On the alterations in the action of digitalis produced by febrile temperature / by T. Lauder Brunton and J. Theodore Cash.

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BY T. LAUDER BRUNTON, M.D., F.R.S., AND J. THEODORE CASH, M.D.

It not unfrequently happens that the physician who prescribes some powerful medicine in order to relieve the diseased condition in his patient is disappointed in the expectation he has formed, and finds that the exhibition of the medicine in disease is not followed by the result which he had been led to expect by the action of the drug on healthy animals or on healthy men. Digitalis is a marked example of this kind of drug. When given to animals or to healthy men it slows the pulse often to a very considerable extent. When given in pneumonia it was found by Thomas [1] to have but little action on the pulse before and up to the crisis of the disease. The curves of pulse and temperature obtained from patients treated with digitalis were almost the same as from those who were subjected to a purely expectant treatment. In some cases the pulse alone was distinctly affected, in a few the pulse and temperature both fell slightly, and occasionally they conformed to the rules laid down by Wunderlich regarding the action of digitalis in typhoid fever.[2]

[1] Thomas, *Archiv. d. Heilk.*, 1884, v. pp. 30 and 167.

[2] Wunderlich, "Medical Thermometry," *Sydenham Society's Translation*, p. 324. These rules are that digitalis in the quantity of two to four grammes (ʒss–ʒj nearly), or even more (in divided doses extending over from three to five days), given in the second and third week of a severe case of typhoid, immediately produces a slight moderation of temperature in a great number of instances, or perhaps a considerable fall of temperature, which during the time of the exacerbation may amount to 2° C. or more (3·6° F.). This fall does not generally last more than about a day after the exhibition of the remedy. Then the temperature

Generally the action of digitalis first became perceptible after the crisis of the pneumonia was passed. It was then evidenced by an abnormally low temperature and pulse-rate which was much more usually observed when digitalis had been given, than when a purely expectant system of treatment had been followed. Wunderlich's observations agree with those of Thomas in this respect, that he found digitalis slowed the pulse markedly in typhoid when the fever was moderate.

An attempt to ascertain the reason why digitalis does not slow the pulse in pneumonia, at least while the disease is at or near its height, was made several years ago by one of us.[1]

The absence of any slowing action of digitalis upon the pulse might be due to one of several causes. It might, for example, be due to paralysis of that part of the nervous system which in a condition of health usually restrains the cardiac beats, and prevents the pulse from becoming too rapid. Or it might be due to stimulation of the heart itself or its accelerating nerves, quickening the pulse in spite of the restraining action of the controlling or inhibitory mechanism.

Without entering more minutely into the nature of this controlling or inhibitory mechanism, we may broadly divide it into two parts, central and peripheral. The central portion is that part of the medulla oblongata from which the vagus roots spring; the peripheral part consists of the termination of the inhibitory fibres of the vagus in the heart.

It is evident that if the peripheral endings are paralysed, the power of the medullary vagus-centre to restrain the heart will be as completely destroyed as that of a rider to rein in his horse after the bit has fallen from its mouth. But the inhibitory mechanism may be paralysed centrally as well as peripherally. The controlling nervous mechanism in the medulla may become inactive and exercise no restraining action upon the heart, although the vagus fibres are still unaffected, and are able to produce slowness of the pulse or even actual stoppage

rises again, and in cases favourably affected does not again attain the previous height, but remains stationary, with very powerfully-depressed pulse, at moderate heights, whilst defervescence takes place as usual, and the pulse first recovers itself from its artificial retardation about four days after the use of the digitalis, whilst convalescence has meanwhile advanced.

[1] Brunton, *St. Bartholomew's Hospital Reports*, 1871, vol. vii. p. 216.

of the heart whenever they are stimulated. The accelerating mechanism of the heart may, like the inhibitory, be divided into central and peripheral portions. The peripheral part is located in the heart itself, and is closely associated, if not indeed identical with the motor-ganglia by which the cardiac pulsations are maintained. When the frog's heart after isolation from the body is warmed artificially it begins to pulsate more and more rapidly as the temperature rises, until finally the pulsations become indistinct and vermicular, and the heart stands still in a state of complete contraction or heat-rigor, as it is called.

The exact position of the accelerating centre of the heart in the brain or spinal cord has not been accurately ascertained ; the accelerating impulses, however, pass by the sympathetic filaments which usually accompany the vertebral artery and pass from the lowest cervical ganglia to the heart. We have then, roughly speaking, four pieces of nervous mechanism to consider : (1) vagus roots, (2) vagus ends, (3) sympathetic roots, (4) cardiac ganglia.

We have to ascertain, if possible, what the alteration in one or more of those structures are which deprive digitalis of its power to slow the pulse in patients suffering from pneumonia. As pneumonia is a disease in which the temperature rises high, the first idea which occurs to us is, that the presence of the pyrexia itself is the reason why the drug does not act as in health, or as it does in cases of typhoid fever when the temperature elevation is moderate, as observed by Wunderlich.

We have therefore attempted as a first step in our investigation to ascertain the effect of rise of temperature alone on the pulse in the cat, which animal we employed in the present research. In a former series of experiments made by one of us [1] on the effect of heat upon the pulse in the rabbit, it was found that the pulse-rate increased with considerable regularity as the temperature of the body rose, as is shown by the following experiments in one of which the vagi were uncut and in others were cut. At the commencement of the experiment there were slight irregularities as before, which have not been copied here After the temperature had risen above a point which is marked by thick type in the table, the pulse-rate began to fall.

[1] Brunton, *op. cit.*

RABBIT VAGI UNCUT.

Temp.	Pulse in 15″.
37°·7 (100°F.)	71
38°·3 (101°F.)	73
38°·8 (102°F.)	76
39°·4 (103°F.)	77
40°· (104°·2F.)	82
40°·5 (105°F.)	85
41°·1 (106°F.)	89
41°·6 (107°F.)	91
42°·2 (108°F.)	94
42°·7 (109°F.)	96
43°·3 (110°F.)	97
43°·8 (111°F.)	**102**
44°·1 (111°·5F.)	102
44°·1 (111°·5F.)	37

RABBIT BOTH VAGI CUT.

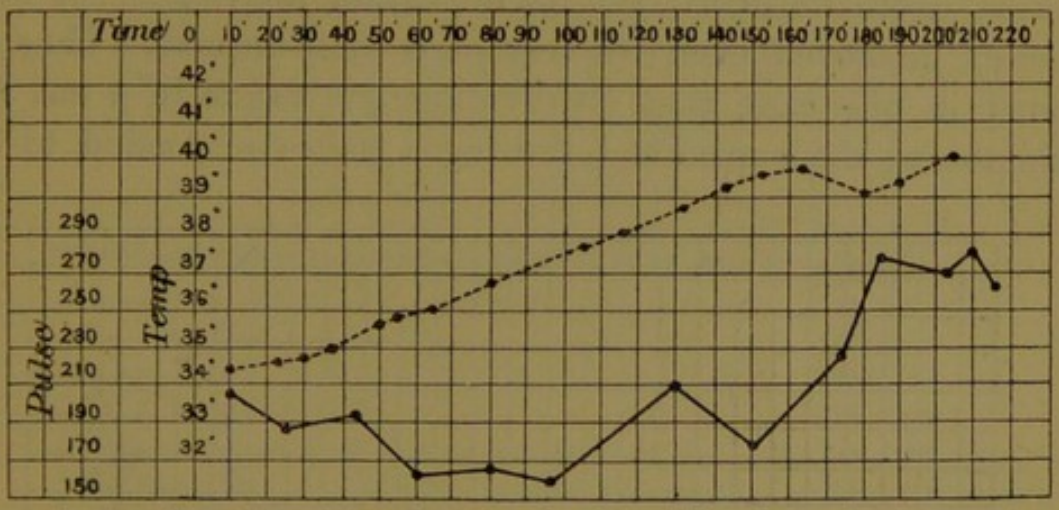
Temp.	Pulse in 15″.
39°·1 (102°·4F.)	83
39°·4 (103°F.)	84
40° (104°F.)	87
40°·5 (105°F.)	91
41°·1 (106°F.)	91
41°·6 (107°F.)	97
42°·2 (108°F.)	101
43°·5 (110°·3F.)	**110**
43°·8 (111°F.)	108
44° (112°F.)	109
45° (113°F.)	90
45°·1 (113°·2F.)	35
45 ·2 (113 ·5F.)	18
45 ·4 (113 ·8F.)	10

In experiments of the same kind which we have made upon cats, we have noticed that the pulse does not rise at first so regularly in proportion to the temperature as it does in the rabbit, but on the contrary may remain only a little above the normal until the temperature of the body rises to a point ranging in different animals from 39° C. and 42° C., when the pulse-rate suddenly begins to rise with greater rapidity. In most of the animals examined this point is between 40°·5 C. and 42° C., although in some it may be as low as 30°·7 C. The suddenness of this rise at once suggests paralysis of the inhibitory nerves as its cause. This paralysis might be, as we have already said, either central or peripheral.

In the experiments on the rabbit already referred to, it was found that the peripheral terminations of the vagus retained their power, although weakened, up to the death of the animal, at a temperature of 45°·3 C. Peripheral paralysis of the vagus of the cat seemed therefore unlikely. The idea that the paralysis was central appeared to us more probable and agreed with what is known of the normal action of the vagus upon the heart of the cat and the rabbit. In both animals stimulation of the vagus trunk is followed by a slowing and stoppage of the pulse at least at ordinary temperatures. The nerve centre in the medulla which regulates the cardiac beats through the vagus appears, however, to act much less powerfully as a rule in the rabbit than in the cat, so that in the rabbit the pulse is normally much quicker than in the cat, and does not rise to anything like the same extent when the influence of the vagus centre upon it is abolished by cutting across the trunks of the nerves, or

paralysing their terminations in the heart by means of atropine. This being the case we should expect that paralysis of the vagus centre in the rabbit by heat would not be marked by any sudden increase in the pulse-rate, and that we should simply find—as actually occurred—that the pulse rose proportionately to the temperature from the stimulating action of heat upon the heart itself. In the cat, however, we should expect the sudden removal of the inhibitory influence normally exerted by the vagus centre to be evidenced by a rapid rise in the pulse-rate out of proportion to the rise in temperature, and this is what we have actually found.

On looking over the accompanying charts of the relationship between pulse-rate and temperature, it will be noticed that at first the pulse remains nearly at its normal, or increases slightly, as we should expect from the stimulation of the cardiac ganglia by heat, but it does not rise regularly in proportion to the temperature. Then after the temperature has risen to a certain



The unbroken line shows the pulse-rate, the dotted line shows the temperature in the axilla in all the figures.

FIG. 1.- Shows the effect of rise of temperature alone. At the 195th minute both vagi were cut ; the section was not followed immediately by any apparent effect. After eight minutes more, the pulse-rate rose slightly and then fell.

extent, the pulse-rate goes up with a sudden bound, suggestive as we have already said of vagus paralysis. However probable it may be that the paralysis is of central origin in the cat, it would be wrong to assume it as a certainty, more especially as both in this animal and in the rabbit the inhibitory power of the vagus trunk over the heart is diminished though not

entirely destroyed by very high temperatures. We have therefore tested the point experimentally, and it will be seen from Fig. 1 that when the temperature had risen in the axilla to 40° C. the inhibitory action of the vagus was completely abolished, so that section of both vagi produced no effect whatever in the pulse-rate. To ascertain whether or not the paralysis was central we stimulated the peripheral trunk of the vagus, and found that it still retained at this time a powerful inhibitory action upon the heart, though somewhat less than at the normal temperature.

We may conclude then, that the rapid rise in the pulse-rate which a high temperature occasions in the cat is chiefly of central origin, and is due to partial paralysis of the vagus centre, which is aided by a diminished action of the peripheral ends of the vagus and increased action of the cardiac ganglia.

Although the vagus centre is so much weakened by the action of the heat that it ceases to exercise any inhibitory action upon the heart, yet its functional activity is not completely destroyed even by very high temperatures. Thus we found in one case, that on dividing one vagus in a cat and stimulating the central end, the vagus centre responded to the

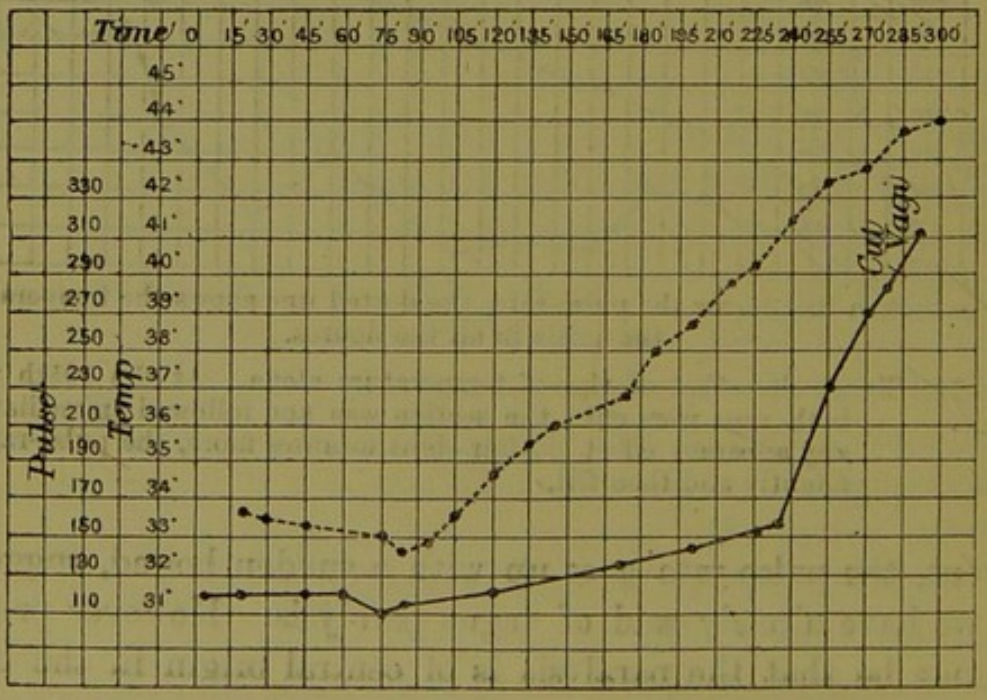


FIG. 2.—Shows the effect of rise of temperature after injection of digitalis. At the 45th minute ·75 cc. (12 minims) tincture of digitalis were injected, and another similar injection was made at the 55th minute. At the 65th minute the heating was begun.

stimulus, and we obtained through it and through the other vagus trunk which remained intact, a reflex action upon the heart, the pulse becoming distinctly slower although the temperature of the animal had risen to 46°·6 in the rectum, and 45° in the axilla, and death occurred from heat (hyperpyrexia) almost immediately afterwards.

The action of heat upon the pulse seems to be influenced to a large extent by the action of digitalis. When this drug was introduced into the circulation by the femoral vein in doses of ·25 cc., twice or thrice repeated before the temperature of the animal began to be raised, the pulse-rate remained for a long time comparatively low, and did not begin to rise suddenly until a higher temperature had been reached than in the unpoisoned animal.

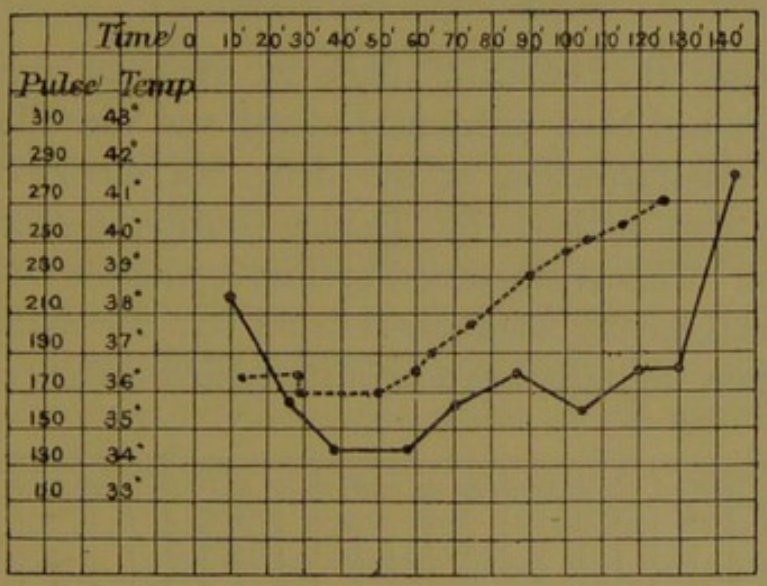


FIG. 3.—Shows the effect of rise of temperature after the administration of digitalis. At the 30th minute tincture of digitalis was injected, and warming was begun. At the 90th minute natural respiration ceased, and it had to be continued artificially.

In Figs. 2 and 3 it will be seen that the sudden rise in pulse-rate does not occur until the axillary temperature has reached 41° to 41°·5 C., as compared with 39° C. in the animal to which no drug had been administered. When given to a cat in which the temperature had already been raised artificially to 39° it reduced the pulse-rate, and prevented any sudden rise occurring, although the temperature in the axilla afterwards rose to 40°·5 C. (Fig. 4). The charts which we have selected illustrate the results which we have obtained in our research, but the results

have been confirmed by other experiments which we have not thought it necessary to give in detail.

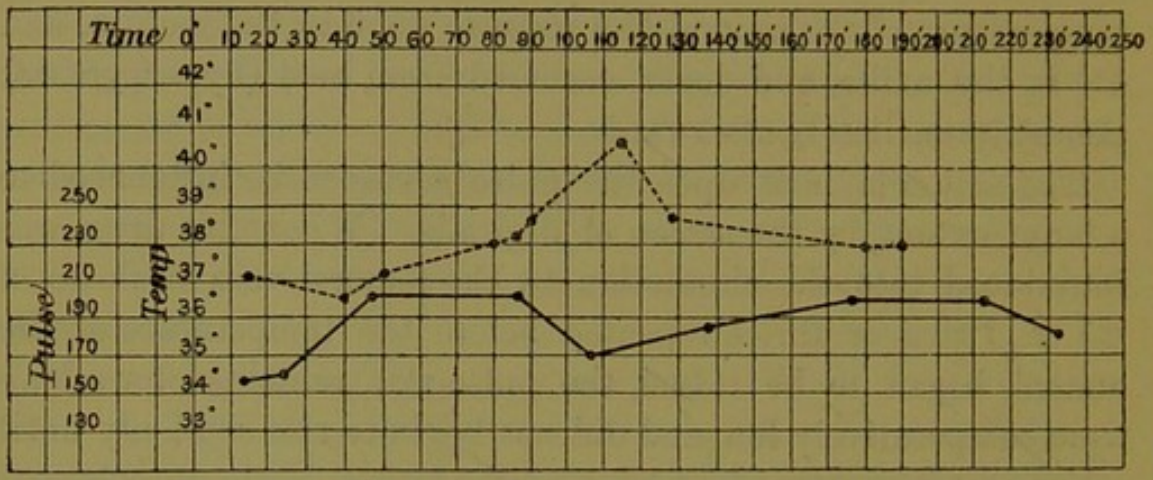


FIG. 4.—Shows the action of digitalis when given after the temperature has already risen. At the 30th minute the warming was begun; at the 100th minute ·75 cc. of tincture of digitalis was injected.

On testing the effect of digitalis upon an animal whose temperature had been previously raised and was allowed to fall after the administration of the drug, we observed an effect similar to that noticed by Thomas during defervescence in pneumonia. This is illustrated by Fig. 5, where the temperature of the animal having been raised to 38°·6 in the axilla and 38°·8 in the rectum, digitalis was administered and cooling commenced.

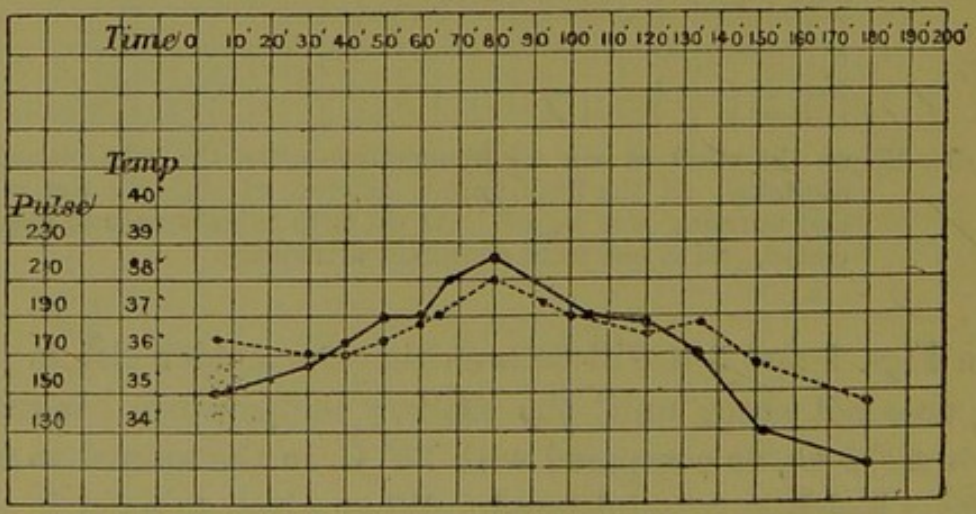


FIG. 5.—Shows the effect of digitalis given shortly before cooling. At the 25th minute warming commenced; at the 75th minute ·75 cc. tincture of digitalis was injected, and at the 80th minute cooling was commenced.

The pulse *at once began to fall* with a rapidity somewhat out of proportion to the fall of temperature, so that when the

temperature had reached the normal in the axilla and rectum the pulse had fallen below its original rate. It will be noticed that the temperature both in the axilla and rectum fell considerably below the original at the end of the experiment. This might be regarded as a further correspondence between our experiments and the observations of Thomas in pneumonia, but we cannot lay any stress upon it, as the temperature of all animals tends to sink when they are kept in a position of immobility, as in our experiment, even when no digitalis is given.

We may now summarise the results of our experiments on the effect of heat upon the pulse, and on the modification it produces on the action of digitalis.

In the cat and probably all animals in which the vagus centre exerts, as it does in man, a considerable restraining influence upon the pulse, rise of temperature causes at first a slight quickening of the pulse, which is probably due to stimulation of the cardiac ganglia.

This quickening does not increase in such constant proportion to the temperature as it does in rabbits, in which the vagus centre normally acts but slightly upon the heart.

When the temperature rises in the cat above a certain point it weakens the action of the peripheral ends of the vagus on the heart, and also weakens the vagus centre in the medulla.

The action of heat upon those two parts of the nervous system appears to be of the same kind, but it differs in degree; the centre appearing to be more affected than the periphery, so that its inhibitory action is completely abolished at a time when the peripheral ends still retain their functional activity to a great extent.

Though the inhibitory centre in the medulla is rendered inactive by the heat so that it does not act on the heart, it is not completely paralysed, and is still able to restrain the heart when it is called into action by a powerful stimulus, such as strong galvanisation of one of its afferent nerves.

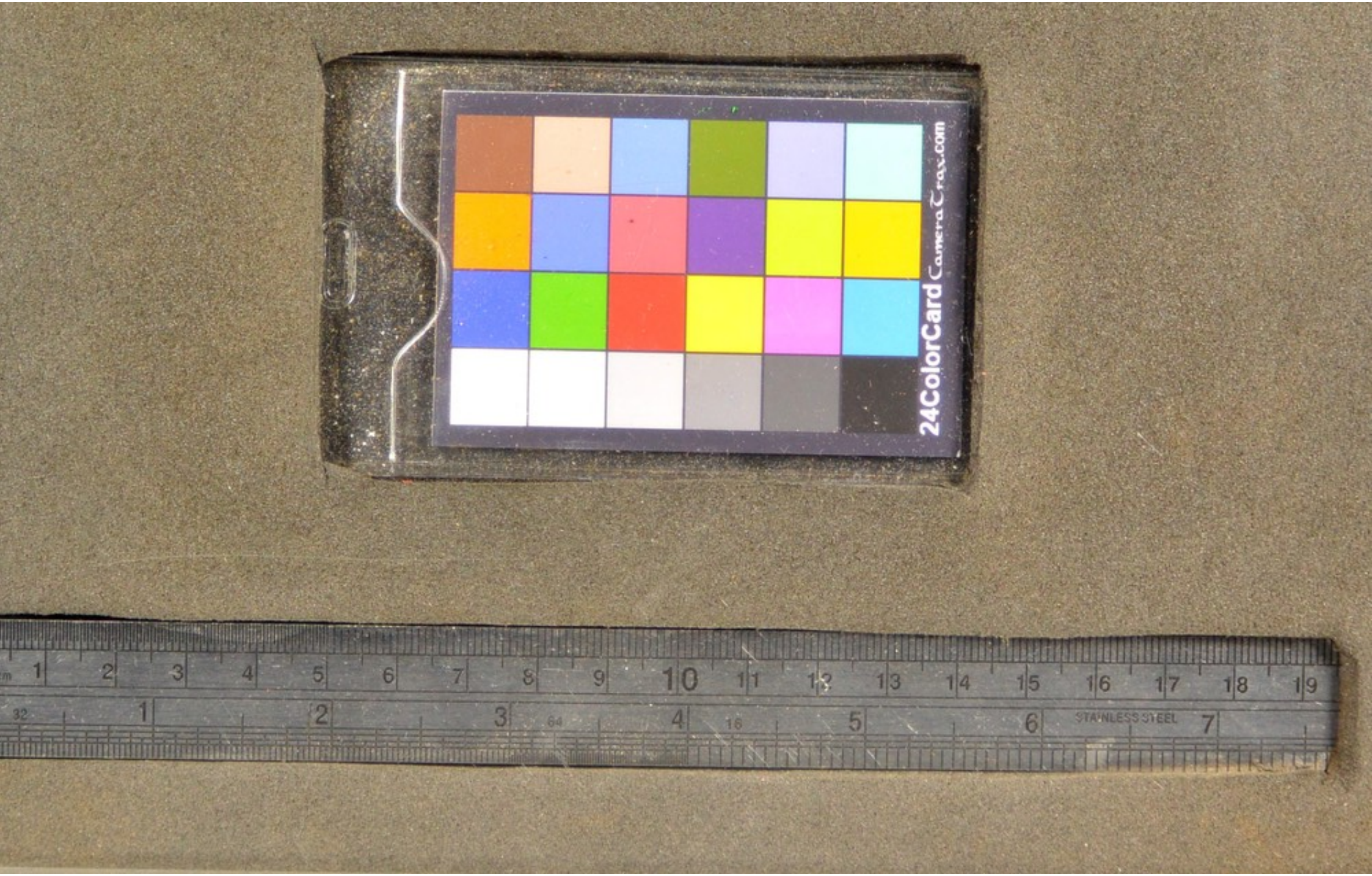
The action of digitalis upon it is that of a stimulant increasing its activity, and is very much like the effect which we should expect from gentle instead of strong stimulation from one of its afferent nerves.

The practical conclusion which results from our experiments

is, that a high temperature lessens the inhibitory power of the vagus centre in the medulla to such an extent that digitalis, and probably all drugs which act like digitalis on this centre lose, to a great extent, their power to restrain the action of the heart and slow the pulse.

The administration of digitalis, or of drugs which act like it, to patients in a febrile condition, is, therefore, likely to have much less effect on the pulse than at the normal temperature, and if the temperature be very high they may have no effect at all whilst this persists.

When the temperature begins to fall the pulse naturally becomes slower, and this slowness is increased if digitalis has been given at the height of the fever. It is, therefore, evident that digitalis and its congeners, if they are given at all when the temperature is high, should be given with great care, for otherwise the medical man may be induced, by the apparent inaction of the remedy, to push its administration too far during the fever, with the consequence of producing too great depression of the pulse during defervescence.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