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THE MODE OF ACTION OF NICOTINE AND CURARI, DETERMINED BY THE FORM OF THE CONTRACTION CURVE AND THE METHOD OF TEMPERATURE COEFFICIENTS.

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In recent years there has been a tendency to attribute to a physical rather than to a chemical process, the action of many substances which have an effect upon the organism when given in very minute quantities. In very few cases, however, has the physical view been worked out in any detail. The actions of nicotine and of curari have been investigated by Prof. Langley on the lines of physiological experiment, and he advocates the view that these, and other similar bodies, in producing their specific effects form reversible chemical combinations with certain constituents—"receptive substances"—of the cells. In the following pages I have tested the mode of action of nicotine and curari, on the skeletal muscles of the frog, by mathematical and physico-chemical methods.

1. Mathematical consideration of the curves of muscular contraction and relaxation.

The action of nicotine and of Ringer's solution after nicotine.

The apparatus used for recording the contractions was that designed by Mr Keith Lucas for Prof. Langley. The point of the lever described a vertical straight line on a stationary drum. The muscle used in all cases unless otherwise stated was the *rectus abdominis* of *Rana Temporaria*. It was allowed to relax completely in Ringer's solution under the weight of the lever (about 2·5 gr.) before being immersed in the nicotine solution.

Curves of contraction, recorded on a slowly rotating drum, were obtained by the use of dilute (·00003 %) nicotine. Within the limits of error I found the curves of contraction followed the equation,

$$y = k\,(1 - e^{-\lambda t}),$$

where y is the height of contraction, and t is the time measured from the beginning of the contraction.

The method used for verifying the equation of the curve was as follows:—The ordinates measured *down* from the asymptote (the full height of contraction, $y = k$) were taken at equal intervals of time from the tracing. These should be in geometrical progression.

For example, if AB, CD, EF, GH,... be drawn at equal intervals of time to meet the asymptote in A, C, E, G,... and the curve in B, D, F, H,... then $\frac{AB}{CD} = \frac{CD}{EF} = \frac{EF}{GH} = \ldots$. If the interval of time were n minutes,

$$y_t = k\,(1 - e^{-\lambda t}),$$

$$y_{t+n} = k\,(1 - e^{-\lambda (t+n)}),$$

$$\frac{k - y_t}{k - y_{t+n}} = \frac{ke^{-\lambda t}}{ke^{-\lambda (t+n)}} = e^{\lambda n},$$

which is a constant not depending on t.

The ratios of successive ordinates at equal intervals of time were taken, and found to be practically the same all along the curve. Below are given a few typical results selected at random.

I. Interval 2′.

Ratios of successive ordinates:—·63, ·68, ·77, ·71, ·73, ·71, ·77, ·81, ·76, ·75, ·77, ·76, ·75.

II. Interval 3′.

Ratios of successive ordinates:—·75, ·75, ·90, ·88, ·89, ·79, ·82, ·86, ·89, ·84, ·82, ·85, ·87, ·88.

III. Interval ½′.

Ratios of successive ordinates:—·82, ·81, ·83, ·86, ·85, ·86, ·86, ·86, ·85, ·85, ·86, ·86, ·89, ·89, ·89, ·89, ·89, ·89, ·90, ·90.

IV. Interval 1·5′.

Ratios of successive ordinates:—·83, ·77, ·72, ·71, ·69, ·74, ·75, ·74, ·77, ·74, ·74, ·71.

V. Interval 40″.

Ratios of successive ordinates:—·74, ·77, ·77, ·78, ·78, ·76, ·72, ·77, ·70, ·64, ·78.

VI. Interval 40″.

Ratios of successive ordinates:—·93, ·93, ·94, ·93, ·93, ·93, ·94, ·94, ·94, ·94, ·94, ·94.

Some twenty of such curves were analysed and the same results appeared in all. Thus the curve of nicotine contraction follows the equation,

$$y = k\,(1 - e^{-\lambda t}).$$

The next point to determine was the equation of the curve of relaxation when a *rectus abdominis* muscle which had contracted in dilute nicotine was washed with, and left to relax in, Ringer's solution.

The curve obeyed the equation,

$$y = ke^{-\lambda t}.$$

Below are given a few typical results. The ordinates are here measured from the level to which the muscle finally relaxes after 4 or 5 hours.

I. Time interval 20′.

Ratios of successive ordinates:—·41, ·71, ·84, ·81, ·85, ·80, ·80, ·79, ·82, ·78, ·81, ·81.

II. Time interval 20′.

Ratios of successive ordinates:—·88, ·77, ·70, ·68, ·71, ·70, ·77, ·67.

III. Time interval 25′.

Ratios of successive ordinates:—·74, ·64, ·63, ·69, ·75, ·69, ·69, ·64.

Quite at the end of a relaxation (or contraction) when the quantities to be measured are so small (1 mm. or less) that errors of observation make the ratios irregular, the ratios are omitted. The usual height of contraction is of the order of several centimetres, and exact measurements are easily made.

The question arises, What reasonably simple explanation can we give of the equations $y = k\,(1 - e^{-\lambda t})$, during contraction, and $y = ke^{-\lambda t}$, during relaxation? The answer must in all probability be a simple one: otherwise we should not have the extraordinary coincidence of such simple equations holding for such long periods of time. Two possible solutions can be advanced. The form of the curve is due either (*a*) to the gradual diffusion of the nicotine inwards, or (*b*) to a gradual combination (chemical or otherwise) between nicotine and some substance in the muscle.

(*a*) Let us suppose that the height of contraction, y, is directly proportional to $(N - M)$, where N is the amount of nicotine that has diffused in at any time, and M is the minimum amount that will cause any contraction at all. By N_0 is meant the concentration of nicotine in the bathing fluid.

Then the rate of diffusion inwards is proportional to the difference between the concentrations inside and outside.

i.e. $\frac{dN}{dt}$ is proportional to $(N_0 - N) = \lambda (N_0 - N)$,

i.e. $$\int_0^N \frac{dN}{N_0 - N} = \int_0^t \lambda dt,$$

i.e. $$\log \frac{N_0 - N}{N_0} = -\lambda t,$$

i.e. $$N = N_0 (1 - e^{-\lambda t}).$$

Now, by hypothesis y is proportional to $N - M$,

i.e. $$y = k' (N_0 - M - N_0 e^{-\lambda t}) = k' (N_0 - M) (1 - e^{-\lambda t + \log \frac{N_0}{N_0 - M}}),$$

which becomes

$$y = k (1 - e^{-\lambda t}),$$

if we measure the time from a time $\frac{1}{\lambda} \log \frac{N_0}{N_0 - M}$ after the muscle was immersed in nicotine.

For the relaxation we have, when the concentration of nicotine outside is zero,

$$-\frac{dN}{dt} = \lambda N.$$

This gives $y + k'M = k'N_0 e^{-\lambda t}$, and $y + k'M$ is the height above a certain line very nearly at the final position of relaxation.

(*b*) Let us, on the other hand, suppose that nicotine combines, for example chemically, with some constituent A of the muscle, and that the height of contraction y is directly proportional to

$$(NA) - M,$$

where (NA) is the amount of the compound formed by nicotine with that constituent, and M is the least amount necessary for any contraction to occur.

It is quite reasonable to suppose that diffusion is so rapid as not sensibly to affect anything but the initial shape of the curve. We have

$$N + A \rightleftarrows NA.$$

The action is undoubtedly reversible as complete relaxation in Ringer's solution can be obtained.

As Arrhenius points out[1] the ordinary laws of chemical dynamics can be taken as true for heterogeneous, as well as for homogeneous media, provided that diffusion can go on with sufficient rapidity.

[1] *Immuno-Chemistry*, p. 142, 1907.

Let the velocity constants for the action $\longrightarrow$ be k and $\longleftarrow$ be k': we have:

$$\frac{d(NA)}{dt} = k(N)(A) - k'(NA).$$

Now $(A) + (NA) = X$, a constant, the number of molecules of the substance A present.

$$\therefore \frac{d(NA)}{dt} = -(k' + kN)(NA) + k(N)X,$$

i.e. $$\int_0^{(NA)} \frac{-d(NA)[k' + k(N)]}{k(N)X - [k' + k(N)](NA)} = \int_0^t -dt[k' + k(N)],$$

which gives

$$(NA) = \frac{k(N)X}{k' + k(N)}\{1 - e^{-[k' + k(N)]t}\}.$$

This, as above, on measuring the time from a suitable place, becomes:

$$y = \mu\left\{\frac{k(N)X}{[k' + k(N)]} - M\right\}\{1 - e^{-[k' + k(N)]t}\}.$$

(N) is here the concentration of nicotine both inside and outside the muscle, supposed to have become equal in a comparatively short time.

For the relaxation we have

$$y + M\mu = \mu(NA)_0 e^{-k't},$$

where $(NA)_0$ is the initial amount of NA present.

To decide between the hypotheses (a) and (b) two methods may be used, (A) and (B) below.

A. The total height of contraction should be, according to (a) (the physical hypothesis) proportional to $N - M$, and according to (b) (the chemical hypothesis) proportional to $\frac{N}{k' + kN} - M$.

To decide this a *rectus abdominis* muscle, lightly weighted, was allowed to stay successively in the following concentrations of nicotine, until fully contracted in each.

Strength of nicotine	$N = \cdot000008\ \%_0 \times 1$,	$\cdot000008\ \%_0 \times 1{\cdot}96$,
Height of contraction	$y = 4$ mm.,	11·9 mm.,
	$N = \cdot000008\ \%_0 \times 2{\cdot}89$,	$\cdot000008\ \%_0 \times 3{\cdot}77$,
	$y = 16{\cdot}7$ mm.,	20·3 mm.,
	$N = \cdot000008\ \%_0 \times 4{\cdot}63$,	$\cdot000008\ \%_0 \times 6{\cdot}23$,
	$y = 21{\cdot}6$ mm.,	24 mm.

Here the product $(a - y)(b + N)$ where $a = 33{\cdot}8$, $b = 1{\cdot}54$, has the following values:

76·0, 76·6, 75·5, 72·0, 75·3, 75·5.

(N is taken as 1 when the real value is ·000008 %). Hence $(33{\cdot}8-y)(1{\cdot}54+N)$ is almost exactly constant and equal to a mean value 75·2.

This becomes $$y=33{\cdot}8-\frac{75{\cdot}2}{1{\cdot}54+N},$$

or $$y=\frac{48{\cdot}8N}{N+1{\cdot}54}-15.$$

This is exactly of the form required of the height of contraction,

$$y=\frac{N}{k'+kN}-M,$$

and is very strong evidence in favour of the hypothesis of a combination between nicotine and some constituent of the muscle.

B. The physical hypothesis leads to an equation

$$y=\mu'(1-e^{-\lambda t}),$$

where λ, and therefore $e^{-\lambda}$, does not depend on N, the strength of nicotine in the solution: the hypothesis of combination to an equation

$$y=\mu'(1-e^{-(k'+kN)t}).$$

Experimentally the equation of the curve is found to be

$$y=\mu'(1-e^{-at}).$$

e^{-a} is given below for several different pairs of contractions. Two halves of the same *rectus abdominis* were treated with different concentrations of nicotine, and the e^{-a} of each resulting curve calculated. If the action were physical in nature e^{-a} should be identical for the two different concentrations.

I.	(*a*)	One half in ·0001 %,	$e^{-a}=$·50.
	(*b*)	Other half in ·000066 %,	$e^{-a}=$·57.
II.	(*a*)	One half in ·0001 %,	$e^{-a}=$·47.
	(*b*)	Other half in ·000066 %,	$e^{-a}=$·64.
III.	(*a*)	One half in ·00012 %,	$e^{-a}=$·51.
	(*b*)	Other half in ·00004 %,	$e^{-a}=$·70.
IV.	(*a*)	One half in ·0001 %,	$e^{-a}=$·62.
	(*b*)	Other half in ·00005 %,	$e^{-a}=$·67.
V.	(*a*)	One half in ·0008 %,	$e^{-a}=$·33.
	(*b*)	Other half in ·00012 %,	$e^{-a}=$·60.

Thus in every case the e^{-a} of the lower concentration is greater than the e^{-a} of the higher concentration. This inequality is not explicable on a purely physical hypothesis of diffusion. According to the chemical hypothesis

$$e^{-a}=e^{-(k'+kN)},$$

Increasing N therefore increases a, and therefore decreases e^{-a}. Hence the fact that at the lower concentration e^{-a} is the greater is exactly as it should be on the hypothesis of a chemical combination.

One or two accessory points may be noticed. In finding the equations of the curves one of two cases usually arose.

(*a*) If the muscle were quite fresh the curve rose initially much faster than required by the equation to the greater part of the curve.

(*b*) If it were kept 24 hours in Ringer's solution, or contracted in nicotine once, and then relaxed again in Ringer's solution, it contracted initially rather slower than required by the greater part of the curve.

The explanation of (*b*) seems to be that diffusion into the fibres was not instantaneous, and therefore initially, with less nicotine inside, the rate of contraction was less than the calculated rate.

The explanation of (*a*) I believe to be as follows. The equation of the curve in these cases can be written,

$$y = k(1 - e^{-\lambda t}) + k'(1 - e^{-\lambda' t}),$$

where λ is something like 10 times as great as λ'. This means that two separate fibres are contracting, one many times faster than the other. The contraction of the first is complete in (say) a minute, while the second is only complete in ten. This *may* be due, not to two different fibres, but to two different types of contraction in the same fibre. There is in fact evidence[1] in some muscles of several different fibres, contracting at different rates.

The usual relaxation in Ringer's solution is also generally much more rapid at first than would be expected. The curve of relaxation can in these cases again be analysed into two exponential curves. In one case a muscle was left to contract *all day* in ·00003 % nicotine and then allowed to relax in Ringer's solution: only one half of the total relaxation occurred and the initial relaxation followed the equation as well as the later. Apparently here there was a pure case of the *slow* fibres alone relaxing.

Thus the activity of the quickly contracting and relaxing fibres is much sooner abolished in dilute nicotine than the activity of the slower working fibres. The quick fibres seem to pass from their tonic contraction in dilute nicotine to a state of permanent shortening. The slow fibres survive much longer.

[1] Cf. Langley, *op. cit.* p. 248. 1909.

The action of curari.

Curari and nicotine are "antagonistic" drugs. Prof. Langley[1] has given reasons for supposing that curari, like nicotine, combines with the "receptive substance" of muscles. He also shows that the curari compound, whose existence causes no contraction, is more stable than the nicotine compound.

I have applied an analysis of the curves of relaxation under the action of curari, similar to that given above for the curves of relaxation in Ringer's solution after nicotine.

I give details of two experiments.

I. A *rectus abdominis* muscle was immersed in ·0006 % nicotine and then in ·0006 % nicotine + ·05 % curari. A complete relaxation occurred from a height about ·8 cm. in a muscle of about 2·2 cm. This relaxation took 25 minutes to reach completion, the first half taking 3·5 minutes. The equation of the curve was approximately $y = ke^{-\lambda t}$.

II. A muscle was put in ·0001 % nicotine, and then in ·0001 % nicotine + ·0006 % curari. The heights above the asymptote at equal intervals of time, 40 minutes, are in the ratios

·76, ·78, ·80, ·78, ·80, ·84, ·76, ·77.

The ratios are therefore constant, and the curve of relaxation is $y = ke^{-\lambda t}$.

This may have, as before, two possible explanations. On a hypothesis of combination the form of the curve does not enable us to decide whether the curari is combining with some distinct substance, or whether it is turning nicotine out of some combination, and replacing it. The latter can be proved to necessitate a curve, $y = k(1 - e^{-\lambda t})$, though the mathematical analysis proving it is complicated and unnecessary here.

2. The temperature coefficients of the contraction caused by nicotine and of the subsequent relaxation caused by curari.

Nicotine.

It is well known that Arrhenius and others have shown that the temperature coefficient is much higher in chemical than in physical processes. Although the difference is not absolutely to be relied on as a distinguishing character, it gives evidence of considerable weight in a case of this kind.

[1] This *Journal*, xxxix. p. 235. 1909, and other papers.

The constant calculated was that employed in most works on Physical Chemistry[1], and may be obtained from the equation,

$$v_2 = v_1 e^{\frac{\mu}{2}\frac{T_2 - T_1}{T_2 T_1}},$$

where v_2 and v_1 are the velocities of contraction at temperatures T_2 and T_1. My reasons for using the constant μ are, (1) it is more general than any other, (2) it can be compared with the value of μ found by Arrhenius[2] for many biological actions. $\mu = 17{,}850$ corresponds to a velocity at 17° C. three times that of the same action at 7° C.

The method was as follows:

A *rectus abdominis* muscle from a large female frog was dissected out and divided carefully down the tendon in the middle line. The two parts, even if not of the same size and strength, are probably of almost exactly the same quality as regards susceptibility to stimulation and velocity of contraction. The two halves were immersed in dilute nicotine at temperatures T_2 and T_1 respectively, and the equations of the resulting curves were obtained.

Suppose that the equations were:

$$y = k_2 (1 - 10^{-\lambda_2 t}), \text{ at temperature } T_2,$$

$$y = k_1 (1 - 10^{-\lambda_1 t}), \text{ at temperature } T_1.$$

Then we wish to know the ratio of the times in which the two muscles reach the same percentage of their total contractions. The equations may be written

$$y_1 = k_2 (1 - 10^{-\lambda_2 t}) \text{ and } y_1 = k_1 (1 - 10^{-\lambda_2 \frac{t\lambda_1}{\lambda_2}}).$$

Then the first one is at the same stage of contraction (say any given percentage of its total contraction) at time t, that the second is at time $t\frac{\lambda_2}{\lambda_1}$, for then

$$y_1 = k_1 (1 - 10^{-\lambda_2 t \frac{\lambda_2}{\lambda_1}\frac{\lambda_1}{\lambda_2}}) = k_1 (1 - 10^{-\lambda_2 t}),$$

and hence

$$\frac{y_1}{k_1} = \frac{y_2}{k_2}.$$

Hence

$$\frac{v_2}{v_1} = \frac{\frac{1}{t}}{\frac{1}{t\frac{\lambda_2}{\lambda_1}}} = \frac{\lambda_2}{\lambda_1}.$$

[1] Cf. Nernst. *Theoretical Chemistry*, p. 673 *et seq.*

[2] Arrhenius. *Immuno-Chemistry*, 1907.

Hence $$\lambda_2 = \lambda_1 e^{\frac{\mu}{2}\frac{T_2 - T_1}{T_2 T_1}},$$

and from this μ can be calculated. This method was later replaced by finding the times in which the two halves reached a given proportion (·6 or ·8) of their total contraction. This was far easier, but inasmuch as it depends on only one measurement, and the former depends on taking the mean of many, it is less rigid. However as the results obtained from the simpler method seemed to agree very well with those obtained from the more rigid, it was uniformly adopted in the later calculations.

I. Left half in ·00003 % nicotine at 19·65° C.:

$$y = 22{\cdot}3\ (1 - 10^{-0{\cdot}1190t}).$$

Right half in ·00003 % nicotine at 8·3° C.:

$$y = 20{\cdot}9\ (1 - 10^{-0{\cdot}0311t}).$$

$$\frac{v_2}{v_1} = \frac{{\cdot}1190}{{\cdot}0311} = 3{\cdot}82,$$

$$\mu = 19{,}550.$$

II. $T_1 = 6{\cdot}6°$ C., $T_2 = 16{\cdot}3°$ C.

$$\mu = 17{,}900.$$

III. $T_1 = 6°$ C., $T_2 = 20{\cdot}4°$ C., Nicotine ·001 %.

$$\mu = 16{,}700.$$

IV. ·00004 % nicotine. $\mu = 14{,}220.$

V. ·001 % nicotine. $\mu = 16{,}700.$

VI. ·0006 % nicotine. $\mu = 19{,}000.$

The small variations in the temperature coefficient are probably due to differences in the two halves of the same muscle. The assumption that the two halves are the same in quality is not entirely justified except by taking the mean of several observations. The mean value of μ is

$$\mu = 17{,}340.$$

This is far too high for the action to be purely physical. For example for diffusion through a membrane the effect of change of temperature is given by

$$\mu = 289 \text{ (approx.)}.$$

If it were not that the hypothesis of physical diffusion alone is not sufficient to explain the considerations given in Section 1 of this paper, the high value of μ might be explained as the temperature coefficient of the permeability of the walls of the muscle fibres. It is quite possible that the chemical nature of the walls varies with the tempera-

ture, and that the permeability, and consequently the rate of diffusion inwards, have a very high temperature coefficient[1]. However, since the hypothesis of physical diffusion is insufficient, we must turn to that of a combination between nicotine and a "receptive substance." The high value of μ then shows that this combination is of an ordinary chemical nature.

In the preceding observations the percentage of nicotine was sufficiently small to give the specific action of the poison, *i.e.* an action on the "receptive substance." When the percentage of nicotine passes a certain limit the general muscle substance is also affected, and according to Prof. Langley two actions on the general muscle substance are to be distinguished, viz. a stimulating action soon over, and a very slow action causing rigor. I have not attempted to determine separately the temperature coefficients of these reactions of the general muscle substance, but I have in a few cases determined the temperature coefficients of the total initial contraction caused by strong nicotine. The curves were no longer exponential curves, but might have their equations written $y=f(t)$, and $y=f(\lambda t)$: in other words the curves might be made identical by plotting one of them with a larger time scale. The constant λ, or the ratio of the times to equal heights in the two contractions, gives us the temperature coefficient. The temperatures were in all cases about 5° C. and about 18° C., except for the secondary rise of the sartorius (No. 4) when they were 16° and 26° C.

1. *Rectus abdominis*, nicotine ·1 %. $\mu=14{,}500$.

2. *Rectus abdominis*, nicotine 1 %. $\mu=15{,}240$.

3. *Sartorius*, nicotine 1 %. The primary contraction was taken, *i.e.* the rise which occurs before the secondary (rigor) rise began.

Exp. i. $\mu=14{,}000$.
Exp. ii. $\mu=14{,}900$.
Exp. iii. $\mu=15{,}000$.

4. *Sartorius*, nicotine 1 %. Contraction taken after the secondary rise was well established.

Exp. i. $\mu=11{,}500$.
Exp. ii. $\mu=23{,}500$.

It will be seen that the temperature coefficient of the primary contraction caused by strong nicotine is much the same as that caused by very dilute nicotine: again therefore we have evidence that nicotine is acting by means of a chemical combination.

[1] It is possible that the physiological permeability of a membrane depends on its power of combining with the substance it transmits. In which case the rate of diffusion inwards would increase rapidly with the temperature.

The action of curari.

I. Two halves *A* and *B* were immersed (i) in ·0006 % nicotine, and then (ii) in ·0006 % nicotine + ·05 % curari.

A at 8·2° C., *B* at 17·2° C.

The ratio of the rates of relaxation was 1·50.

$$\mu = 7{,}400.$$

II. In a similar experiment the ratio, for a difference of 14° C., was 1·63.

$$\mu = 5{,}700.$$

The action of curari therefore seems to be by means of a chemical combination. The value of μ is lower than for nicotine contraction. This may be simply a peculiarity of the combination between curari and "receptive substance," or it may be due to the mechanical viscosity of the contracted muscle which does not relax as fast as the curari compound is formed.

In conclusion I should like to express my thanks to Prof. Langley for his kindness in helping me, both by criticism and advice: and to Mr C. G. Darwin of Trinity College, for his aid in my analysis of the curves.

Conclusions.

1. The curve of contraction of a *rectus abdominis* muscle in dilute nicotine follows an equation

$$y = k(1 - e^{-\lambda t}),$$

where y is the height of contraction, t is the time, k and λ are constants for that particular curve.

2. The curve of relaxation of a *rectus abdominis* muscle, which has contracted in dilute nicotine, and is then placed in Ringer's solution, or in a solution of curari, follows the equation

$$y = ke^{-\lambda t}.$$

3. Two hypotheses to account for this are considered:

(*a*) that of a gradual diffusion of the drug in or out,

(*b*) that of a gradual combination of the drug with some constituent of the muscle.

Two methods, (*A*) comparison of total heights, (*B*) comparison of velocities of contraction, at the same temperature with different

strengths of nicotine, point to the hypothesis of a combination as the only possible one.

4. The temperature coefficient μ, of the velocity of contraction, shows that the combination between nicotine or curari and the combining constituent of the muscle is of an ordinary chemical nature. This combination is a reversible one between two molecules

$$N + A \rightleftarrows NA,$$

and the height of contraction at any moment is proportional to $(NA - M)$, where NA is the amount of the compound formed at that moment, and M is the minimum amount necessary to cause any contraction. Curari also combines chemically with a constituent of the muscle.

5. Muscular contractions of either the *sartorius* or *rectus abdominis* in very widely different concentrations of nicotine (·00003 % to 1 %) give values of μ never very far from 16,000. These values lie very close to those given by Arrhenius for many biological actions. This corresponds to a velocity at 17° C. about 2·8 times that at 7° C. The μ of the action of curari corresponds to a velocity at 17° C. about 1·5 times that at 7° C.

6. Evidence for the existence of two (or more) different types of fibres (or contractions) in the same muscle is given by a mathematical analysis of the curves. The quicker moving fibre (or contraction) is destroyed much sooner than the slower, if left in dilute nicotine and Ringer's solution.