sex of Chaetocladium was grown with either sex of Parasitella, both species acted as host to the other parasite and galls were produced characteristic of both Parasitella and Chaetocladium. The parasitic behavior of Chaetocladium has been described in detail by Burgeff.[2]

THE PHYSIOLOGICAL PRINCIPLE OF MINIMUM WORK. I. THE VASCULAR SYSTEM AND THE COST OF BLOOD VOLUME

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Introduction.—Physiological organization, like gravitation, is a "stubborn fact," and it is one task of theoretical physiology to find quantitative laws which describe organization in its various aspects. Just as the laws of thermodynamics were known before the kinetic theory of gases was developed, so it is not impossible that some quantitative generalizations may be arrived at in physiology which are independent of the discrete mechanisms in living things, but which apply to organic systems considered statistically. One such generalization is the principle of the maintenance of steady states—a principle which furnishes definite equations (of the type indicating equality of intake and output of elementary substances) applicable to the hypothetical normal individual. The purpose of these studies is to discuss the possible application of a second principle, the principle of minimum work, to problems concerning the operation of physiological systems.

The concept of adaptation has been treated in a quantitative manner by experimental morphologists, students of growth and form, who have shown again and again the tendency toward perfect fitness between structure and function in all sorts of plants and animals. Only rarely, however, has the concept of fitness been used as a *premise* for physiological deductions. The beginnings of theoretical or deductive physiology are to be found in the works of Galileo[1] and of Borelli,[2] who argued from the principle of similitude, as others have done since. Thompson's fascinating book[3] contains a wealth of material on this subject. Henderson's classic essay[4] covers the history of the teleological problem, and presents his own proof that the teleological aspect of nature (until Darwin's time associated with the minutiae of biological adaptations, and in the latter part of the last century associated with primitive theological doctrine) has its real roots in the properties of matter and in the laws of physics and chemistry. Thus it may be seen that organization is a legitimate field for scientific inquiry and not an "affair of the reflective judgment."

No one can escape the impression of a physiological determinism as exemplified by the narrowness of the "physiological range;" but the hypothesis of the constancy of the internal environment, being in effect a denial of adaptive change, holds out no hope whatever of interpreting quantitatively the phenomena of organization. Let us start then from the basis that organization and adaptation are observed facts, presumably conforming to definite laws because, statistically at least, there is some sort of uniformity or determinism in their appearances. And let us assume that the best quantitative statement embodying the concept of organizatin is a principle which states that the cost of operation of physiological systems tends to be a minimum, and that cost is to be measured in units, like the Calorie and the erg, which have dimensions equivalent to those of *work*.

The specific problems to be discussed all center around oxygen transport in man. Oxygen transport is the oldest and the most advanced field of quantitative physiological inquiry, and, therefore, it is the most suitable subject for theoretical studies. The functions which must be performed by the oxygen transport system, if a steady state is to be maintained, are relatively clear-cut, the factors involved in the efficiency of transport are discernible to a large extent, and there is little doubt that, through all the trials and errors of individual growth and evolution, an efficient mode of operation has been arrived at. (For physiological studies the main anatomical features may be taken as given in outline, and similarly properties of the red blood corpuscle, etc.) That the normal or average operation of oxygen transport *is* the most efficient or economical operation, will not be the special burden of the argument; but, by assuming this as a postulate generalized from observation, the analysis of the factors involved becomes less cumbersome. Moreover, the result at least contributes to a description of a theoretically efficient system with which the actual manner of operation may be compared, thus bringing to light discrepancies and new problems, and throwing into relief the exceptional and the truly pathological. The principle of economy is more fundamental than any particular conclusion based on fallible appreciation of the factors determining cost and function in any given case, but a large discrepancy, between the theoretical result and the actual normal operation, inevitably suggests an unknown factor to be searched for. The theoretical problem is essentially to find the best fit between criteria of cost and function, *and* the deductions from some precise quantitative statement of the general principle of economy. To evaluate certain general equations numerically, a table of "standard values" has been compiled, and the special tentative assumption is made that the basal state, represented by values given in the table, is a state at which all the factors to be discussed operate together most efficiently. Any modification of this assumption merely requires the sub-

stitution of different values in the equations, granting the latter to be applicable.   We may now proceed to some specific problems.

The Vascular System and the Cost of Blood Volume.—If we examine the arterial system bearing in mind the question of economy, we find that there are two main antagonistic factors.   If the vessels are too small, the work

TABLE OF "STANDARD" VALUES AND MISCELLANEOUS DATA

Values for factors representative of normal basal conditions, collected mostly from physiological texts, are given in brackets, following the definitions of the numbered symbols, these having been taken as the primary factors.   Some values for derived factors (un-numbered) are included.   Most of the definitions refer particularly to blood vessels considered, section by section, as cylindrical tubes of uniform radius.   Units are in c.g.s. system, unless otherwise noted.

1. r = the radius [for capillaries, 3.5×10^{-4} cm.].
2. l = the length [for capillaries, 0.05 cm.]
    s = the surface area, = $2\pi r l$.
    vol. = the volume = $l\pi r^2$ = $rs/2$.
3. u = the velocity of blood, e.g., of a blood corpuscle [for capillaries, 0.05 cm./sec.].
    n = the average number of capillaries through which blood is circulating at any instant.
    f = rate of blood flow in a vessel, i.e., the amount of flow in cubic centimeters per second.
4. nf = the total blood flow per second [for basal conditions in man, 83.3 cc./sec.].
    In the text nf will not be used as a symbol—it will be clear from the context whether f refers to a single vessel or to the total flow.
5. η = the viscosity [for blood of average composition at 37°, 0.028].

From the above, we find: f, for a capillary, = $u\pi r^2$ = 1.925×10^{-8} cc./sec.; vol., for a capillary, = 1.925×10^{-8} cc.; and n vol., the total active capillary volume, = nf vol./f = 83.3 cc.

Poisseuille's well-known equation for the flow of liquids in tubes is the following:

$$p = \frac{f \cdot l \cdot 8\eta}{\pi r^4}$$

where p is the difference in pressure, in dynes per square centimeter, between the two ends of the tube.   Applied to capillary flow, using values given above, we find: p = 4575 dynes/cm.² (or, dividing by 1333 to convert to mm. of Hg, p = 3.43 mm. Hg). When it was thought that in capillaries the fall in pressure was about 40 mm. Hg, it was the fashion to regard Poisseuille's equation as inapplicable to capillary flow.   But the direct determinations cited by Krogh[6] are only a trifle higher than the value derived above.   This recent work thus restores a much desired consistency in the subject of hemodynamics.   In capillaries the pressure *gradient* is higher than elsewhere, but, the capillaries being very *short*, the loss in pressure in these is only a small fraction of the total blood pressure.

The work done in unit time against friction in a tube (neglecting eddies and intermittent acceleration attending pulsating flow) is given by the product pf.   For the effective work (approximately) of the heart, taking p = 174,000 dynes /cm.² (= 130 mm. Hg for the systemic blood pressure) we have: pf = 1.45×10^7 ergs/sec. (or, multiplying by 2.065×10^{-6} we have: pf = 30 Cals./day).

For the total circulating blood volume, let us take the value 5000 cc., of which, it is estimated, 1500 cc. are in the arteries of the greater circulation.

required to drive the blood through them becomes too great; if the volume of the vessels is too large, the volume of blood, being equally large, becomes a burden to the whole body. The problem is therefore to determine whether there is a compromise which is more efficient than any other, and to study the interplay of the factors.

Poisseuille's equation (see reference table) for the law of flow in cylindrical tubes may be taken as a very fair approximation giving the relationships required. If both sides of the equation, as given in the table, are multiplied by f, the flow, one obtains the work, pf, in ergs per second, lost through friction—a function we may call simply the friction—for any uniform section of the arterial system. Thus:

$$pf = \frac{f^2 \cdot l \cdot 8\eta}{\pi r^4} .$$ (1)

To study the antagonism between the friction and the volume of blood, the latter factor must be multiplied by a dimensional constant. Let b, then, be the cost of blood in ergs per second per cubic centimeter of whole blood of average composition (and let B be the cost in Calories per day per cc. of blood). There is, as far as I can see, nothing arbitrary about this step: it is certain that the maintenance of blood requires fuel. (The cost of blood may, however, be a complex account distributed among such factors as the small metabolism of blood itself, the cost of upkeep of all the constituents, perhaps especially of hemoglobin, the cost of the containing vessels, and the burden placed upon the body in general by the mere weight of blood.) The cost of blood, in ergs per sec. per cc., is then given, for any particular section of the arterial system, by the expression $b$vol., or $bl\pi r^2$. The total work, E, involved in operating a section of artery is then given by the equation

$$E = pf + b\text{vol.} = \frac{f^2 \cdot l \cdot 8\eta}{\pi r^4} + bl\pi r^2.$$ (2)

Now the condition for maximum economy of work, given the flow, f, and the length, l, of some arterial section, is that the total work, E, shall be a minimum. We have then two variables, E, and the radius, r. Differentiating and equating to zero, we obtain:

$$\frac{dE}{dr} = -\frac{4f^2 \cdot l \cdot 8\eta}{\pi r^5} + 2bl\pi r = 0$$ (3)

and, therefore,

$$b = \frac{2f^2 \cdot 8\eta}{\pi^2 r^6} .$$ (4)

According to the assumptions stated, equation 4 is the general equation which must be fulfilled for maximum economy of work in any section of

artery. It will be referred to again in other connections. For the present we will use it to make an estimate of the value of b as follows. From equations 1 and 4 we may derive the equation

$$pf = 0.5bl\pi r^2 = 0.5b\text{vol.} \tag{5}$$

At maximum efficiency equation 5 holds for any and all parts of the arterial system, and also for the whole system. For the latter case the total effective work of the left ventricle, pf, may be estimated (neglecting work done in the intermittent acceleration of blood), and the volume of blood in the arterial system may be roughly estimated. Values from the table may be substituted, then, as follows:

$$b = \frac{2pf}{\text{vol.}} = \frac{2 \cdot 174 \cdot 10^3 \cdot 83.3}{1500} = 19,300 \text{ ergs/cc. sec., or}$$

$$B = 0.04 \text{ Cal./cc. day.}$$

This result may be interpreted as follows: were blood a cheaper material than is shown by the value obtained, one might expect all arteries to be uniformly larger than they are, thereby greatly reducing the burden on the heart. (For example, doubling the radii of all arteries, the lengths of which are constant, would mean a four-fold increase in volume, and a reduction of the work of the heart to one-sixteenth!) And conversely, if blood were a more expensive material we would be in danger of annihilation by a scant-blooded, large-hearted race. The result obtained, considered as a first approximation, rests upon the general concepts of evolution and physiological fitness. We may test the plausibility of the result by comparison with other tissues. Taking 2500 Calories per day as the basal energy expenditure of a man weighing 70 kg., the rate per gram is 0.036 Calorie. Compared with this value, the result 0.040 Calorie per cc. of blood appears plausible. But the cost of blood has been estimated by comparison with the mechanical work of the heart, an organ the efficiency of which is about 30 per cent. The "true" cost of blood should therefore be about 0.13 Cal. per day, or more nearly comparable to the energy requirements of the more active tissues of the body. The deduction from the principle of economy of operation of physiological systems is therefore not unreasonable.

From a consideration of the energy relations in the arterial system we may now turn to the capillaries. To begin with let us assume that the capillaries are subject to the same conditions as the arterial system. We may substitute directly in equation 4 the values for capillaries from the

standard set, since now we are dealing with a relatively homogeneous section of the vascular system. Thus we obtain:

$$b = \frac{2(1.925 \cdot 10^{-8})^2 \cdot 8(0.028)}{\pi^2 (3.5 \cdot 10^{-4})^6} \doteq 9180 \text{ ergs/cc. sec., or}$$

$$B = 0.019 \text{ Cal./cc. day.}$$

We might, however, make an alternative assumption in this case, namely, that for an individual in a given state, the variables to be considered as determined (the factors to be kept constant in differentiating the equation) should be the flow, f, as before, and the *surface area*, s (instead of the length) of the capillary. Since $s = 2\pi r l$, and vol. $= rs/2$, we may write equation 2 in the form:

$$E = \frac{f^2 \cdot s \cdot 8\eta}{2\pi^2 r^5} + \frac{brs}{2}.$$

Differentiating as before, we obtain:

$$\frac{dE}{dr} = -\frac{5f^2 \cdot s \cdot 8\eta}{2\pi^2 r^6} + \frac{bs}{2} = 0, \text{ and } b = \frac{5f^2 \cdot 8\eta}{\pi^2 r^6}. \tag{6}$$

Comparing equation 4 with equation 6, it is seen that the value of b determined by the latter will be 5/2 greater than the value obtained by the former. The alternative assumption leads to the result:

$$B = 0.019 \cdot 2.5 = 0.047 \text{ Cal./cc. day.}$$

The last assumption is perhaps theoretically preferable, and it leads to a closer agreement between the value of B as obtained from the observed relations in capillaries with the value obtained from estimates of relations existing in the arterial system as a whole. The approximate agreement, in either case, based on figures differing enormously in magnitude, strongly supports the reasoning involved in the application of the principle of minimum work. If we had, for example, used the first value obtained for b (19,300), and substituted this in equation 6, we could have made a fair estimate of the radius of a capillary or the flow of blood through it, one of the latter being known.

Many relations are contained in equations 4 and 6, and one of these may be appropriately mentioned here. If equation 4 is written in the forms:

$$f^2 = \frac{r^6 \pi^2 b}{16\eta} \qquad f = r^3 \sqrt{\frac{\pi^2 b}{16\eta}} \quad \text{or} \quad f = kr^3 \tag{7}$$

we see one of the simplest requirements for maximum efficiency in the circulation—namely that the flow of blood past any section shall every-

where bear the same relation to the cube of the radius of the vessel at that point. In terms of velocity, since the velocity, u, is given by the relation $u = f/\pi r^2$, we have from equation 7 the requirement: $u = r\sqrt{\dfrac{b}{16\eta}} = k'r$, in words, that the velocity of blood is proportional to the radius of the vessel. We have already made three estimates of b: (1) from relations in the arterial system as a whole (19,300), (2) and (3) from relations in capillaries according to two possible assumptions (9180 and 22,950). A fourth estimate may be made from observations of the velocity of blood in a single artery. Tschuewsky[5] has determined the velocity of blood in, and the radius of, the carotid artery in dogs. Averaging five normal cases from page 270 of his paper, one finds: $r = 0.159$ cm., and $u = 25.5$ cm./sec. Assuming the "standard" viscosity, $b = (0.669 \; u/r)^2 = 11,520$ ergs/cc. sec. The agreement, in order of magnitude, between these results is, I think, convincing evidence that the cost of blood volume is operative in determining conditions in the vascular system, from a capillary to an artery of a diameter at least five hundred times greater.

For larger arteries than those considered above, the simple equations no longer hold. Equation 1 only accounts for a small portion of the mechanical work required for the flow of blood in the *aorta*—most of the work required is to produce the intermittent acceleration of the blood at each heart beat, the lesser part to overcome friction. Values for b, derived from conditions prevailing in the aorta, would be much too small unless the total energy involved in the flow of blood were taken into account. This is the same as saying that the aorta, compared to the rest of the vascular system, seems to be disproportionately large—a fact which has long been recognized. From the standpoint of economy of work, the aorta is analogous to the large pipe which connects a pumping station with a reservoir—the function of the reservoir being performed by the elasticity of the aorta. The large pipe minimizes the high acceleration associated with intermittent flow, and the reservoir largely converts the intermittent into a continuous flow. The work required to overcome the inertia of blood is only significant when the velocity is high; hence, the larger the animal the larger must be the aorta in comparison to the rest of the vascular system and the normal blood flow of the animal.

The bearing of these results on the process of oxygen exchange in capillaries will be dealt with in a succeeding part.

To express here my gratitude to Professor Henderson, for much enlightenment shed upon confused questions time after time, is a genuine satisfaction. To Dr. F. H. Pike's early insistence that physiology is "a problem in maxima and minima" I owe the basic idea of this paper.

[1] Galilei, Galileo, *Dialogues Concerning Two New Sciences* (Leyden, 1638), Trans. Crew and de Salvio, Macmillan Co., 1914 (v. pp. 130–3 and 150).

[2] Borelli, G. A., *De motu animalium*, Rome, 1681.

[3] Thompson, D. W., "On Growth and Form," Camb. Univ. Press, 1917.

[4] Henderson, L. J., "The Order of Nature," Harvard Univ. Press, 2nd ed., 1925.

[5] Tschuewsky, J. A., *Pfluger's Arch.*, **97**, 1903 (210–288).

[6] Krogh, A., "The Anatomy and Physiology of the Capillaries," Yale Univ. Press, 1922.

Previous work on the economy of the circulation is to be found in the articles by W. R. Hess. (See especially, *Pfluger's Arch.*, **168**, 1917 (439–490). In this paper he deals with the compromise between resistance to flow and the volume of a vessel. He develops equations (which can be derived from those given in the present paper), but, failing to recognize the significance of his units, the dimensions of his constants, and particularly the fact that economy is a question of *work*, he misses what seems to be the essence of the problem. The fundamental equations given in the present paper cannot be derived from those of Hess.)

THE SIGNIFICANCE OF CHANGES IN THE ELECTRICAL RESISTANCE OF THE BODY DURING SLEEP

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Our knowledge regarding the changes which take place in the body during sleep is still very limited. Like most other things common to our daily life, sleep has always, except on a few occasions, enjoyed almost complete immunity from experimental investigation, and at the same time it has been the topic of an almost endless number of theories and speculations. Some experiments on blood pressure, pulse rate, and respiration, and a few measurements of the intensity of sleep have been made. Of these the experiments on the intensity of sleep were most interesting and promising. The first investigations along this line were undertaken in 1863 by Kohlschütter,[1] a student of Fechner; and since then a few other investigators, Monninghoff and Piesbergen,[2] Michelson,[3] Howell,[4] have either repeated or slightly extended the original experiments. Depth of sleep was measured in terms of the intensity of acoustic stimulus necessary to awaken the subjects. The stimuli were repeated at short intervals and in progressively increasing intensities. The results of these experiments showed that the intensity or depth of sleep increases very quickly, reaches a maximum before the end of the second hour, and then decreases again equally rapidly to a low level at which it remains, with small fluctuations, until the end of the sleep period. This result is obviously not in agreement with general experience. It is a fact of common observation that