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The Three Phases of Nerve Heat Production.

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The heat production of stimulated nerve occurs in two main stages, initial and recovery. The first object of this paper is to define and distinguish the initial heat more clearly; the second is to present fresh evidence that the recovery heat occurs in two phases, the first complete in a few seconds, the second only in 30 minutes.

Since an earlier paper (Hill, 1932, *a*) was written, various attempts have been made to quicken up the recording system of thermopile and galvanometer, so as to secure a sharper analysis of the heat. A new thermopile has been constructed by Mr. A. C. Downing, with soldered constantan-iron couples and bakelite insulation. It is very rapid in its action—far more rapid than the galvanometer. It is no more sensitive than the old one, but possesses the great advantage for some purposes that it is so well shielded from heat leaking from the stimulating electrodes that a correction is seldom necessary.

A single galvanometer can be used to record the heat, but if so it must be a very sensitive one and consequently slow. Amplification, therefore, with a photo-electric cell coupling two galvanometers has been employed, which introduces no lag except that of the second galvanometer. The latter must be one of short period. The photo-relay is superior to the thermal relay which introduces considerable extra lag. In most of the critical experiments a Zernicke moving coil galvanometer (Zb) of period 1·8 second was coupled by a Cu_2O photo-cell either to a Downing moving magnet galvanometer, or to a Moll galvanometer of period about 1·2 second. With this arrangement a full deflection is reached about $2\frac{1}{2}$ seconds after introducing a constant current.

At high sensitivity random disturbances, mechanical, thermal and electrical, are serious, but these have been avoided (*a*) by the use of Julius suspensions for both galvanometers, (*b*) by the closed thermostat described in the following paper, (*c*) by better insulation, and (*d*) in certain experiments by taking the mean of a large number of records.

Stimulation and all other details of technique were as described before (Hill, 1932, *a*); the nerves were from large Hungarian frogs (*R. esc.*).

The experiment shown in fig. 1 is one of the most decisive. The temperature was rather low (15·7° C.) so the nerve processes were somewhat slower—and therefore more easy to analyse—than at the usual room temperature of about 20° C. The quick galvanometer system was employed. Analysis was in blocks of heat of $\frac{3}{4}$-second duration, using a heating control of the same duration; the mean of 29 records of 9 seconds (12 units) maximal stimulation was employed; stimulation was at 460 shocks per second, at about 4-minute intervals. The results are given in Table I.

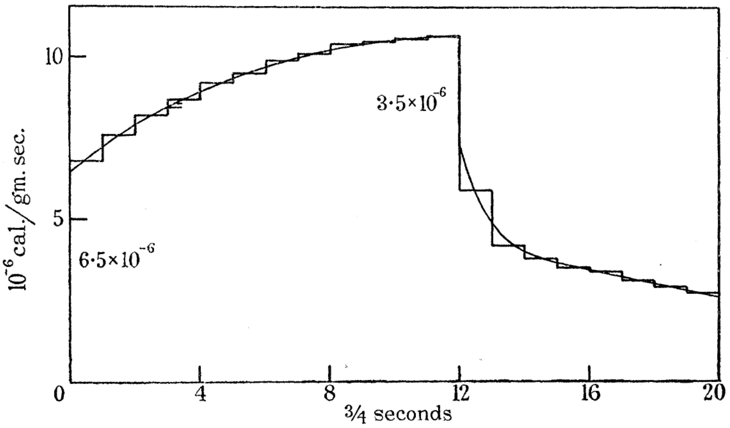

FIG. 1.—Analysis, in $\frac{3}{4}$-second time units, of heat rate during and after 9 seconds stimulation of frog's nerves at 15·7° C. See Table I and text.

By reason of the quick galvanometer system and the accuracy of the mean of 29 records, the analysis is quite determinate in spite of the short interval ($\frac{3}{4}$ second) employed. The "remainders" are very small and the solution is smooth. The initial heat is sharply defined, both at the beginning and at the end of stimulation, and it is noticeable that the latter ($3{\cdot}5 \times 10^{-6}$ cal./gm. sec.) is much less than the former ($6{\cdot}5 \times 10^{-6}$ cal./gm. sec.). This "fatigue" effect is the reason why the curve tends to reach a maximum instead of continuing to rise. It is intermediate in type between curves IV and V, fig. 6.

Another example is given in fig. 2, together with the means of the records from which the analyses were made. The initial heat again is quite definite; it decreases, but not much, during stimulation. The curves can be compared with the calculated ones of fig. 4.

Fig. 3 (see Table II) represents the analysis in three different time units, 1, 2 and 4 seconds respectively, of the deflection caused by 16 seconds stimulation. Although of course the first is the most decisive the others yield

Table I.—Analysis of record of 9 seconds stimulus at 15·7° C. (See fig. 1.)

Time, $\frac{3}{4}$ second.	0.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
Mean record	0	7	54	127	213	300	388	475	560	646	728	810	888
$\frac{3}{4}$-second control	0	100	617	918	936	903	855	808	762	720	680	643	610
Solution*	75	83	91	97	102	106	110	112	115	116	117	118	66
Remainder	0	0	0	−2	1	1	1	0	−1	−1	−1	0	1

Time, $\frac{3}{4}$ second.	13.	14.	15.	16.	17.	18.	19.	20.	21.	22.	23.	24.
Mean record	958	994	1000	995	986	975	962	946	930	915	898	881
$\frac{3}{4}$-second control	578	550	524	500	478	459	440	422	406	392	378	365
Solution*	47	42	39	38	34	32	30	27	24	22	20	—
Remainder	2	0	−1	−1	0	0	1	1	−1	0	0	—

* For absolute units, calories per gram per second, multiply by $0 \cdot 0902 \times 10^{-6}$.

practically the same solution, and they require respectively not more than 1/4 and 1/16 of the amount of calculation. With the apparatus available it is clear that no greater accuracy would be reached by working in time units less than 1 second. In this case the initial heat is practically the same at the

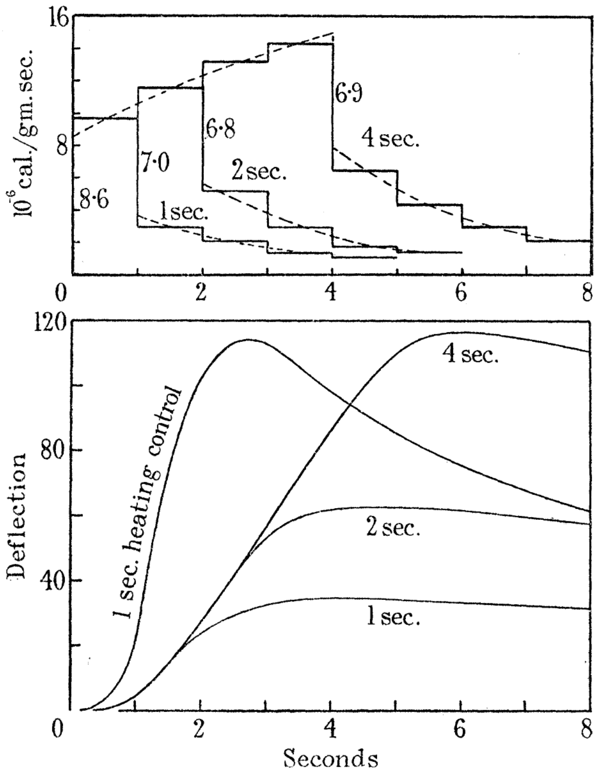

FIG. 2.—*Experiment of May* 31, 1932, at 19° C. Records begun about 4 hours after dissection. Maximal shocks, 370/second.

Below: Records reduced to same scale, 4 seconds stimuli (mean of 26), 2-seconds (mean of 24), 1-second (mean of 25), and 1-second heating control.

Above: Analysis of records for the three cases. The broken lines are smooth curves interpolated between the blocks. The initial heat at the beginning is $8 \cdot 6 \times 10^{-6}$ cal./gm. sec.; at the end of 1 second it has fallen to $7 \cdot 0 \times 10^{-6}$ cal./gm. sec., after which, for the next 3 seconds, it does not fall appreciably further.

end as at the beginning of stimulation; consequently the curve is of type I (or II), fig. 6.

Another analysis of 12 seconds stimulation with rapid recording is given elsewhere (Hill, 1932, *b*, fig. 7, p. 21). A curve properly interpolated between the solutions gives 7×10^{-6} cal./gm. sec. as the initial heat rate at the beginning

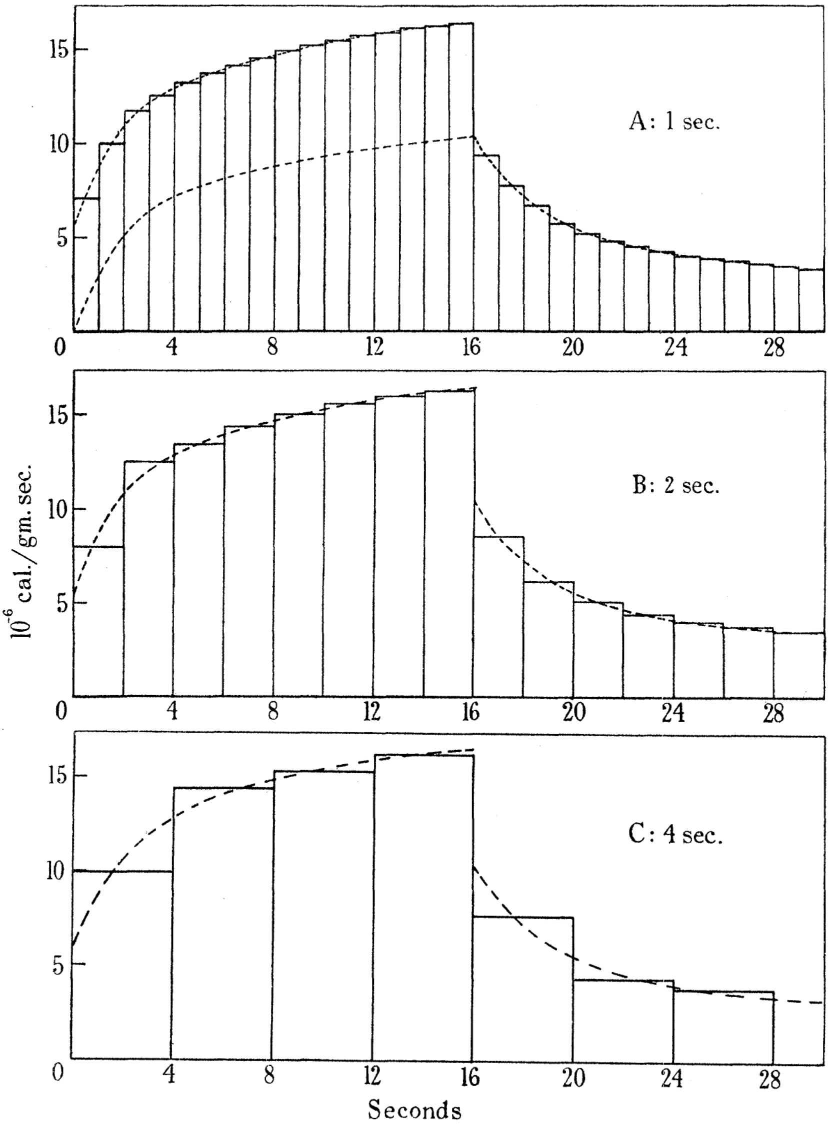

FIG. 3.—Analysis of records of 16 seconds stimulus, A in 1-second, B in 2-seconds, C in 4-seconds time units, for comparison. See Table II for description. The upper broken line is interpolated to give the course of the heat production. The lower broken line in A gives the recovery heat alone, after subtracting the initial heat from the total.

Table II.—*Experiment of October* 11, 1932, at 18·5° C., with four pairs of nerves of Hungarian frog, *R. esc.* 16-seconds stimuli at 8-minutes intervals, mean of 19 given in 0·05 mm. units. Nearly maximal stimulation, at 380/sec. for 14, 575/sec. for 2, 600/sec. for 3. 1-second heating control = 133 × 10^{-6} cal./gm.

Time, seconds :	0.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
Mean deflection	0	13	68	146	230	314	393	468	541	610	676	740	801	858	913	965
Control	0	247	956	1000	898	806	726	657	598	549	505	469	436	407	381	358
Solution A	53	75	88	94	99	103	106	109	112	114	116	118	119	121	122	123
Remainder	0	0	−1	0	0	1	1	0	0	0	0	0	0	0	−1	−2
Solution B	60	—	94	—	101	—	108	—	113	—	117	—	120	—	122	—
Remainder	0	—	−3	—	3	—	1	—	0	—	−1	—	0	—	0	—
Solution C	74	—	—	—	108	—	—	—	114	—	—	—	121	—	—	—
Remainder	0	—	—	—	0	—	—	—	0	—	—	—	0	—	—	—

Time, seconds :	16.	17.	18.	19.	20.	21.	22.	23.	24.	25.	26.	27.	28.	29.	30.
Mean deflection	1017	1055	1043	1018	989	958	927	897	870	843	819	797	776	757	739
Control	337	318	302	287	273	260	248	238	228	219	210	202	194	186	179
Solution A	70	58	50	43	39	36	34	32	30	29	28	27	26	25	—
Remainder	−1	2	−1	−2	−2	−1	2	−1	0	−1	−1	0	0	0	1
Solution B	64	—	46	—	38	—	33	—	30	—	28	—	26	—	—
Remainder	0	—	−3	—	2	—	1	—	0	—	−1	—	0	—	0
Solution C	58	—	—	—	33	—	—	—	29	—	—	—	—	—	—
Remainder	0	—	—	—	0	—	—	—	0	—	—	—	—	—	—

Solution A is in 1-second time units by the 1-second control; B is in 2-second units by a built-up 2-second control; C is in 4-second units by a built-up 4-second control. Each solution is in thousandths of the corresponding control. The initial heat rate is 5·7 × 10^{-6} cal./gm. sec. at the beginning and 6·0 × 10^{-6} cal./gm. sec. at the end of the stimulus. See fig. 3.

and 5×10^{-6} cal./gm. sec. at the end of stimulation. The curve is of type III, fig. 6.

These examples make it clear that there is an abrupt rise in the rate of heat production at the beginning of stimulation and an abrupt fall at its end. The only possible interpretation of these sudden changes is that during stimulation there is a distinct phase of heat production—what we call the initial heat—which starts and ends abruptly. The available technique does not enable us to decide whether the initial heat corresponding to a given impulse occurs actually during the impulse or a short time afterwards. It is arguable that none of the heat appears during the actual passage of the conducted wave but only, say, 1/5 of a second afterwards. However this may be, there is no doubt from the analyses that there is a separate phase of heat production closely associated, if not actually simultaneous with the conduction of the impulse.

In earlier experiments in which analysis was carried out in 1-second time units, the first block of the analysis was taken as representing the initial heat. This, it is clear, involves a certain error, for even the first second must contain recovery heat. When analysis is done in 2-seconds time units the error would be more serious. The intersection, therefore, with the vertical axis, of a smooth curve drawn through the final results of the analysis has been used to give the value of the initial heat rate at the beginning of stimulation. The intersection of a smooth curve drawn through the results after stimulation, with the ordinate at the end of stimulation, similarly supplies the initial heat rate at that moment. Very consistent estimates of the abrupt rise and fall of heat rate at the beginning and end of stimulation can be made in this way. These abrupt changes are what is meant by the initial heat. They are not necessarily the same at the beginning and end of a stimulus. Usually there is a slight decrease, sometimes a considerable decrease, in the initial heat rate during a stimulus (say) of 16 seconds duration at a high frequency.

Referring now to the recovery heat, it is evident from the curves given here and elsewhere that there is a rather rapid fall in rate immediately after the end of stimulation, which is followed by a very slow fall continuing, as will be shown in subsequent papers, for 25 to 35 minutes at 20° C. It is possible to reach a steady rate of heat production if stimulation, at not too high a frequency, be continued for 25 to 35 minutes. This agrees with the finding that the recovery heat production from a single stimulus persists for a similar time. Let us assume that this slow recovery process is represented by an exponential term Be^{-bt}, where b is given the value $0 \cdot 003$, which is such that the slow process is half complete in about 4 minutes, 99% complete in about 25 minutes.

From the analyses given it is evident that the rapid phase of recovery is complete in a few seconds, and measurement of the fall of the curve after the end of stimulation in a number of records has given $2\frac{1}{2}$ seconds as about the time required for the rapid process to reach half its initial rate. Let us assume that the rapid recovery phase is represented by another exponential term Ae^{-at}, where a is taken as $0\cdot25$, which is such that the "A" process would be half complete in $2\frac{1}{2}$ seconds, 99% complete in 18 seconds. Let I be the rate of initial heat production during a stimulus, and suppose that any element $\mathrm{I}\delta\theta$ of initial heat is followed by a proportional element of recovery heat, whose rate at time t is

$$\frac{\mathrm{I}\delta\theta}{k}(\mathrm{A}e^{-at}+\mathrm{B}e^{-bt}).$$

The total amount of recovery heat, obtained by integration, is

$$\frac{\mathrm{I}\delta\theta}{k}\left(\frac{\mathrm{A}}{a}+\frac{\mathrm{B}}{b}\right),$$

so the ratio of recovery to initial heat is

$$\frac{1}{k}\left(\frac{\mathrm{A}}{a}+\frac{\mathrm{B}}{b}\right).$$

Let us take

$$\frac{1}{k}\left(\frac{\mathrm{A}}{a}+\frac{\mathrm{B}}{b}\right)=24\cdot7,$$

which is about the value found in a subsequent paper.

Let stimulation continue for time T and then stop. At any subsequent time t the rate of recovery heat production is

$$\int_{\theta=0}^{\theta=\mathrm{T}}\frac{1}{k}\,[\mathrm{A}e^{-a(t-\theta)}+\mathrm{B}e^{-b(t-\theta)}]\,d\theta,$$

which (if I be constant) is

$$\frac{1}{k}\left[\frac{\mathrm{A}}{a}(e^{-a(t-\mathrm{T})}-e^{-at})+\frac{\mathrm{B}}{b}(e^{-b(t-\mathrm{T})}-e^{-bt})\right].$$

The rate of the "A" process at time $t=\mathrm{T}$, *i.e.*, immediately at the end of stimulation, is $\frac{\mathrm{A}}{a}(1-e^{-a\mathrm{T}})$, that of the "B" process $\frac{\mathrm{B}}{b}(1-e^{-b\mathrm{T}})$. The former can be read off from the analyses, as the drop in recovery heat that occurs in 15 seconds or so. The latter is what then remains.

Thus, knowing a and b, A, B and k can be determined in a number of experiments. Round values so found are $\mathrm{A}/a=10$, $\mathrm{B}/b=200$, $k=8\cdot5$.

Fig. 4 shows the rate of heat production during and after stimuli of 2, 4, 8, 16 and 32 seconds duration, as calculated from the formulæ and constants given above, assuming a uniform rate of initial heat production of 6. The curves are very similar to those actually observed; see for example fig. 2 above, and figs. 11, 12 and 13 in a previous paper (Hill, 1932, *a*). The likeness is most striking in those cases in which the rate of initial heat production is approximately constant during stimulation. In many experiments, however, *e.g.*, that of fig. 1 above, the rate of initial heat production diminishes considerably during a stimulus; this is particularly so at 0° C., see, *e.g.*, figs. 14 and

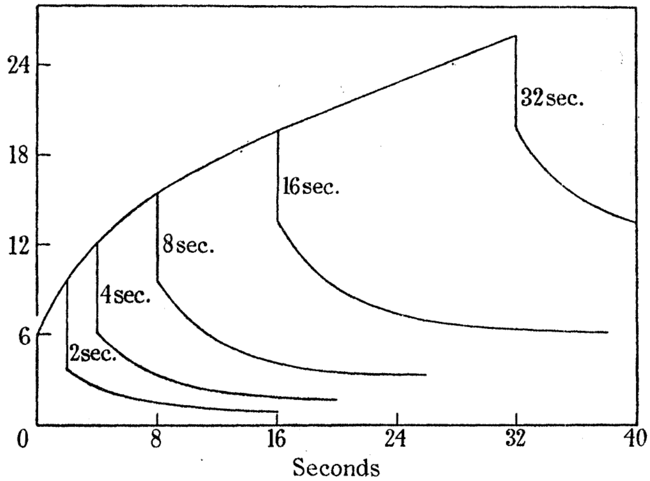

Fig. 4.—Calculated curves of total heat rate, during and after stimuli of various lengths, assuming a uniform rate of initial heat production of 6 during stimulation and the equations and constants given in the text.

16 of the paper referred to above. The consequence of this is that the rate of total heat production does not go on rising so fast as in the calculated curve of fig. 4; it may become constant, or even begin to diminish. Indeed, with a stimulus of sufficiently high frequency continued for some time such "fatigue" invariably occurs. It is possible to take account, in the equations, of the decrease of I, the initial heat rate, and in fig. 5 is an example of 32 seconds stimulation calculated from the same constants as before but assuming that the initial heat rate starting from 8·5 falls exponentially to 5·3 at the end of 32 seconds, and would fall further to 2·5 were stimulation continued indefinitely. This curve is so strikingly similar, and in such varied respects, to many actually observed that little doubt can remain of the general validity of the assumptions on which it is calculated.

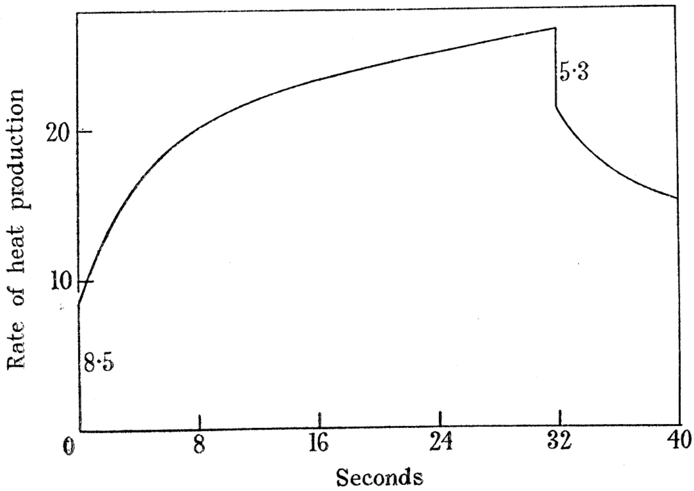

FIG. 5.—Calculated curve of total heat rate, during and after a 32 seconds stimulus, assuming equations and constants given in the text. The rate of initial heat production is supposed to start at 8·5 and to decrease exponentially to 5·3 at 32 seconds (to 2·55 at $t=\infty$).

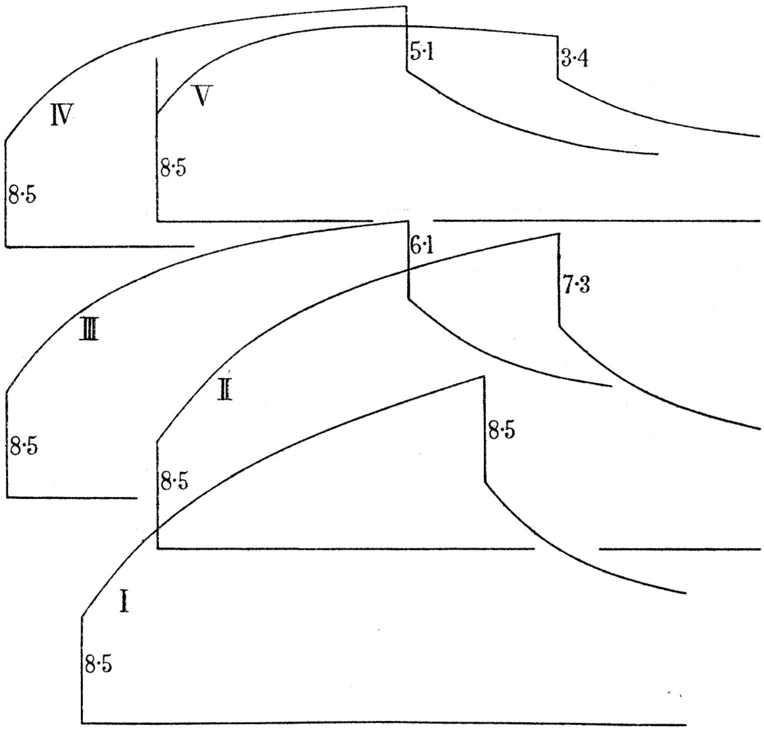

FIG. 6.—Calculated curves of total heat rate, during and after a 16 seconds stimulus, assuming the equations and constants given in the text. The rate of initial heat production is supposed to start always at the same value (8·5) and then either to continue uniformly (curve I), or to decrease exponentially (curves II to V) as follows: II—To 7·3 at 16 seconds, to 4·24 at ∞; III—To 6·15 at 16 seconds, to 4·25 at ∞; IV—To 5·1 at 16 seconds, to 4·25 at ∞; V—To 3·4 at 16 seconds, to 1·7 at ∞.

In fig. 6 various calculated curves are given for the experiment with 16 seconds stimulation, with the same constants as before, but with the initial heat decreasing to various degrees during the stimulus. No case has been found which does not conform to one or other of the types shown. It is clear that "fatigue" setting in during stimulation is the reason why the heat rate curves deviate from a constant type.

It is possible to change the form of the heat rate curve by various means, some of which will be referred to in the following papers. Fig. 7 gives an example of the same nerves, first in 5% CO_2, then later in 10% CO_2, in oxygen.

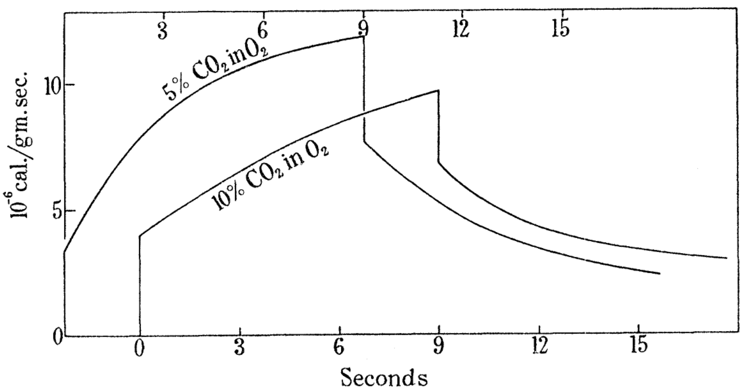

Fig. 7.—Effect of CO_2 on nerve heat production. Experiment of October 24, 1932, at 17½° C. Quick galvanometer system. Analyses in ¾-second time units of mean of: 5% CO_2, 14 records; 10% CO_2, 18 records; at 3 to 4 minute intervals, of 9 seconds stimulation by nearly maximal shocks, 420/second. Nerves dissected 10–11 a.m., 5% CO_2 in at 12.45 p.m., records 2–3 p.m., 10% CO_2 in at 3.15 p.m., records 4.15 to 5.15 p.m. Note the slower rise, due to decreasing initial heat rate, in 10% CO_2.

In the former the initial heat remained constant, or even increased a little, during stimulation; in the latter it decreased considerably. The CO_2 may have caused a "Treppe" at the lower concentration, and an increase of the refractory period during stimulation at the higher.

Summary.

(1) The process of activity in frog's medullated nerve occurs in at least three phases:—

(a) That in which the initial heat is liberated: this may or may not coincide in time with the actual transmission of the impulse, but it certainly does not lag behind it by more than a fraction of a second.

(*b*) That in which the rapid " A " process of recovery occurs: at 20° C. in frog's nerve this runs to half completion in 2 or 3 seconds and to completion (within 1%) in about 20 seconds.

(*c*) That in which the slow " B " process of recovery occurs: this runs to half completion in 4 or 5 minutes, to completion (within 1%) in 25 to 35 minutes.

(2) The total heat liberated in the rapid " A " process of recovery is about equal to the initial heat; that in the slow " B " process is many times greater.

(3) The initial heat rate may diminish rather rapidly during stimulation, particularly at a high frequency or a low temperature.

REFERENCES.

Hill, A. V. (1932, *a*) 'Proc Roy. Soc.,' B, vol. **111**, p. 106.

—— (1932, *b*). "Chemical Wave Transmission in Nerve," Cambridge University Press.

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The Steady State of Heat Production of Nerve.

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[Plate 11.]

At rest at 20° C. in oxygen a frog's nerve produces heat at a rate of about 70×10^{-6} cal./gm. sec. (Beresina, 1932). All activity is superimposed upon this " basal " state. If a nerve be stimulated at not too high a frequency its rate of heat production rises, until in 25 to 40 minutes (at 20° C.) it reaches a steady level in excess of the " basal." If the stimulus be then stopped the rate of heat production gradually returns to its initial " basal " value. The process is illustrated in fig. 1. The frequency was low (9·7 shocks per second) and the final value reached by the extra heat production after 35 minutes stimulation was $9 \cdot 7 \times 10^{-6}$ cal./gm. sec. or 10^{-6} cal./gm. impulse.

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