1947 by Guyton (25). The second entry, namely, $C_L R$/respiratory period, with C_L and R in consistent units, may be understood as a ratio of a relaxation time (comparable to RC of electric circuit theory) to an actual period time. The low value of 0.034 is not surprising when it is noted that inspiration or expiration occupies only a portion of the breath cycle at rest and also that breathing rate may rise by 3–4 times. At maximal rate the ratio of relaxation time to inspiration or expiration time would be much closer to unity. Crosfill and Widdicombe (17) obtained values for the RC relaxation time in individual animals; log-log plotting of their data gives a somatic index in the range 0.25–0.33, in agreement with that for respiratory period obtained from the inverse of frequency

period is also implicit in the classical work of Otis, Fenn, and Rahn (47) on deduction of optimum or natural breathing frequencies.

DISCUSSION

Allometry or log-log plotting of physiological (or engineering) variables almost always gives good results if applied to a size range of 100 times or more; the shrew-elephant range is 50–60 million and mouse-steer range about 25,000. This is to be expected, since in almost any complex mechanical-chemical system, such as an internal combustion engine or mammal, there must exist a deterministic relationship between total system size and basic dimensional variables.

The comparative neglect of allometry by physiologists is evidently due in part to its name. In his well-known book Huxley (30) used allometry almost exclusively for somatic form analysis, which left the impression it was somehow peculiar to morphology. However, Brody (10) gave many examples of linearization of physiological variables by power law methods, most notably for metabolism, oxygen uptake, food intake, and nitrogen excretion rates. Metabolic and respiratory scaling was considered by Krogh (35) in connection with the surface law. Further progress was hampered however, by an insistence on the "even" somatic exponents $\frac{1}{3}$, $\frac{2}{3}$, $\frac{3}{4}$, and 1, due to what can now be seen as naive application of dimensional analysis. Books on dimensional theory by Duncan (20), Johnstone and Thring (32), and others show that nonintegral power laws of the type in Table 1 are commonly found in engineering, and particularly with analysis of data on models and systems of varying size.

In previous reports the author (54–56) suggested that dimensional constants and dimensionless numbers obtained by power law cancellation be interpreted as invariants or similarity criteria which define the normal "mammalian design." Dimensional constants, define ortions of mammals. Exactly the same sort of ning has been used for analysis of numerous logical artifacts. In the case of internal combustion s, for example, one finds that homology is defined e dimensional constants of fuel, air, metals, etc, pertinent similarity criteria include volume ratios, re ratios, flow ratios, thermodynamic combustion ria, temperature ratios, etc.

he log-log plotting technique tends to minimize idual species differences, which is desirable for an all prediction formula. Values found in detailed studies on individual animals may then be compared with predicted figures at a given weight, with the goal of demonstrating physiological specialization. The allometric coefficients and confidence limits of Table 1 can easily be further tested since they predict an unlimited number of specific values for respiratory variables. Interesting results would probably be obtained in studies of athletic versus pastoral mammals, cetaceans, high-altitude dwellers, and also in animals of more extreme weights, such as the mouse, horse, and possibly elephant or whale.

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