THE DISTRIBUTION OF TEMPERATURE CHARACTERISTICS FOR BIOLOGICAL PROCESSES; CRITICAL INCREMENTS FOR HEART RATES.

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I.

Observations illustrating the changes in velocities or frequencies of vital activities with alteration of temperature are sufficiently numerous to permit the demonstration that temperature characteristics deduced for these data fall into definite classes (Crozier, 1924). Proof of this point is important for the conception that temperature characteristics may be used for the recognition of specific controlling processes or reactions in living matter. The chemical identification of these processes may thus be made possible, but this undertaking must be very carefully approached. The term "temperature characteristic" was deliberately introduced (Crozier, 1924–25, a) to provide a name for the quantity $E$, or $\mu$, in the van't Hoff-Arrhenius equation, which should be free from the connotation of any particular view as to the mechanism of "activation." With this understanding the name "critical increment" may, however, still be employed as a convenient alternative, for it has long been recognized that the magnitudes of the temperature coefficients of biological processes as a rule correspond to those for common chemical reaction velocities. It is not to be supposed that the pursuit of this view requires denial that the temperature characteristics as measured may in some instances be referable to heats of reaction, for the descriptive equation for reaction velocity (Arrhenius) and the van't Hoff isochore are of course identical in form; in fact the formal relationship $m = m_0 \exp (-A/T)$ may hold with some precision for a variety of phenomena. But it may be pointed out at once that if in measuring the relations between velocities of vital processes and temperature one really had to do predominantly
or even frequently with shifts of mass action equilibria, then it would be reasonable to expect the quite frequent occurrence of values of $E$ which would correspond with heats of neutralization and the like. In point of fact, however, the magnitudes 13,000, 14,000, and 15,000 cal. turn out to be strikingly infrequent (Fig. 1).

If it were to be supposed that the relationships between velocities of vital processes and temperature are really incapable of being used for purposes of identifying controlling reactions, but on the contrary are obscurely influenced by protoplasmic fluidity and other factors (cf. Snyder, 1911; Matisse, 1921), then it would be inexplicable that the same values of temperature characteristics should be obtained for homologous processes in diverse organisms (Crozier, 1924–25, a, b; Crozier and Stier, 1924–25, a, c, d; Glaser, 1924–25, 1925–26); the experimental interconversion of temperature characteristics (Crozier and Stier, 1924–25, a; 1925–26) would be senseless; and there would, indeed, be no reason assignable for the fact that the Arrhenius-Marcelin-J. Rice equation does adequately describe, in the overwhelming majority of cases, the connection between velocity and temperature.

Aside from the analysis of adequate data relating to suitable phenomena, there is another method of testing the hypothesis of recurrent, discrete, recognizable, temperature characteristics. On the view that these quantities are easily modified to various degrees by differ-

1 The attempt to introduce considerations of protoplasmic fluidity, presumably as influencing diffusion, requires a theory of the general control of organic activities by the whole body of the cell rather than at surfaces. This is unnecessary, and at present inadmissible. When dealing with such processes as muscle relaxation (Fulton, 1925) and ameboid progression it may be necessary, for other reasons, however, to reckon with protoplasmic consistency. The serious obstacle arises that cytoplasmic viscosity of different cells (e.g. eggs of Cummingia and of Nereis) varies with temperature in totally unlike ways (cf. Weber, 1916; Heilbrunn, 1924; Pantin, 1924); there is no evidence of corresponding variations in temperature characteristics. Several writers (Snyder, 1911; Pantin, 1924) have sought to "correct" temperature coefficients for viscosity effects, under the delusion that the $Q_10$ ratio should be constant—a performance for which there is no justification.

That physical changes may be important for the production of certain types of alteration in the log $V - 1/T$ graph has been expressly recognized (Crozier and Stier, 1924–25, d). But these changes may be of a relatively clear-cut character, and their interpretation is not expected to present insuperable difficulty.
ent influences, a frequency polygon of the values deduced from numerous sets of observations should take the form of a relatively simple frequency distribution. The actual polygon so obtained (Fig. 1) is definitely multimodal.

II.

For the compilation of Fig. 1 use has been made of a large number of series of observations, in greater part derived from published material\(^2\) but including also a number of unpublished series. By a series is meant a set of data secured by one observer, pertaining to a given process, in a given organism. Such series are quite obviously of uneven value. Inherent differences are connected with the types of processes considered. Thus there is reason to expect measurements of growth, for example, to involve phenomena which need not be disturbing for the study of rapidly transpiring events such as the succession of heart beats; these require separate analysis. Individual series differ greatly in the numbers of observations, and in the numbers of organisms employed, as well as in the suitability of the experimental arrangements and in the accuracy, the range, and the spacing of the working temperatures. Nevertheless it has been sought to include all known available series, excluding only those in which the experimental temperatures are very few (2 or 3) and widely separated, since the possible occurrence of breaks (Crozier, 1924–25, a; Crozier and Federighi, 1923–24) at intermediate temperatures may render such observations of very doubtful significance. The sharpness of the separation of the modes in Fig. 1 is much increased if one tries to select those phenomena which seem a priori most likely to be suitable for significant measurement.

The method of computation has been illustrated in former papers, and is apparent in the accompanying figures. The various sets of data have been separately plotted at least three times, with different values of the coordinate units, and the best fitting lines satisfying the relation \(\text{log velocity} = - K \exp \left( \frac{\mu}{RT} \right)\) have been used to calculate

\(^2\) See Kanitz (1915; 1923); Przibram (1923); and papers in *J. Gen. Physiol.*, 1924–25, 1925–26, vols. vii, viii, ix.
Fig. 1. Frequency of occurrence of values of $\mu$ in series of data pertaining to diverse biological phenomena. See text.
The values thus independently obtained have checked to within a degree which does not alter the positions of the entries in Fig. 1.

The diversities of organisms, of technical precision, and of intrinsic weights of observations involved in the data giving rise to Fig. 1 provide every opportunity for the operation of statistical factors of chance. The non-existence of discrete, recurrent, magnitudes of $\mu$ should therefore be expected to produce in Fig. 1 a single moded frequency distribution. The most reasonable interpretation of the apparent facts, on the other hand, accepts the view that in living matter of various sorts there frequently recur certain processes, manifest as controlling processes, which are similar to the extent that they exhibit sensibly identical temperature characteristics. It should be noted that the peaks in Fig. 1 agree perfectly with magnitudes of $\mu$ which seem to rest upon the most solid observational basis.

The most probable values of these critical increments cannot be ascertained from the graph in Fig. 1. Thus there is evidence that the frequently obtained values 11,000+ and 12,000+ are organically distinct; similar consideration holds for 16,000+ and 18,000+. In the region of higher magnitudes (20,000 and above) the number of instances is insufficient, but there are available unexceptionable individual series of data yielding, for example, $\mu = 23,500$, $\mu = 32,000$. The most probable values of the characteristics typically encountered are not required for the present discussion, which aims merely to demonstrate the repeated occurrence of recognizably discrete magnitudes. This does not involve the assertion that the value of a temperature characteristic must be regarded as unmodifiable. If real fluctuation does occur, it is in Fig. 1 massed with deviations due to inadequacies of observation. The problem of modification of critical increment is one of peculiar fascination and great possibilities, as I have already intimated (Crozier, 1924–25, b), but its discussion must await further experimentation.

By proper choice of abscissa the calculation is reduced to one setting of the slide rule. This method is much better than reliance upon a nomogram, since it is possible in fitting the lines to give weight to the latitude of variation (Crozier and Federighi, 1924–25; 1925).
Fig. 2. Comparative distribution and frequencies of temperature characteristics obtained from (A) data pertaining to heart activities (solid black circles), and (B) all non-heart observations (white circles). As explained in the text, it is probable that many series of observations are in need of revision; this is due in part to the fact that with isolated hearts time may be a significant variable.
III.

The heart rate is easily observed in many animals, and numerous sets of data giving its variation with temperature have been published. It is proposed to illustrate with these data, and with the results from some new experiments, one further aspect of the probable occurrence in living matter of a system of processes which, in one or another case, control the change in rates of vital phenomena as determined by temperature alterations. Heart rate observations are particularly suitable because of the infrequent occurrence of breaks at intermediate temperatures. Fig. 2 shows the frequency distribution of temperature characteristics for heart activities (A), and enables its modes to be compared with those in the curve (B) for values of μ derived from all other (non-heart) sets of observations entering into Fig. 1. Again the

![Graph showing heat liberation and velocity of contraction](image-url)

**Fig. 3.** Heat liberation per second of stimulation, frog skeletal muscle (Hartree and Hill, 1921).

Velocity of contraction to maximum, frog heart muscle (Eckstein, 1920). Different preparations distinguished by symbols. At very low temperatures, irregularities appear, as is not uncommon.
probable significance of the polygon $A$ can be enhanced if one were to omit certain dubious instances.

Fig. 4. Observations on frog hearts. Data from:
I. Clark (1920–21), heart perfused with oxygenated Ringer solution (×); with alkaline Ringer solution (○). Snyder (1907), (○).
II. Personal observations, one series.
III. Snyder (1907), two series.
IV. Gellhorn (1924).
V. Ishihama (1924), latency in contraction of sinus (○) and of ventricle (×).
VI. Burdon-Sanderson and Page (1879–80), refractory period.
In I, III, and V series not significantly different have been combined by multiplication of one by a factor; each has its own symbol.
It is obvious that the two distributions are similar; their modes are coincident. Therefore, the processes which in different cases control the frequency of the heart beat are similar in kind and in variety.

Fig. 5. Observations on heart beat frequency in two similar embryos of the lake white fish Corregonus (Hubbs and Crozier 1919-20). Development had been undergone at low temperature. A temperature of 14–16° produces a frequency of contraction which is very little exceeded at higher temperatures. But the break comes at different temperatures in the two cases. Attempting to average observations, at each of a number of temperatures, from several individuals, would in the presence of such differences be very likely to produce a curvilinear relation between log frequency and 1/T. In the event that breaks of different sort are present in some individuals but not in others, averaging leads to additional difficulties.

The experiments of Knowlton and Starling (1912) have been sometimes appealed to as giving evidence against the existence of a “temperature coefficient” for heart beat frequency. Knowlton and Starling (loc. cit.) give data for two experiments only, one series of readings with one dog heart and one with one cat heart; the perfusion pressure was varied, and the reflection of this is superimposed upon the temperature effect; in the range 37.5–27°C. the critical increment is 11,300, as found in some other cases; below 27° the alterations in arterial pressure obscure the results, which, however, are not inconsistent with the conclusion that the increment is really about 17,000. The deduction is permissible that under the conditions of their experiments (i.e. heart-lung preparation) the velocity of an oxidative process (Crozier, 1924-25, b) controls the frequency of heart beat.
to those governing the velocities of many other sorts of cellular phenomena.

Since it is legitimate to consider that the frequency of heart beat is in many cases dependent upon properties of cardiac muscle (for some recent evidence, cf. Copenhaver, 1925), I have not hesitated to put together in Fig. 2 increments referring to heart rates of intact animals, of isolated hearts, and to properties of cardiac muscle. It is of interest to notice that the velocity of contraction of frog heart muscle (Eckstein, 1920 (Fig. 3)) provides an increment identical with that for heat liberation (per gm. per second during stimulation) of frog skeletal muscle (Hartree and Hill, 1921). The refractory period of frog heart (Burdon-Sanderson and Page, 1879–80 (Fig. 4)) and the muscular latency (Ishihama, 1924 (Fig. 4)) show an increment which does not differ from that for latency in frog gastrocnemius (Burnett, 1906–07, $\mu = 10,800$; also data of Woolley, 1900, in Crozier, 1924–25, b); the increment for latency in smooth muscle seems de-
nately different (data of Viale, 1921, on stomach rings of winter frogs, give \( \mu = 13,000 \pm \); of Schultze, 1897, 12,200; of Stewart, 1900-01, on cat’s bladder, 17,000).

Complete presentation of the material summarized in Figs. 1 and 2 is unnecessary. The heart rate data illustrate so well the kinds of relations observed that a fairly complete representation of instances for the hearts of amphibians, reptiles, and mammals is given in Figs. 4, 9, 10, and 11. (A few cases illustrated in previous papers are omitted.)

![Diagram](image)

**Fig. 7.** The frequency of frog heart beat may be increased without sensible change of increment; lower plot, perfused with Ringer solution; upper, with Ringer plus horse serum plus adrenalin 1:500,000 (from Gellhorn, 1924).

A difficulty which arises in the interpretation of many series of published observations is due to the presentation of *average* figures derived from several individuals supposed to be similar. One sort of confusion which thus becomes possible will be understood from Fig. 5. The most significant values of \( \mu \) are obtained from numerous observations upon one object.

It is clear that the same magnitudes of \( \mu \) are repeatedly encountered. The \( \mu \) may be constant even when the frequency is increased during growth (Fig. 6) or through alteration of the perfusing fluid (Fig. 7).
But the same kind of isolated heart may show different values for \( \mu \), quite definitely distinct, apart from deliberate experimental interference (see Fig. 8). This has a direct bearing upon the interpretation of attempts to alter the temperature coefficient of heart activity by chemical means.\(^6\)

![Graph showing the value of \( \mu \) for frog heart beat frequency](image)

Fig. 8. The value of \( \mu \) for frog heart beat frequency may differ independently of deliberate experimental treatment; I and III, perfused with Ringer solution plus horse serum; II, Ringer solution; IV, Ringer and tyramin (data from Gellhorn, 1924).

Nevertheless it is clear that the temperature characteristics for heart processes are of the same categories, quantitatively, throughout the vertebrate series (Figs. 4, 9, 10). The increments obtained with one type of heart (e.g. amphibian (Fig. 4)) are of the same classes as those encountered in other types. The occurrence of several definite \( \mu \) for the same

\(^6\) Cf. Clark (1920-21); Bouckaert, Bouckaert, and Noyons (1922); Sollmann, Mendenhall, and Stingel (1914-15).
activity, even in the same individual (cf. Crozier and Stier, 1924–25, a), is fully consistent with the idea that the control of vital processes depends, not upon a single sort of process, but upon a nexus of inter-

related chemical reactions, constantly proceeding but with individually variable rates. The examination of all available information leads to the suspicion that this complex system of controlling reactions
is in certain essential details constant, in living matter of whatever kind."
IV.

SUMMARY.

Disregarding sources of variation known to be present in the unselected data, it is shown that the frequency distribution of temperature characteristics (critical increments) calculated from all known series of observations, pertaining to a great variety of vital processes, exhibits a number of discrete modes. This leads to the view, already derived from evidence of a more specific sort, that such critical increments may be used to characterize definite processes in a controlling system of reactions which seems to be of widespread occurrence in living matter.

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