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Homeostasis and Heterostasis: from Invariant to Dimensionless Numbers*

BRUNO GÜNTHER[1], ENRIQUE MORGADO[2, 3], RAÚL F JIMÉNEZ[4]

[1] Professor Emeritus of Physiology and Physiopathology, Universidad de Concepción, Chile; Universidad de Valparaíso, Chile.
[2] Physiopathology Program, Faculty of Medical Sciences, Universidad de Santiago, Santiago, Chile.
[3] Physiopathology Program. Institute of Biomedical Science, Faculty of Medicine, Universidad de Chile, Santiago, Chile.
[4] Department of Mathematics, Faculty of Physical Science and Mathematics, Universidad de Concepción, Concepción, Chile.

ABSTRACT

In the present paper we have examined the applicability of dimensionless and invariant numbers (DN & IN) to the analysis of the cardiovascular system of mammals, whose functions were measured at standard metabolic conditions. The calculated IN did not change when we compared these figures with those obtained in dogs while they were submitted to graded exercise on a treadmill. In both instances, rest and exercise, the constancy of the IN prevailed, in accordance with Cannon's principle of "homeostasis" (1929). On the contrary, when dogs were examined during a standardized hypovolemic shock, we observed a breakdown of the IN, and the resulting DN evolved as a reliable index of the condition of "heterostasis" as defined by H. Selye. The robustness of the homeostatic regulations is based on high-gain integral feedback mechanisms, while "heterostasis" could be associated with low-gain integral feedback processes, when organisms are submitted to unitary step disturbances or to changes of the set-point at the entrance of the feedback loop.

Key terms: Dimensional analysis, Biological similarities, Allometric equations, Rest and exercise, Hemorrhagic shock, Integral feedback.

INTRODUCTION

Huxley's (1932) allometric equation ($Y = a W^b$) is universally utilized in the biological sciences for intra-and inter-species comparisons. Among hundreds of empirical allometric equations obtained from mammals in strictly standardized conditions, it has been possible to calculate several invariant numbers (IN) by applying Buckingham's Pi-theorem. As a counterpart, the theory of biological similarity from Lambert and Teissier (1927) and (Günther, 1975) allows us to predict the allometric exponent (b) as a function of body weight (W), which is equivalent to Newton's "reduced exponent", which is based on the dimensional analysis from the MLT - system of physics, where M is mass, L is length, and T is time. However, a question may be raised concerning the extrapolation of the above-mentioned studies, which were performed at basal conditions, to other functional circumstances, such as to organisms submitted to different work-loads or to pathological conditions during an experimental hypovolemic shock.

In a recent paper, Günther and Morgado (2002) obtained an invariant number for the respiratory system of newborn and adult mammals, which were deduced from a set of four empirical allometric equations. According to Stahl (1962), invariant and dimensionless numbers constitute "design parameters," which remain constant even at different periods of life. When this invariant number (IN) was calculated for fetal-newborn conditions versus adult conditions, the numerical results were almost identical. It is

Corresponding Author: Dr. Enrique Morgado. Programa de Fisiopatología, Instituto de Ciencias Biomédicas. Facultad de Medicina. Universidad de Chile. Casilla 16038. Santiago de Chile. Telephone: (56 2) 2741560. Fax: (56 2) 2741628. E-mail: emorgado@machi.med.uchile.cl

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worth mentioning that the empirical allometric equations of fetal-newborn and of adults organisms were not the same (Mortola, 1987, 2001), and therefore the resulting equivalences represented a real surprise.

Based on this evidence we decided to apply the concepts of invariant and dimensionless numbers (IN) to a set of six allometric equations from the cardiovascular system of mammals, either a) during rest, b) during standardized exercise, or c) in pathological condition (hypovolemic shock), the latter being a paradigm of a quantitative analysis of an abnormal functional network.

More recently, two different holistic approaches have been successfully applied, one to predict the numerical values of the allometric exponents (b) for many cardiovascular and respiratory functions in mammals (West *et al.*, 1997) and the other to postulate a general model of integral negative feedback control which may explain the robustness of all homeostatic mechanisms (Csete and Doyle, 2002) as well as its failure, as appears in Hans Selye's (1973) "heterostasis."

ON INVARIANT NUMBERS (IN)

The quantitative analysis, or morphological or physiological variables, which were measured in mammals of different size, can be accomplished on the basis of several allometric equations of empirical origin (Huxley, 1932), since the log-log transformation of the experimental data yields - by means of regression analysis - the corresponding allometric equation, which reads as follows:

$$Y = a\,X^{b} \tag{1}$$

where **Y** is any biological function that can be defined by means of the MLT- system of physics (M is mass, L is length and T is time); **X** is body mass (M) or body weight (W) as the most convenient reference system; **a** is an empirical parameter, when the reference system (X) is unity, and **b** is the allometric exponent, which can be predicted from one of the theories of biological similarities (Lambert and Teissier, 1927; Günther, 1975).

The quantitative analysis of the cardiovascular system of mammals (Günther and León de la Barra, 1966), whose functions were measured in standardized laboratory conditions, could be achieved by means of Buckingham's Pi-theorem when applied to a set of empirical allometric equations, which finally yielded the following **dimensionless and invariant number**:

$$IN_1 = \frac{P \cdot (\bar{v})^3 \cdot T^3}{\dot{V}o_2 \cdot TRP \cdot Q_b} = \frac{5.8 \times 10^4}{1.95 \times 10} = 2.989 \times 102 \approx 300 \tag{2}$$

Table I shows, first, the dimensional analysis (MLT-systems of physics) of six different functions, second, the physical units employed, and third, the numerical values of parameters **a** and the corresponding allometric exponents **b**. On the other hand, the allometric exponent **b** of the same invariant number (IN_1) reads as follows:

$$W^{b} = \frac{W^{0.023}\,(W^{0.07})^3\,(W^{0.27})^3}{W^{0.73}W^{-0.68}W^{0.99}} \tag{3}$$

while the corresponding log W-values are the following:

$$b = 0.023 + (3 \times 0.07) + (3 \times 0.27) - (0.73\text{-}0.68\text{+}0.99) = 1.043\text{-}1.040 = 0.003$$

therefore, the above-mentioned invariant number (IN_1) is equivalent to

$$IN_1 = 300W^{0.003} \tag{4}$$

DIMENSIONLESS NUMBERS

This study differs from its predecessors (Günther and León de la Barra, 1966; Günther, 1975) in two primary aspects: first, instead of Buckingham's Pi-theorem, which is based on dimensional analysis, two matrices and three equations of conditions (Ipsen, 1960), we have chosen to replace the above-mentioned strictly mathematical criterion with Stahl's (1962) cancellation procedure, which is based on one of the following two operations:

$$W^{b_1}W^{b_2} = W^{b_1 + b_2} \text{ - or - } \frac{W^{b_1}}{W^{b_2}} = W^{b_1 - b_2} \tag{5}$$

TABLE I

Allometric parameters (**a**) and exponents (**b**) of six empirical cardiovascular variables measured in mammals. Body weights (W) are given in grams (Günther & León de la Barra, 1966; Günther, 1975; Peters, 1983).

Item	Variable	M	L	T	Units (cgs)	Parameter	Exponent
		α	β	γ		**(a)**	**(b)**
1	Systemic arterial pressure (P)	1	-1	-2	dynes · cm^{-2}	1.17×10^{5}	0.023
2	Mean blood velocity ($\overline{V}$)	0	1	-1	cm · s^{-1}	1.84×10^{1}	0.07
3	Duration of one cardiac cycle (T)	0	0	1	s	4.3×10^{-2}	0.27
4	Basal oxygen consumption ($\dot{V}_{02}$)	0	3	-1	cm^3 · s^{-1}	1.06×10^{-3}	0.73
5	Total peripheral resistance (TPR)	1	-4	-1	dynes · s · cm^{-5}	3.35×10^{6}	-0.68
6	Total blood volume (Q_b)	0	3	0	cm^3	5.5×10^{1}	0.99

and second, by the cgs-system (c is centimeter, g is gram, s is second), which is replaced by the physical units commonly utilized in physiology and also in the medical practice (liters, mmHg, cmH_2O, minutes or days), and in consequence, the numerical value of parameter **a** should be entirely different.

With the aim of studying other dimensionless numbers ($DN = M^0L^0T^0 = 1.0$), we have combined six empirical allometric equations pertaining to other human organ systems, which yielded a new dimensionless number

$$W^{b1}W^{b2} = W^{b1 + b2} \quad (6)$$

where:

P is the mean systemic arterial pressure (mmHg), $\mathbf{Q_b}$ is the total blood volume (L), **U** is the urinary output flow (L d^{-1}), **C** is the lung and thoracic compliance (L $(cmH_2O)^{-1}$), $\mathbf{V_T}$ is tidal air (L), and $\mathbf{F_r}$ **is** the respiratory frequency (min^{-1}),

The combination of these six empirical allometric equations is illustrated in (Fig. 1).

Parameter $\mathbf{a_2}$ will be (see Table II)

$$\mathbf{a_2} = \frac{100 \times 5 \times 1.5}{0.13 \times 0.5 \times 14} = \frac{750}{0.91} = 824 \quad (7)$$

Finally, exponent **b** results from

$$W^b = \frac{W^{0.032} \cdot W^{1.0} \cdot W^{0.75}}{W^{1.04} \cdot W^{1.0} \cdot W^{-0.25}} \quad (8)$$

whose log W yields the reduced allometric exponent

$$b = (0.032 + 1.0 + 0.75)-(1.04 + 1.0 -0.25) = -0.008$$

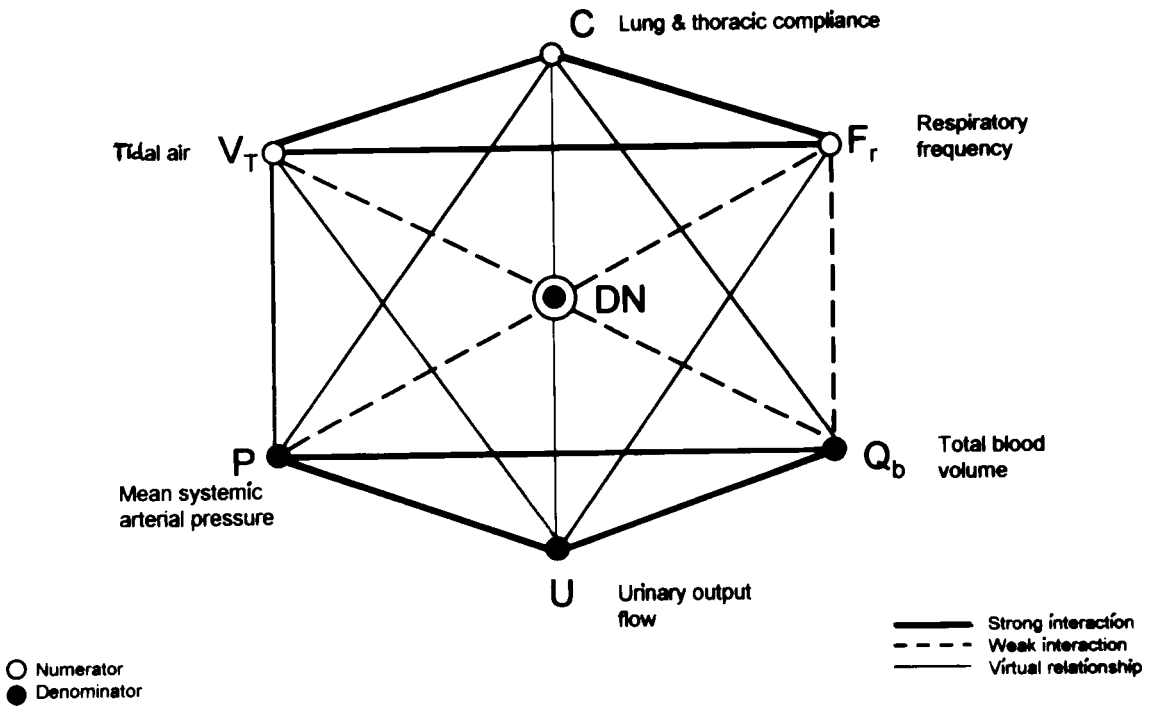

Figure 1
Functional relationships among six independent cardiovascular variables, which yields a dimensionless number (DN). The magnitude of the interactions is tentatively indicated by means of different kinds lines.

TABLE II

Empirical allometric equations from humans, when expressed in practical units, parameters (a) and the corresponding exponents (b); from Günther (1975) and Peters (1983).

Item	Variable	Units	Parameters (a)	Exponent (b) (slope ± S_b)
1	Mean systemic arterial pressure	mmHg	100	0.032
2	Total blood volume	L	5	1.0 ± 0.001
3	Urinary output flow	$L \cdot d^{-1}$	1.5	0.75 ± 0.05
4	Lung & thoracic compliance	$L \cdot (cmH_20)^{-1}$	0.13	1.04 ± 0.015
5	Tidal air	L	0.5	1.0
6	Respiratory frequency	min^{-1}	14	-0.25

Therefore, the second dimensionless number (DN_2) reads as follows

(9) $$DN_2 = 824 \cdot W^{-0.008}$$

INVARIANT NUMBERS (IN) DURING REST AND EXERCISE

Although the six variables, which make up the first invariant numbers (IN_1), vary markedly between the initial standing position and the standardized exercises on the treadmill, as shown in Table III and Figure 2 and also as illustrated by means of the ratio (E_{max}/Resting) from 0.625, for the duration of the cardiac cycle (T), while the ratio is 3.6 times for the oxygen consumption ($\dot{V}o_2$). Nevertheless, the above-mentioned ratio for the invariant numbers (IN) fluctuates only slightly (E/R=1.03). From these data we may conclude the robustness of the homeostatic

TABLE III

Metabolic and cardiovascular changes in a 21.5 kg mongrel dog, both during resting conditions and graded exercise (Barger et al., 1956).

Conditions	PAS (dynes/cm^2)	$\bar{v}$ (cm/s)	T (s)	Vo_2 (cm^3 / s)	TPR $\frac{\text{dynes x s}}{\text{cm}^5}$	a = IN_1
Standing	106 640	47.6	0.6	3.97	1595	176.5
Exercise						
3 mph – 0°	170 624	59.5	0.54	6.55	2050	189.7
3 mph – 5°	159 960	70.2	0.46	9.97	1680	144.7
3 mph – 10°	149 296	95.23	0.375	14.25	1180	182.0
Ratio = E/R Exercise/Resting	1.40	2.0	0.625	3.60	0.74	1.03

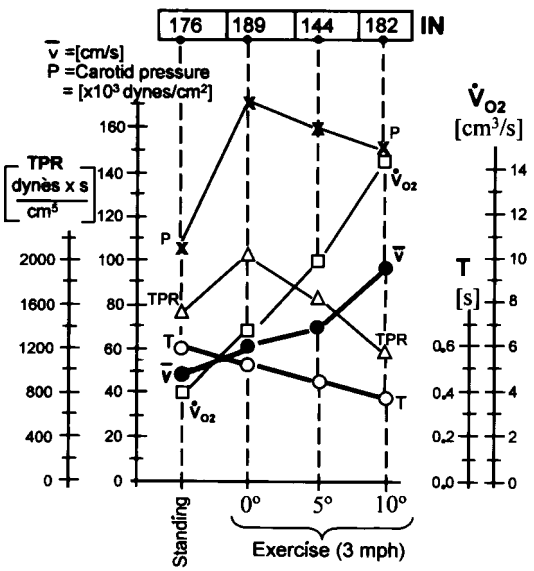

Figure 2

Cardiovascular effects of graded exercise on six variables as functions of time. Abscissa: slope of the treadmill in degrees for a common exercise speed of 3 mph. Upper line: the numerical values of the invariant numbers (IN), confirming the robustness of homeostasis. The black lines (T = duration of one cardiac cycle and $\bar{v}$ = mean blood velocity) correspond both to cubic functional relationships.

regulations, which are present in organisms at rest, but also during intense exercise, whose maximal responses are "fight or flight."

THE HYPOVOLEMIC SHOCK AS A PARADIGM OF "HETEROSTASIS"

Blood loss is a common feature in human pathology that can be quantitatively analyzed in the laboratory and whose uncertain outcome can finally yield the hemorrhagic shock syndrome.

In accordance with eqn. 6, the first dimensionless number (DN_1) may be useful to our purpose, assuming that the six variables are affected by blood-loss in the following manner (in comparison with the values of eqn. 7): the systemic arterial pressure may be reduced to 50% of the normal value, as well as the total blood volume (2.5 L), while the daily urinary output may be only to 0.3 Ld^{-1}, the thoracic and lung compliance is assumed to be slightly less than the normal (0.10 L/cm H_2O), while the tidal air may has been reduced to 0.4 L, and the respiratory frequency is increased to 20 respiration per minute (tachypnea). In this case the estimated value of parameter $\mathbf{a_2}$ will be

$$(10) \qquad \mathbf{a_2} = \frac{40 \times 2.5 \times 0.30}{0.10 \times 0.4 \times 20} = \frac{30}{0.8} = 37.5$$

In consequence, parameter **a** varies from 824, as calculated in accordance to eqn. 7, to 37.5 during an hypovolemic shock, which is equivalent to 4.5% of the normal value for DN_1. This dramatic reduction of the DN during shock (Fig. 3) can be attributed to the fact that the DN_1 is the result of a product of a sextet of variables and does not correspond to a simple summation of the above mentioned six functions.

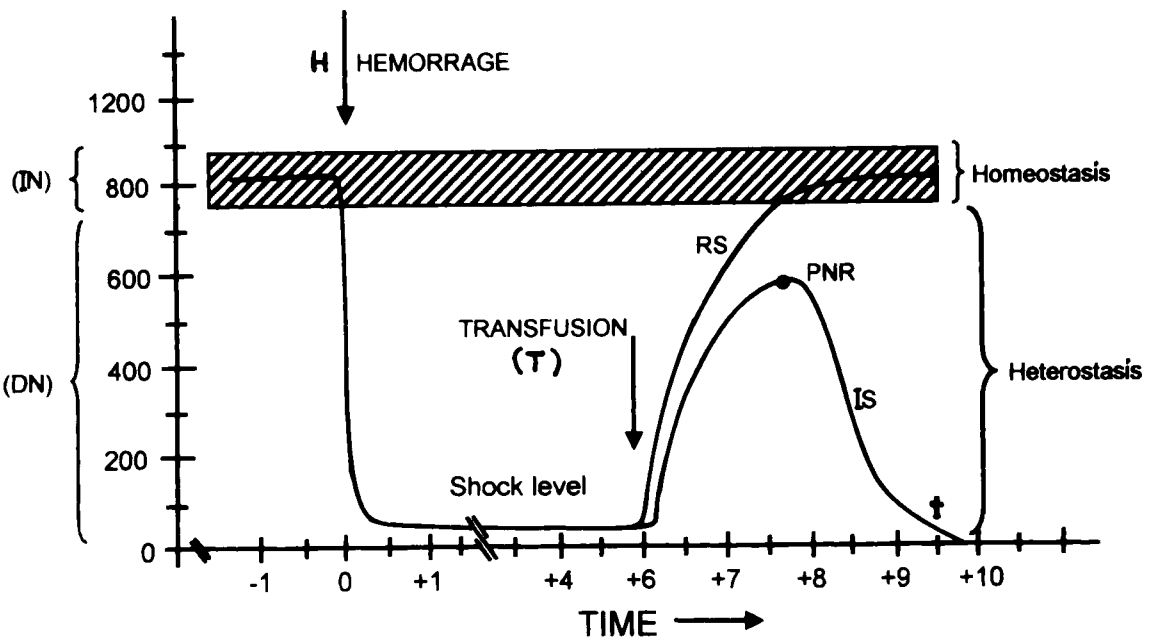

Figure 3
Evolution of a dimensionless number (DN) during an hemorrhagic shock syndrome. Ordinate: Invariant number (IN) or dimensionless number (DN), in arbitrary units. Abscissa: time, also in arbitrary units. H = hemorrhage, Tr = blood transfusion of the shed blood, with a complete recovery of the circulatory functions (reversible shock, RS), or else, a partial recovery, up to the "Point of No Return" (PNR), which corresponds to an irreversible shock syndrome (IS) and the eventual fatal outcome (†).

THE MECHANISMS OF BIOLOGICAL REGULATIONS

A) "Homeostasis" or a high gain integral negative feedback system.

The final steady-state condition, which characterizes all regulatory processes in living beings, is a dynamic phenomenon, leading to equilibrium between inflow and outflow in a given compartment, despite occasional disturbances, either from outside or inside of the system. On the other hand, the reference values for each function are determined by genetic factors, which are transmitted from generation to generation through the millennia, while they are submitted to the process of natural selection. The regulatory circuits belong primarily to the integral negative feedback type (Csete and Doyle, 2002) as represented in Figure 4, which is composed of two compartments (A and C), a reference value (r), and occasional input disturbances (d). Furthermore, when the closed-loop is disturbed (d) by a unitary step function (0.1),

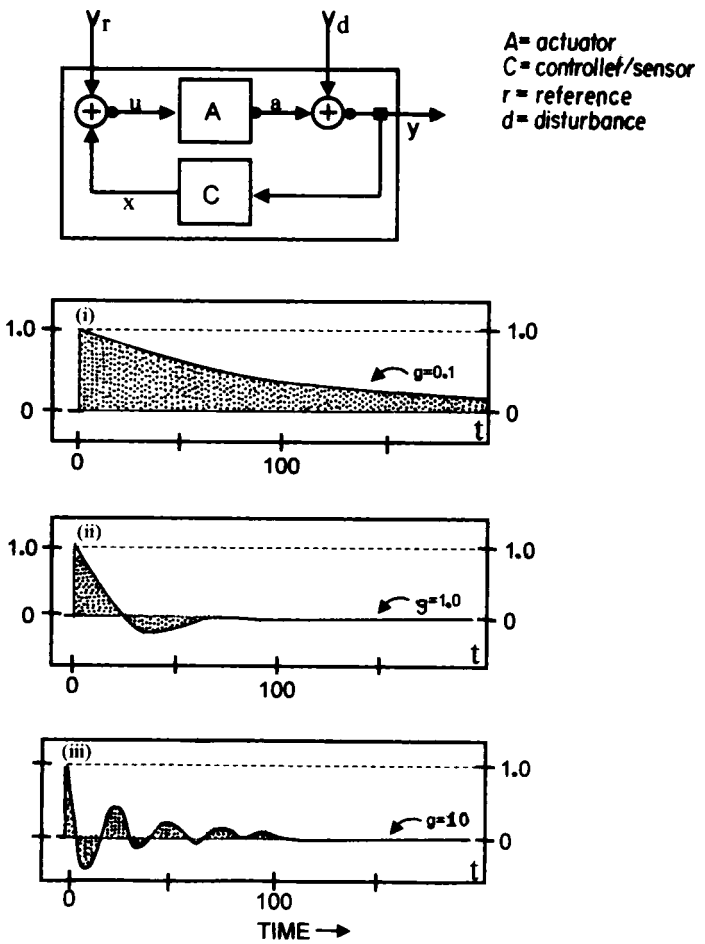

Figure 4

Block diagram of an integral negative feedback system, with three types of responses to an unitary step function (disturbance d)

i) low gain of the actor A (heterostasis),

ii) higher gain (g = 1.0) with a monophasic response,

iii) oscillatory response at high gain (g = 10).

Note that in the two last responses to a unitary step disturbance, the zero error level is rapidly attained (homeostasis). Adapted from Csete and Doyle, 2002.

the consequences at the output (y) depends upon the gain of the compartment A (actor). In the event that the gain (g) is low (g=0.1), the step function causes a permanent but declining deviation from zero, whereas a higher gain (1.0 < g < 10), the displacement of the error signal is only momentary, since very rapidly a zero error level is reached again. In consequence, the high gain (g) of actor (A) is correlated with the condition of Cannon's "homeostasis" (1929) or of the status of a healthy organism.

B) "Heterostasis" or a low gain integral negative feedback system

If the disturbance (d) is considered as an analogous of a physical "action," the organism may respond with a "reaction," as was originally postulated in the physical sciences by Isaac Newton (action = reaction), although the latter is of the opposite sign (Fig. 5). However, in living beings these "reactions" can be lesser or greater than the "action," depending upon

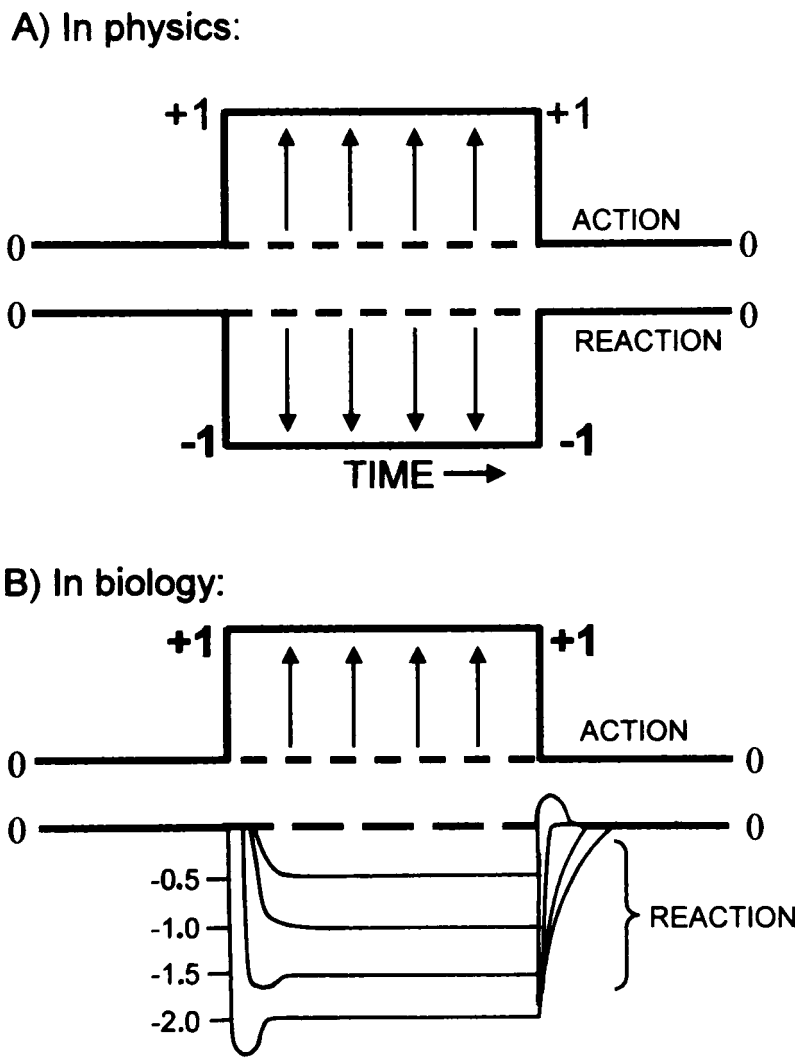

Figure 5.
The classical Newtonian "action and reaction," which are equal and of opposite sign. However, in the biological sciences, the effect of an "action" depends upon the reactivity of the organism involved and in consequence the "reaction" can be of quite different magnitude.

the reactivity of the corresponding organism. In sum, a permanent major or minor deviation from the normal condition (zero error), may indicate that the organism is in the condition of Selye's "heterostasis" or is affected by a disease. When the gain (g) of compartment (A) has been restored, either spontaneously or else after medical intervention, the corresponding function returns to the normal value (zero error).

Thus, the "heterostasis" phenomenon can be observed as a transitory or a constant response to a unitary step function (Fig. 4), or as a permanent steady state condition due to a shift of the reference value (r), which commonly is designed as a change of the "set point."

Since homeostasis and heterostasis are based on the same closed circuit of integral negative feedback system, the transition from one to the other is of reversible nature. Thus, the reduced gain ($g < 1.0$) may be originated by a hypometabolic state, as for instance: lack of substrate, severe ischemia, and oxygen lack, accumulation of lactate or of hidronium ions, among many other causes.

DISCUSSION

In contrast with the physical and chemical sciences, where hundreds of dimensionless numbers or groups of numbers are known (Weast, 1983), in the biological sciences, and particularly in medicine, to our knowledge, this does not happen, other than the occasional quotation of Reynolds number in hemodynamics or aerodynamics, concerning the ratio between inertial and viscous forces, or else, of Froude's number, which deals with the ratio between inertial and gravitational forces.

The first attempt to introduce dimensional analysis and the principles of similarity into the biological sciences was made by D'Arcy Thompson (1952). Of particular importance for the falsification of these theoretical approaches has been the intra-species or the inter-species empirical studies of numerous functions by means of Huxley's (1) allometric power equation, where body mass (M) or body weight (W) were utilized at the most convenient reference system.

Finally, from a set of allometric equations it has been possible to obtain dimensionless and invariant numbers, as holistic indices for morphological or physiological characteristic of living beings. For this purpose, two procedures have been essayed. First, Buckingham's Pi-theorem, and Stahl's (1962) cancellation procedure; the former is an entirely mathematical algorithm, whereas in the latter, biological criteria have the primacy.

In the normal conditions of life, it is relevant that a set of six or more cardiovascular and metabolic functions, when expressed quantitatively as invariant numbers (IN), remain almost constant during rest and different work loads, which means that the IN represent a design index of the whole system, regardless of the activity spectrum (rest-exercise). In consequence, when the condition of "homeostasis" prevails, the IN is a reliable index of normality. On the contrary, "heterostasis" implies the breakdown of the above-mentioned invariant numbers (IN), and it is possible to correlate this phenomenon with the conversion of the IN into the dimensionless numbers (DN) with its characteristic variability. The hemorrhagic model of shock helps to understand many other modalities of shock, because blood loss is a common feature of clinical shocks, and its evolution depends upon the magnitude of the blood deficit and of the compensatory cardiovascular regulatory mechanisms.

We would like to emphasize that the "point of no-return (PNR)" is a critical event, whose validity is restricted to the present experimental model (Vivaldi, *et al.* 1983), since in the human clinic it is seldom possible to detect signs or symptoms that may indicate the beginning of the fatal outcome.

In sum, homeostasis is associated with the robustness of negative integral feedback systems, while heterostasis is concerned with the existence of the same loop, but with low gain, yielding step function deviations from the normal set points, as exemplified by fever episodes, arterial hypertension or persistent headaches, among many others pathologies.

Size-invariant dimensionless groups can be obtained by dividing two or more

empirical allometric equations in accordance with Stahl's cancellation procedure. For instance, the ratio between items 3 and 4 in Table IV yields the interspecies comparison of the duration of one respiratory cycle and one cardiac cycle in mammals, irrespective of their body sizes:

$$\frac{R_r}{H_r} = \frac{1.12 \cdot W^{0.26}}{0.25 \cdot W^{0.25}} = 4.5 \cdot W^{0.01} \quad (11)$$

being R_r the respiratory rate; H_r the heart rate and W the body weight (kg).

The ratio of parameters (a) yields 1.12/ 0.25 = 4.5, whereas the allometric exponent ratio ($W^{b_1}W^{b_2} = W^{b_{1+}b_2}$) is b = 0.01 (Table IV) is almost zero, which confirms the dimensionless condition ($DN = M^0 L^0 T^0$).

In sum, for all mammals, from the 3-gram shrew to the 3-ton elephant, the duration of 4.5 cardiac cycles is equivalent to one respiratory cycle, a general rule that

TABLE IV

Ten size-independent dimensionless groups in mammals

					Parameter	Exponent	References
Item	Variable	Units	Intercept: a (W = 1 kg)	Slope: (b)	Ratio a_1/a_2	Ratio b_1/b_2	
1	Total blood volume	ml	76	1.0	13.3	0.02	Peters, 1983
2	Volume of the heart	ml	5.72	0.98			Peters, 1983
3	Duration of one respiratory cycle	s	1.12	0.26	4.5	0.01	Calder, 1984
4	Duration of one cardiac cycle	s	0.25	0.25			Calder, 1984
5	98 % growth time	yr	1.21	0.26	3.4	0.01	Calder, 1984
6	50 % growth time	yr	0.35	0.25			Calder, 1984
7	Inulin plasma clearance	min	6.51	0.27	3.8	0.05	Calder, 1984
8	PAH plasma clearance	min	1.70	0.22			Calder, 1984
9	Lifespan in captivity	yr	11.6	0.20	64	- 0.05	Peters, 1983
10	Gestational period	yr	0.18	0.25			Peters, 1983
11	Systemic blood pressure	Pa	1500	0.032	6.52	- 0.04	Peters, 1983
12	Plasma colloid osmotic pressure	Pa	2300	0.075			Peters, 1983
13	Total lung volume	ml	53.5	1.06	7.0	0.02	Peters, 1983
14	Tidal volume	ml	7.7	1.04			Peters, 1983
15	Total peripheral resistance	$Pa \cdot m^{-3} \cdot s$	0.255	- 0.68	36.4	- 0.02	Peters, 1983
16	Total airway resistance	$Pa \cdot m^{-3} \cdot s$	0.007	- 0.70			Peters, 1983
17	Pulse wave velocity	$m \cdot s^{-1}$	7.80	0.02	26.0	- 0.05	McMahon & Bonner, 1983
18	Blood flow velocity	$m \cdot s^{-1}$	0.30	0.07			McMahon & Bonner, 1983
19	Cardiac output	$ml \cdot s^{-1}$	2.78	0.790	13.6	0.04	Peters, 1983
20	Standard metabolic rate	$ml \cdot s^{-1}$	0.205	0.751			Peters, 1983

could be obtained only from the scaling of dimensionless numbers.

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