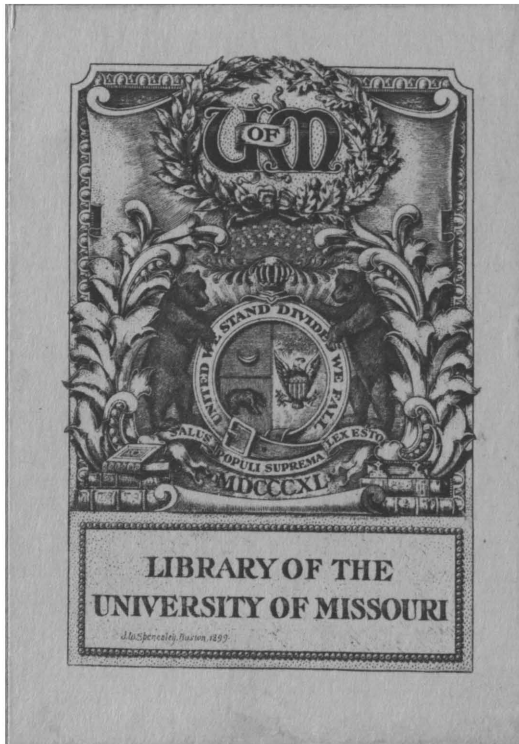


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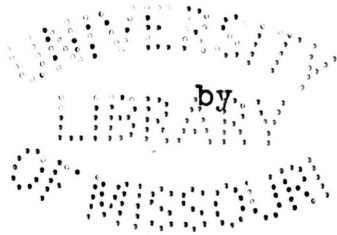
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THE ACTION OF DIGITALIS ON THE
CARDIAC INHIBITORY CENTRE.



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THE ACTION OF DIGITALIS ON THE
CARDIAC INHIBITORY CENTRE .

PART I - HISTORICAL .

Introduction.

So long has digitalis been in use as a clinical drug and so long has its action been the subject of experimentation that it would seem that there is little hope of presenting anything new on the subject. Yet so long as every detail of such a subject is not fully understood, and so long as there is diversity of opinion as to the action there is room for work whether entirely new or confirmatory. It is in the hope of confirming some older theories by newer methods that the present work is undertaken.

The first attempt at a scientific observation of the action of digitalis was by the English physician Withering⁴⁸ in 1785. He pointed out the slowing of the heart under the action of the drug and suggested that a closer study be made. Previous to his time brews of the leaves and various parts of the plant had been used as household remedies in England but with little or no definite knowledge of the true action. The following year Schiemann⁴³ made observations on the slowing action of digitalis on the heart of cats and dogs. He also attempt-

ed to show the action of this drug on the kidneys. He seems to be the first to make any experimental observations on the subject. Beddoes³ in 1801, pointed out the increase in blood pressure which he had measured by a mechanical device. In the same year Kinglake observed the slowing of the pulse rate and the strengthening of the heart beat with greater output of blood to the aorta. Brodie¹¹ in 1811 noted the effect of digitalis on the respiratory and brain function and the late failure of the heart. Mossman in 1812 came to the conclusion that there was slowing of the heart rate without an increase of muscular action.

In 1839 Blake⁶ made decided advance when he used the method of injecting the infusion of digitalis into the circulation and produced thereby the effect of the rise of blood pressure. He also noted the slowing and systolic stoppage of the heart of mammals. The chief effects of the drug he ascribed to the action on the heart muscle itself.

Stanisus⁴⁵ in 1851 compared the action of digitalis on the frog and cat. He irrigated the heart with a solution of the drug and reported no effect. Traube⁴⁶ in the same year observed the effect of digitalis on the vagus centre, which he considered the chief point of action. He considered that the medullary cardiac inhibitory centre was responsible, through its tone, for holding the heart in check. He thought that all the slowing effect of digitalis was due to stimulation, and the subsequent acceleration to fatigue or paralysis of this centre. He continued his

work and by 1861 he had modified his views to some extent but still held that the action on the vagus was of chief importance. Lenz³², a student of Bidder, in 1853 reported findings somewhat in opposition to Traube.

In the next decade there were a number of workers who attacked the problem in various ways either repeating the work of previous investigators by way of confirmation or attempting to point out wherein their observations were at fault. Boehm⁵ in 1872 showed for the first time that after digitalis a weaker strength of stimulation applied to the vagus was required to inhibit the heart than previously. This he attributed to change of irritability of the muscle tissue.

In 1882 Schmiedeberg⁴⁴ published the results of his work upon classification of the pharmacological group of digitalis bodies. He did not confine his researches to the extracts of Digitalis purpurea but considered those of Oleander and a number of those plants whose extracts had been used in medicine but were not fully understood. He examined the physical properties and determined formulae, or at least the empirical formulae, for many of them as well as the physiological classification. According to the physical properties Schmiedeberg classified the pharmacological group of digitalins as follows:-

I Crystallizable Glucoside.

- 1, Digitalin $(C_5H_8O_2)_n$.
- 2, Antiarin $C_{14}H_{20}O_5$.
- 3, Helleborein $C_{26}H_{24}O_{15}$.
- 4, Evonymin.

5, Thevetin $C_{54}H_{48}O_2$.

II Partly crystalizable substances not glucosides.

6, Digitoxin $C_{21}H_{33}O_7$.

7, Strophantin $C_{20}H_{34}O_{10}$.

8, Apocynin.

III Not crystalizable and difficultly soluble in water.

9, Scillain.

10, Adonidin.

11, Oleanderin.

IV Amorphous, slightly soluble in water.

12, Digitalein (Neriin).

13, Apocynein.

14, Convallamarin.

V Plant substances, not yet fully investigated but probably of the class.

15, *Tanghinia venenifera*, Poiret.

16, from the bark of *Nerium odorum* W.2 glucosides
a) Nerioderin-like Oleanderin.
b) Neriadorein-like Digitalein.

17, from the Upas of Singapore, a chemically indifferent substance like strychnine, not well understood.

VI Substances, which beside other actions, have digitalis effects.

18, Erythrophlein, from *Erythropleum guineese* G Do.

19, Phrynin.

Some years earlier, 1874, Schmiederberg had already examined the commercial digitalis preparations with the idea of isolating the pure principles. In the digitalis he found four chief active principles, i.e. digitonin, digitalin,

digetalein, and digitoxin. From the first of these he isolated five decomposition products; digitoresin, digitonein, both risinous glucosides; digitogenin, a crystalline substance; paradigitogenin and digitin. From the digitalin he got digitoresin and digitalresin. From the digitalien he secured a substance that resembled digitalresin. From digitoxin, which is not a glucoside, he procured toxiresin. These two papers of Schmiederberg are very complete and stand as the basis of all chemical knowledge on the subject at the present time. His findings have been confirmed extensively by Kiliani and supplemented to some extent by Cloetta¹⁶ in recent years.

After this time the physiological investigation of digitalis and the various preparations were carried on by a number of investigators. Popper³⁹ in 1889, Tschistowitsch⁴⁷ in 1887, Openchowski³⁸ in 1889, Knoll³¹ in 1890 and 1894 and Bradford and Dean⁷ in 1894 all worked with substances of the digitalis group noting among other effects, those on the pulmonary circulation. Among the earlier workers there was some difference of opinion as to the effect on the pulmonary blood pressure, but the general conclusion that Cushny¹⁷ draws after considering all the work is, that the pressure in the pulmonary artery is not affected to the extent of that in the carotid and perhaps there are only some of the members of the group that are at all effective in this direction.

Of the workers of the last decade there are several who have been active in the investigation of the different factors of digitalis action. Cloetta has

carried on the line of investigation started by Schmiederberg while the work of Dr. Arthur Cushny published in 1884 is a comprehensive study from the physiological side of the most important members of the digitalis group. From the clinical side of the question Mackenzie³⁴ and Lewis³³ have been among the foremost observers. While the work of these last two men has been almost entirely confined to the observation of human cases treated with digitalis yet their observations have been of such careful nature and they have used such accurate mechanical methods in recording blood pressures and taking heart and pulse tracings that their work approaches animal experimentation in exactness. There is also an unquestionable practical value in scientific records of clinical work that is to be had in no other way.

Theories of the Action of Digitalis.

The various ways in which a drug may be able to affect the circulation may be specified as; 1, direct effect upon the smooth muscle tissue in the walls of the arterioles, leading to modification of the stream bed; 2, effects resembling 1, but produced by stimulation of the vasoconstrictor mechanism; 3, changes referable to direct action upon the heart musculature, leading to a change of the nature of the contraction; and 4, effect on the cardiac regulative mechanism, resulting in changes of heart rate. Since the earliest experimental work on digitalis it has been a question as to where the primary effect of this drug fell. Among the earlier workers the tendency was to emphasize some one factor of the entire complex and conclude that the particular factor was the only one, or at least so preeminently the main one that the others were not worthy of consideration. The present day workers are more inclined to give to each factor its proportionate weight while trying to determine the more exact knowledge of each particular phase of the total reaction of the drug.

Of those who have laid emphasis on the vascular constriction, Lenz³² was among the first. He observed a constant pulse rate with a rise of pressure and ascribed the result to the constriction of the smaller blood vessels. Donaldson and Stevens¹⁹ by perfusing the whole circulation of the turtle with .0005 per cent digitaline found that the outflow of fluid from the veins was reduced to half. When

they perfused with physiological normal saline they got a return to the normal condition. They also observed that there was peripheral vascular constriction after the sympathetic system was destroyed. Cushny¹⁷ likewise observed that there was constriction of the vessels after the cord had been destroyed. Ringer and Sainsbury⁴⁰, using similar methods as Donaldson and Stevens but .005 per cent obtained the same constriction, but they were not able to get a return to the normal condition when physiological saline was perfused. Schäfer⁴² obtained the same results as Ringer and Sainsbury. Brunton and Meyer¹³, and also Brunton and Tunnicliffe¹⁴ came to the conclusion that there was constriction in the arterioles and based their judgment on the study of the pulse pressure curve as taken from the aorta. The curve may be altered in the direction they observed in two ways, i.e. by a greater volume of blood being thrown into the vessel or by adminution of the outlet such as would be caused by the constriction of the arterioles. They found that the descending arm of the pulse wave was prolonged and this would indicate that there was such a constriction. Brunton and Tunnicliffe¹⁴ report Galen, Milner, Fothergill, and others as observing constriction in the arterioles of the frogs web after the injection of digitalis; also that Klug²⁸, Legroux, Koppe, and others noted the same sort of constriction in the ears of young rabbits. These tests have been repeated frequently usually but not always in confirmation.

Robert²⁹, working with isolated organs and with decomposing ones, i.e. organs that had been removed from the

body for such length of time that he thought that the nerve endings had degenerated, hoped to get results in which the nerve element could be disregarded. He used the kidney for most of his work. When he perfused the organ through the arteries with digitalis solution, he got marked constriction as measured by the outflow from the veins. Schmiedeberg took issue with him on the ground, 1-that this effect on such tissue was gotten only with strengths of solution that would be out of the question as therapeutic dosage, 2-that the result was not constant, and 3-that muscle tissue under such conditions would contract any way. Schmiedeberg may be well grounded in his objections but the evidence presented seems to be a very strong indication of constriction and probably of muscle tissue direct. Brunton disagrees with Schmiedeberg. Meyer and Gottlieb³⁶ hold that the stoppage of the heart in diastole is due to the constriction of the coronaries. Bastedo thinks that in hypertrophied hearts where the need of food is great or the danger of cumulative action of digitalis is augmented that any slight constriction of the coronaries give a noticable effect. On the other hand, Braun and Mager⁹ think that none of the effects of the drug are due to action on the coronaries.

Gottlieb and Magnus²³ hold that the digitalis group as a whole causes constriction of the splanchnic area with digitoxin as a general constrictor, while strophanthin and digitalin act on the splanchnic vessels first. Dixon¹⁸ found contraction of the coronaries with digitalis solution of a strength of 1 to 20,000 but not in strengths used in therapeutic dosage. Considerable work has been done with

isolated coronary arteries with the general conclusion that they are constricted by digitalis.

Thus there is a large group of workers who hold that the constriction of the vessels is the chief effect of digitalis administration. Whether this is accomplished by the direct action on the smooth muscle tissue of the walls of the arterioles or is the effect of a stimulation of the nerve endings of these muscle fibres is yet an open question. The work of Kobert²⁹, who used drugs that were supposed to destroy the nerve endings and who still got the constriction, points to the direct effect on the muscle tissue.

There is another group of workers who have looked to the muscle changes for the chief effects. Blake was one of the first to note the change in the blood pressure. He observed the rise before the rate change and ascribed it to the effect on the heart muscle. Most others have accounted for this result by the effect on the blood vessels. Briquet¹⁰ however ascribed the rise of pressure to the same cause that Blake did. Donaldson and Stevens were of the opinion that the total work of the heart, considering long periods, was decreased but they found that the distensibility of the heart was increased and this gave the increase of work that was first noted. Boehm and Williams also noted the factor of the change of distensibility.

It was along this line of change in elasticity that Schmiedeberg worked. He found in addition that when the heart stops in the systolic phase that it will continue to beat if the systole is overcome by mechanical distension.

He also found that when the later stages were reached that the heart did not continue to beat if mechanically distended. He therefore concluded that the muscle had lost one of its properties. Schmiedeberg ascribes the rise in the general pressure to the increase of efficiency of the heart and has never given much weight to the vascular constriction theory. Werschinin also holds that the slowing of the heart is independent of any nerve action. Mackenzie on the other hand is able to see no change in the muscle tissue, while Meyer and Gottlieb hold that as yet there is not enough evidence to say just which of the elements of the heart are affected.

Klopotowsky, who has worked on the histological side of the question, finds that in the muscles after acute cases of digitalis poisoning there is parenchymatous and fatty degeneration with increase of connective tissue between the fibres, and some dissociation phenomena. In subacute and chronic cases he notes fatty and parenchymatous degeneration. C. S. Roy⁴¹ found on the examination of the curve of contraction that the relaxation after digitalis was much more rapid. It may readily be conceived that such changes in the contraction phase are the result of changes in the muscle cell, if not as profound as Klopotowsky pointed out they may yet be very definite. This is in the line of the theory of muscular action in the normal and in fact all cell function is looked on as due to internal change. This feature is the one most emphasized by the adherents of the idea that the action of digitalis is purely muscular, and to me it seems the strongest evidence in their favor. The work of Braun and

Mager may be taken as in this line. They found first an amplitude increase, then rate change, and this followed by tone variations. The secondary slowing they ascribed to the muscle entirely since the use of atropin would not remove the effects. The tone and irregular changes they called fatigue phenomena.

As was mentioned the heart may be influenced either by the change in irritability of the muscle or of the nerve endings. The heart muscle, as well as some of the specialized tissue, such as the bundle of His, possess the power of conduction to a marked degree. It then becomes more difficult to determine where the effect falls.

It is hard to prove that it is the lowering of the function of the conducting mechanism and not a change in the irritability of the muscle tissue in response to the stimulus. It has been the aim of several to determine this point. Boehm in 1872 pointed out the change of irritability of the muscle. This he measured by the change in response to stimuli. Mackenzie has shown that digitalis lengthens the time between the auricular and ventricular contraction or may even block the passage of the contraction wave. As he described the change it is not very different in kind from the normal action of the vagus. This seems to support the idea of many that the change of conduction is an effect on the vagus endings or the structures in immediate relation to them. Thus Bastedo states that the conductivity of the sinus node is lowered, while he, Cushny, Mackenzie, Lewis, and others have given definite proof that the conductivity of the bundle

of His is lowered. Some of the evidence of this change is the retarding of the wave of conduction and the fact that digitalis does not affect the fibrillating auricle but does prevent the passage of the flood of impulses from the auricle to the ventricle hence lowers the rhythm of the ventricle.

Klopotosky has shown that in acute digitalis poisoning, the cells of the automatic ganglion within the heart stained by Nissl's method, show the initial stages of perinuclear chromocytolysis in the initial stages. In chronic and subacute poisoning there is disappearance of the chromatin substance and vacuolar and fatty degeneration.

The action of digitalis on the various systems and organs has received considerable attention. The kidneys, the respiratory system, and the alimentary tract have each been considered separately and in their relation to the whole physiological complex.

In the kidneys the marked diuretic effect is not primarily upon the secreting cells, for, according to a rather widely accepted view, digitalis has only slight effect upon glandular tissue. Granting this there remain two other possibilities, i.e. 1, the changes that may be brought about by the action upon the smooth muscle in the walls of the arterioles of the kidney, and 2, the change that may arise from an increase in the general blood pressure. In regard to the first of these possibilities, the work of Kobert points strongly to vasoconstriction independent of nervous control. Bradford and Phillips⁸ show that there is a constriction of the renal vessels with some increase of the flow of urine.

They decided that the increase came from the general rise of blood pressure which put a relatively greater volume of blood through the renal vessels than normally. They did not give much credence to the view that vasomotor changes directly affected the secretion. A present day conception is that the secretion is affected by the speed with which the blood flows through the vessels rather than the pressure that it is under. This theory would account for the increase in flow of urine that they noted and on the grounds of vascular constriction that they observed, increasing the speed of flow.

Bastedo in his text² reports that there is a temporary increase in the flow of the urine but only when the circulation is poor. He ascribes the improvement in renal secretion to the general improvement of the circulation. Meyer³⁵ reports an increase in the flow of urine. He also ascribes the result to the constriction in the splanchnic area, which occurs with much smaller doses than those required to constrict the renal arterioles. It is pretty generally conceded that there is marked vascular constriction in the splanchnic area with light doses, and most observers hold that in the first stages at least the expulsion of this blood is the cause of the seeming dilation of the skin and perhaps of the kidney. The only observers that came to my attention reporting dilation in the kidney are Jonescu and Loewi²⁶. They think that there is a positive dilation in the kidney when it is isolated from the nervous system.

On the respiratory system there is little effect directly. If there is any effect on the vessels it is of a

similar nature to that on other viscera. Bastedo's text states that there is improvement in respiration in the case of edema. Here the constriction of the vessels though slight may tend to remove the stasis.

As to the effect of digitalis on the alimentary tract, the action is not striking. Most of the members of the group have an irritant action on the mucous membranes and thus cause nausea after continued dosage. It has been claimed by some, Donaldson and Stevens and others, that this nausea is brought on by intravenous injections and is therefore an effect on the centre. This is in line with the general conception that the medullary centres are stimulated. In the intestine there is sometimes irritation enough to cause diarrhea, and certain of the group, for example, digitoxin, causes peristalsis. Strophanthin is reported to be a pretty certain stimulant to the muscle of the intestine walls while large doses of digitalis are reported to increase the activity of the stomach and uterus. Thus it is seen that the digitalis group has a rather wide range of effects outside the circulation.

The action of digitalis on the peripheral vessels, on the heart muscle, and on some of the organs having been reviewed, it remains to mention the investigations that have been made upon the cardiac inhibitory mechanism. The first to call attention to this phase of digitalis action was Traube⁴⁶. He was also the strongest supporter of the idea that the chief effect was upon this nerve centre. Traube ascribed all the cardiac slowing to the vagus action and all the later effects

of increase of rate to the paralysis of the inhibitory centre. He modified his view to some extent later but still placed strong emphasis on the changes induced in the vagus control. Some time later Cushny gave expression to the belief that the acceleration was caused in part by the release of the vagus but he ascribed the greatest change to the direct action of digitalis on the muscle tissue. The slowing he attributed for the most part to the stimulation of the vagus centre but also partly to the increase of irritability of the endings in the heart.

The passing of the slowing stage he lays to the fatigue of the centre, or to the change of irritability of the muscle in response to the impulses received. Ackerman¹, Klug, Bubnoff¹⁵, Kaufmann²⁷ and others have shown that electrical stimulus of the vagus trunk gives no response, showing that there is a change in the relation between the nerve and the muscle. This points to loss of vagus control over the heart muscle possibly at the nerve endings. Meyer suggests that the stimulation of the vagus centre is due to the increase of blood pressure and is then an indirect effect. Bernstine⁴ also states that the state of tone of the vagus is due to blood pressure; that the centre is less susceptible to reflex stimuli if the pressure is low. This is perhaps true if the pressure falls to the point of causing slight anemia, (See experimental section). On the other hand Meyer and Gottlieb say that slowing produced by digitalis, so far as the pure principles have been investigated, is due to central vagus stimulation. Ackerman, Gottlieb²², Kochmann³⁰, Cushny¹⁷, Mackenzie³⁴, and a number of other workers have

judged the action to be central basing their belief on the fact that the slowing is not seen after the giving of atropin or after the section of the vagus. So far as ascertainable the release from inhibition when the vagi are sectioned, the failure to get slowing after atropin, and the block effect similar to an electrical stimulation of the vagus trunk are the only tests reported in the literature that have been made to determine the central action. While these views are rather generally accepted yet they are somewhat of the nature of inductive conclusions. It is the purpose of the present work to confirm these conclusions in a more definite way, namely, by the direct investigation of the exclusive action of digitalin upon the cardiac inhibitory centre in the medulla, accomplishing this by making a perfusion of the brain when isolated from the body except for its connections through the vagus trunk.

P A R T II - E X P E R I M E N T A L .

Materials.

In selecting a drug with which to carry on the line of experimentation that I proposed to undertake it was necessary to bear in mind two points, namely; a-that the drug should have the characteristic physiological action of the group in general, and b-that it should be soluble in physiological solutions. Digitalin was selected as best meeting these requirements. An extract, "Pure Digitalin (German)" guaranteed by the Mallinkrodt Chemical Works, was used. This preparation is water soluble and according to Schmiedeberg⁴⁴ contains the chief physiologically active principles of the group. Some of the pure principles of digitalis could have been used and the general action inferred, since we have the statement of Cushny, Meyer and Gottlieb, Braun and Mager, and others that the difference of action is one of quantity and not one of kind. Some of the members act with a little more intensity on some part of the system, say the medullary centers, than others, but none are entirely specific for one tissue or organ. A number of experimenters have compared two or more of the members and find them varying only in strength of action. Since the work in hand is meant to determine some of the general characteristics of the digitalis group and not the action peculiar to any one of the members it was thought that the drug selected best fulfilled

the purpose.

In preparing the digitalin for use in these tests a stock solution was made of the strength of 1 per cent in Ringer's solution. The Ringer's used in these tests, the formula of which was determined by Greene²⁴ in 1898, is that in common use in this laboratory. It consists of the following inorganic salts in the percentages mentioned:

Sodium chloride-----0.7 per cent

Calcium chloride-----0.026 " "

Potassium chloride-----0.03 " "

The stock solution was renewed frequently so that any deterioration in the strength would be avoided. From this stock, dilutions in Ringer's were made for immediate use. The greater number of the tests were run with 0.1 per cent strength but a number were also tried with 0.01 per cent. After a number of preliminary tests these strengths were found to give the most satisfactory results. Weaker strengths, if they act at all, are so slow that effects from anemia of the brain were feared.

The animal selected for the tests was the turtle. The specimens were procured from northern Indiana. They were the Semi Box Turtles, *Emys blandingii*. They have been in use in this laboratory in common with several other species and found not to differ in general character, so that in this instance it is probable that the species differences may be disregarded and the results applied to the whole family. The turtle lends itself to the nature of this experiment very nicely. It has the advantage of having an active vagus and at the same time tissues that are of such

resistance as to stand with little change the shock that is necessary to the carrying out of the test.

Technique.

The technique for making such a perfusion as was desired in these tests had never been described so that it was necessary to make a number of preliminary tests. After repeated trials the following routine was found to give satisfactory results.

The plastron was quickly removed and the dissection made as rapidly as possible, taking care in so far as possible to avoid injury to the blood vessels. Haemorrhage was avoided in order that the heart should have a good circulation for its nourishment and the normal amount of fluid to work against. The jugular veins were isolated and one of them ligated. The vagi were then secured and ligatures laid under them so that they could be lifted. The carotid arteries were then raised and the left one ligated as low as possible. Thus one artery and one vein were left to carry on the circulation to the brain till the preparation was completed. The greatest speed consistent with careful work was used, since Guthrie²⁵ has shown that anemia is very apt to materially affect brain tissue. The neck exclusive of the blood vessels and vagi was now bound with two strong ligatures about half an inch apart and severed between them. The ends of the ligatures were tied together to prevent the neck retracting and putting the nerves on a stretch. This severing of the neck serves a double purpose, i.e., 1-eliminating all chance of any of the perfusing fluids getting back to the heart, 2-and cutting off any other nerve impulses, sensory or motor, that might directly

or indirectly influence the heart, so that the animal was quite the same as though pithed.

The heart was now attached by the tip of the ventricle to a lever which in turn recorded upon a kymographion. The heart was kept from drying by permitting Ringer's solution to drop on it constantly. Suspended in this way the ventricle gives the main stroke to the lever but when this part of the heart is quiescent then the sinus beat becomes noticeable, as seen in Fig. V.

The perfusion was carried out as follows: A four way canula, first described from this laboratory by Gibson and Shultz²¹ was inserted in the left carotid artery. The left artery was chosen in preference to the right in order that the more active right vagus should be disturbed as little as possible. The arms of the Y were connected by rubber tubing to two Marriott's perfusion bottles which contained the Ringer's and the digitalis solutions respectively. The third arm of the canula was closed with a rubber tube and pinch cock, and served as a drain for the bottles, to remove air bubbles, etc. The perfusion bottles were raised to about forty-seven centimeters which height was found to give a pressure adequate to overcome any vasoconstrictions produced by the digitalis solutions during the perfusion. The right carotid artery and the remaining jugular vein were now ligated, a straight bleeding canula inserted in one of the jugular veins and the perfusion started on Ringer's solution. When enough record had been run to give the normal rate the change to the drug was made. To insure the canula being

quickly filled with the drug, a little of the fluid was always drawn off through the third arm of the canula.

The time of perfusion was indicated on the record by a signal magnet while the speed of the drum was indicated by a time magnet writing five second marks.

Results.

From the group of tests that were made in support of this paper, several results were obtained. Chief among these are;

a) stimulation of the cardiac inhibitory centre by digitalin, as shown by the inhibition of the heart during perfusion of the brain as described under "Technique",

b) paralysis of the cardiac inhibitory centre, as shown by the escape of the heart from vagus control while the digitalis solution was still perfusing through the medulla,

c) cumulative effect of digitalis on the cardiac inhibitory centre, as shown by the length of perfusion necessary to get an effect, and the equally long time that is required for recovery with Ringer's solution,

d) other points such as the relative efficiency of the right and left vagi, the part of the heart that is most affected, some evidence of accelerator fibers, etc., though not so directly concerned with the action of digitalis on the cardiac inhibitory centre are developed in these tests and seem worthy of consideration.

Stimulation of the cardiac inhibitory centre.

With the animal prepared and tested as described above, i.e. with the brain isolated except for its connections through the vagus nerves, and the digitalis being perfused to the head only, it would seem next to impossible to get a cardiac inhibition in any other way than through stimulation of the cardiac inhibitory centre. Of the group of thirty

animals tested, twenty-six or 87 per cent gave evidence that the drug acted on the centre. The indication of action upon the centre was looked for in the changes of rate or amplitude in the heart beat. The changes in amplitude were so inconstant and so small in amount that the rate alone was considered.

By referring to table number I, it will be seen that, with the exception of about seven instances in which there was some increase, the rate of contraction was slowed very little until near the time when the maximal effect was attained.

In some instances, what at first sight appeared to be a slowing proved to be a blocking of the impulse from the sinus so that there was a two-one or a three-one rhythm between the sinus and the ventricle. This two-one type of rhythm was especially noted when there was a seeming partial inhibition, that is when the heart escaped periodically for one or two beats.

Another noticeable feature of the change in rate is the suddenness with which the total inhibition appeared. In many instances the rate would be normal till within two or three beats of the inhibition. The beats immediately preceding the total inhibition were usually of a little greater amplitude but no more than the slower rate might account for.

To strengthen the proof that the action was central the vagi were sectioned during the pause of the heart and while the brain was being perfused with digitalis solution. In a number of cases the section of the right vagus resulted in the immediate release of the heart. Typical cases of the inhibition of the heart, which are interpreted as arising from stimulation of the centre by digitalis, are presented in Figs. I to V. Figs. II and III also show the release on

cutting the right vagus. And, further, the heart responded by the usual stoppage when the peripheral end of the cut vagus was stimulated. The reversal of this cycle was seen in the recovery. Usually when there was escape the ventricle began beating at very nearly the normal rate. The recovery picture in figure 1 is rather an exception to what was generally noted.

To interpret all the features of the change in rate of the heart in terms of the action of digitalis on the inhibitory centre would call forth a good deal of theoretical reasoning that would be difficult to check. It does seem however that while the action of digitalis has rather a long latent period that it acts rapidly in the end, or in other words that the border between the normal state of the centre and that of sufficient stimulation to give inhibitory impulses is easily overstepped. The one phase of the action of digitalis that is proven clearly is that there is a marked stimulation of the cardiac inhibitory centre.

That the action might be due to the effect of the Ringer's solution seems improbable since very long perfusion (tested out in the preliminary trials) with this solution gave no indication of a stimulation. Also, that the effects as noted on the cardiac inhibitory centre are due to the action of the drug and not to pressure changes as suggested by Meyer and also by Bernstine, is pretty well proven by the wide range of pressures that were used, varying from about 20 to 47 centimeters of water. In no case did the pressure of the normal perfusion fluid give any perceptible effect as

indicated by contraction rate of the heart, nor so far as can be judged did it prevent the recovery from the inhibitory action of the digitalis. In a few cases the perfusion was going so slowly that it was deemed best to force it by a mechanical pumping pressure. The pressure must have been very much greater in such cases but there were no physiological changes that could be ascribed to this cause.

Paralysis of the centre.

As was mentioned in the section above on Theories of Action, Traube, Cushny, and others concluded that there was a paralysis of the vagus center. Traube based his conclusion, that the cardiac inhibitory centre was paralyzed, upon the subsequent excessive rate which followed the slowing. He believed that the acceleration indicated complete loss of vagus tone, leaving the accelerator mechanism unchecked. Cushny and others noted an excessive rate in digitalis poisoning and thought that it was due in part at least to paralysis of the inhibitory centre. Evidence in substantiation of the views of both Traube and of Cushny is found in the present work, i.e. in a number of cases, the heart escaped from the inhibition while the perfusion was still going on. This escape took much the form of an escape from electrical vagus stimulation. As is shown in the figures at the end of this paper the first few beats after inhibition were of greater amplitude than the normal. However the amplitude and rate both quickly assumed the normal and remained in that state. Subsequent perfusions gave no further noticeable.

That this escape should occur from any other cause than paralysis of the cardiac inhibitory centre is not probable. It is a matter of common physiological knowledge that nerve trunks are not fatigued by the conduction of impulses, at least not till far beyond any time that they were called upon to act in these tests. Nor is there fatigue in the vagus endings of the heart, for Mills³⁷ has shown that in the Slider terrapin that the heart can be continuously inhibited for two hours by electrical stimuli applied to the vagus trunk. In fact he reports one instance of an inhibition of over four hours. In a few instances in this series, after the heart had escaped from the inhibition, the vagus trunk was stimulated electrically resulting in the usual inhibition, as was to be expected. As stated in the last paragraph a second inhibition was never secured by perfusing the digitalis again, whether done in a short time or after Ringer's solution had been perfused for some time. These results speak very strongly for paralysis of the cells of the cardiac inhibitory centre.

It seems to me that the only objection that could be offered to this evidence of paralysis is the conception that there had been such constriction in the vessels that there was no longer a sufficient amount of the drug reaching the cells to give the stimulating effect. There is a decrease in the amount of outflow from the jugular vein indicating constriction of the arteriols, but since there was a fair flow kept up all the time I do not believe that the

decrease is enough to account for the change. Considering the profound histological changes that Klopotosky found in nerve cells, and the persistent effect that the clinicians report, it is small wonder that there should be paralysis when the brain is perfused experimentally with sufficient strengths of the drug or for a sufficient time. In therapeutic use perhaps it would not be a radical conception to assume that the same toxic condition might arise after repeated or heavy dosages.

Cumulative effect of digitalis.

In therapeutic use of digitalis the cumulative factor is given considerable attention. There this action is judged by the long time that is required for the drug to act when given by the mouth as well as by the appearance of the usual digitalis effects after repeated dosage. These effects are lasting also when once acquired. Perhaps both of these factors are dependent on the fact that digitalis is very slowly absorbed into the tissues and equally slowly given off. In the method used in the present work in which the drug is perfused directly into the brain it might be expected that we would get the effect in the very minimal time. It was found that in the group of seven animals tested with .01 per cent of digitalin that the average time till the first noticeable change in heart rate was five minutes, twenty-two seconds, while the shortest time was one minute, fifty-five seconds. The longest time till an effect appeared was eight minutes while the average till the maximal effect was reached was six

minutes, thirteen seconds. There were twenty-one tests made using the .1 per cent strength of digitalin. In this group it was found that the average time till the first noticeable change in heart rate was three minutes, three seconds, while the shortest time was twenty seconds, a mark that was approached in only one or two cases. The average time till the maximal effect was four minutes, fifty-five seconds, with the longest time being eleven minutes. As far as the data goes, it is shown that there is a shorter reaction time when the stronger solution is used, however so far as could be judged the reaction was not different in kind.

The recovery time cannot be averaged in the group of experiments since in so many instances extraneous factors were brought in, such as cutting the vagi or the escape due to paralysis. I believe however that it is a safe estimate to say that it requires as long to remove the effect as to produce it. For example, in experiment number 26 (Fig. I) it required 5 min. and 15 sec. to get the first effect as judged by the change of heart rate, while it was 3 min. and 40 sec. after the Ringer's solution was again perfused till the first heart beat, and 16 min. till the normal rate was restored. This it seems is evidence that digitalis is stored in the tissues.

Another indication of this cumulation is the fact that in several of the tests the inhibitory effect returned after the perfusion of the drug had been replaced with the Ringer's. This may be explained on the assumption that it required a certain length of time for the digitalis to

diffuse through the walls of the capillaries, the lymph spaces, and the cell bodies and that there had already enough drug collected in the lymph to go on to the cell and result in stimulation, even though the diffusion toward the Ringer's within the blood vessels had already set in. This is in keeping with the long time that it takes for the first effects to appear, which must be explained either on the grounds that it takes considerable time for the digitalis to reach the brain cells, or that the changes in the cells necessary to produce the stimulus take place very slowly. Perhaps both factors are involved for it is not probable that diffusion should go on rapidly and at the same time the reaction within the cell be so slow. On the other hand it is not likely that a drug that would react rapidly with the neuroplasm should fail to pass the capillary wall and lymph spaces with ease.

Another phenomenon occurring in two experiments, Nos. 2 and 6, was the recurrence of the inhibition after there had been seeming recovery from the digitalis effect, when the Ringer's solution was stopped, that is, Ringer's solution in the blood vessels but not perfusing at all. This at least shows that there is some of the digitalis retained in the cell or some permanent change in the structure that renders it susceptible to the change in oxygen or carbon dioxide content that comes when the fluid stands in the capillaries. Henderson has shown that excess of carbon dioxide will stimulate the cells of the respiratory

center to activity, and it is not improbable that the same is true of the other medullary centres. Granting that this be true we must still say that the digitalis has increased the irritability of the cells, since the mere withholding of the Ringer's from the normal cells will give no such effect. While these results cannot be classified strictly as cumulative effects yet they render a condition that very much favors cumulative action.

Other points noted.

Relative Efficiency of the Vagi.- Garrey and others have worked out the relative efficiency of the vagi, as well as the parts and functions of the heart that each nerve controls, so thoroughly that nothing new on the subject would be expected in a work not especially devoted to that study. However, in cutting the vagi and noting the immediate release from inhibition, thus proving the stimulation to be central, the following results were noted. They are presented not as something new but because they are strikingly clear, and because the stimulation was applied to a part of the nerve not previously used experimentally.

In several experiments when the inhibition had been obtained through stimulation of the medullary centre by perfusing with digitalis solution, the left vagus was sectioned resulting in no apparent change in the hearts condition. Examples of this are afforded in Exps. No. 26 and 27, figs. I and IV. On the other hand if the right nerve be sectioned there is almost immediate release. Exps. No. 20 and 26, figs. I and III, show the phenomenon nicely. In the face of

the escape that is noted in several other experiments it might be suggested that the heart was quite ready to escape from other cause and that the cutting of the right vagus happened at a fortunate time. The prompt release and the character of the curve following is sufficiently comparable to the physiological type to convince one that we have a true release due to the section of the nerve.

It was found also that subsequent perfusions after the section of the right vagus nerve never resulted in an inhibition, even though the left vagus was intact, while if the right nerve was intact inhibition could be induced a second time. Figures I and III present this finding graphically.

The character of the inhibitory change - Another interesting point was the way in which the different parts of the heart were affected by the inhibitory impulses. For the most part, the ventricle and auricles were completely inhibited, while the large veins and the sinus venosus continued to beat. The adjustment of the lever was not always delicate enough to reproduce the sinus beat in every instance but some of the figures show it fairly well. Upon direct observation of the preparation it was seen in almost every case. This is evidence that in turtles the vagus effect is chiefly a blocking of the impulses from the sinus and great veins.

In laboratory animals and in man, according to Mackenzie, and also Lewis, the blocking of the conduction

of impulses is one of the chief results of the action of digitalis. Theories in the literature on the question of the conductivity of the bundle of His, and the change in irritability of the muscle tissue have been discussed in the section on Theories of Action of Digitalis.

Mackenzie, noting that the block phenomenon under digitalis was very similar to that of vagus stimulation, concluded that the result was due to the action of digitalis on the vagus endings and the structures immediately in connection with them. Since the results in the present test are very similar to those which he describes, and since it is certain that only the centre is acted upon, it may be that more of the results may be due to central action than he ascribed. This of course in no sense disproves any action that digitalis may have on the tissues of the heart when brought in direct contact with them, as in perfusion of the whole circulation.

Evidence of accelerator nerves - So far as I am able to ascertain it has not been definitely proven that the species of turtle used in these tests has any cardiac accelerator nerves. In my tests there is some evidence of such a mechanism. This is based on the following findings:-

Of the eight tests made with .01 per cent digitalis, four or 50 per cent, showed an increase over the normal rate at some time before the slowing took place. The average increase for the four was 9.6 per cent.

Of the tests made with 0.1 per cent digitalis there were five cases of acceleration. In this group the average increase in rate over the normal was 14.5 per cent.

To stop here one would immediately conclude that there was an accelerator mechanism. However it was noted that in each of the instances in which there was acceleration, there was also a decrease in the amplitude. Since the vagus nerves have some control over amplitudes in the hearts contraction, it is possible that there was a diminution in the strength of the beat, thus with the same rate of metabolism permitting a faster rate. On the other hand it is a natural correlation for the amplitude to decrease when the rate increased, when there are no changes in other factors. With the animal prepared as in these tests with no drug reaching the heart it is probable that the metabolism is practically constant, and that one of the changes is probably the result of the other. In these tests there are too many uneliminated possibilities to permit of drawing a conclusion, but at least the evidence suggests an accelerator mechanism.

If there really is such a mechanism, then since all nerve connections were broken except the vagus, it follows that these fibres must run in this nerve trunk. Further their cell bodies must be stimulated by digitalis and also sooner than the cardiac inhibitory centre, for the increase in rate appears before the slowing occurs.

While the data here is not sufficient for a conclusion, yet for further work on the accelerator nerves of

the heart this would seem to be a very suggestive finding.

General stimulation of the central nervous system - One other result remains to be mentioned, i.e., the stimulation that is given to the central nervous system in general when digitalis is perfused through the higher centres. With the spinal cord sectioned these results have no effect on the tracings from the heart so that the evidence must rest on direct observation of the behavior of the animals. When the digitalis solution was first perfused into the brain there was always a response through the motor nerves giving contractions of the muscles about the head and throat that were still in connection with their motor nerves. In the preliminary tests, in which the cord was not severed, there was such a general movement of the skeletal muscles that an even record from the heart could not be gotten. When the head was isolated the muscles of the throat and jaws were very active when the perfusion of digitalis was begun. These movements were seldom seen when the Ringer's solution was started, and then in a lesser degree. Thus it is evident that the stimulating action of digitalis is not confined to the medullary centres but extends in some degree at least to some of the motor centres of the brain and spinal cord.

Summary.

1. Digitalis strongly and directly stimulates the cardiac inhibitory centre of the medulla.
2. There is evidence of paralysis of the centre by excessive action, as is shown by the escape of the heart during perfusion and by the failure of subsequent perfusions to reproduce the inhibition.
3. There is evidence of cumulative effect on the nerve centre, as indicated by the relatively long time required for the action to set in and by the equally long time for the recovery. The recurrence of the inhibition without subsequent perfusion of the drug also points to the same effect.
4. The inhibition through the vagus is of the nature of a blocking of the passage of the impulses from the great veins and sinus venosus to the auricles and ventricle.
5. There is some evidence of an accererator mechanism in this species of turtle, with the nerve fibres coursing in the vagus trunk.
6. There is stimulation of the whole central nervous system by digitalis as is shown by greater skeletal muscular activity indicating stimulation of the motor centres.

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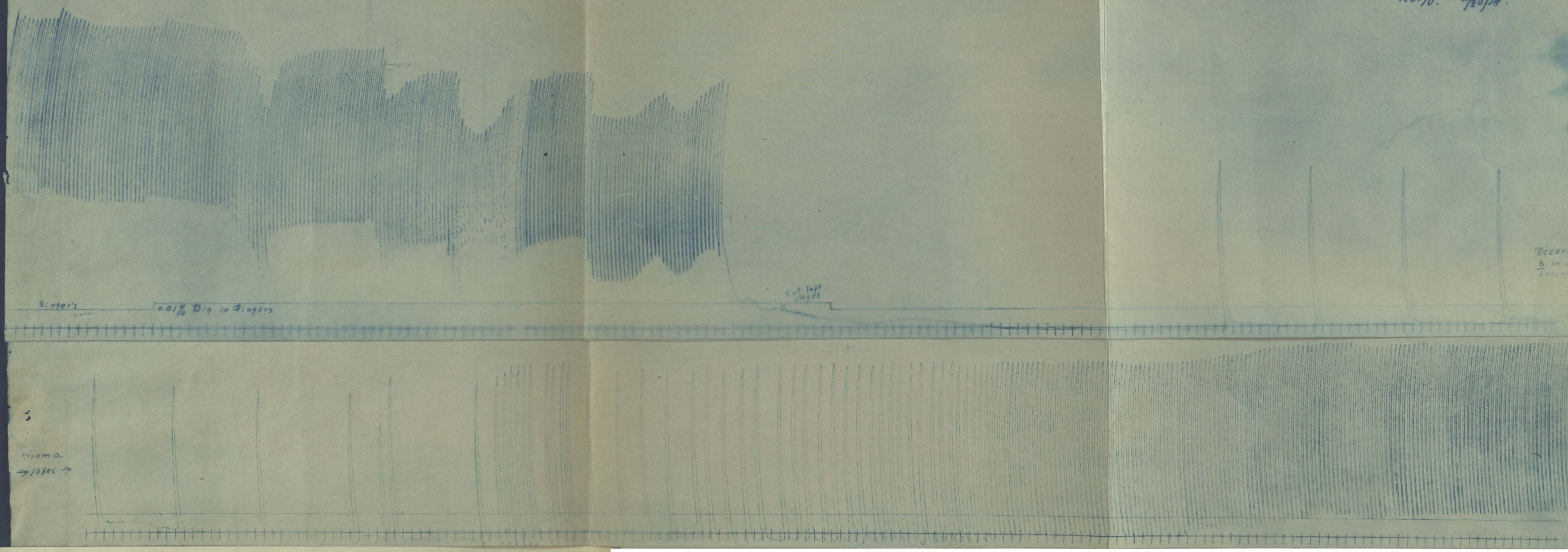
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T A B L E N O . I , C o n t i n u e d .

Exp No	Date	Drug per cent	Time of perfusion		Heart Rates per min.							Amplitude of contr. in m.m.		Time till first effect		Time till maximal effect		Time till escape during perfus.		Recovery, time till first contr.		Ringer's Solution				Remarks.				
					nor- mal	during perfusion							nor- mal	during		min.	sec.	min.	sec.	min.	sec.	min.	sec.	ear- ly rate	lat- er rate		ear- ly ampl.	lat- er ampl.		
						1	2	3	4	5	6	7		early	late															
19	Feb. 13a	.1	0	54	22	21	0	-	-	-	-	-	-	40	45	45	0	42	1	15	0	0	0	15	22	-	42	-	Sinus beating. Another 12 min. perfusion gave no result. Immediate release on cutting right vagus. Never able to get second effect.	
	b	.1	2	0	22	22	0	-	-	-	-	-	-	42	-	-	1	30	3	0	0	0	0	15	18	26	41	36		
20	14I	.1	2	55	19	22	22	0	-	-	-	-	-	38	38	38	2	35	2	35	0	0	0	0	20	21	40	-	Never able to get second effect.	
21	14II	.1	3	45	36	36	36	0	-	-	-	-	-	42	44	43	2	20	2	20	0	30	0	30	-	36	41	41		
22	16a	.1	8	10	24	-	-	-	-	-	-	-	-	35	-	-	0	0	0	0	0	0	0	0	0	-	-	-	-	No effect.
	b	.1	con tin.		28	28	20	-	-	-	-	-	-	32	-	-	3	30	6	50	0	15	0	0	27	30	30	25		
23	19I	.1	7	50	44	43	43	41	0	-	-	-	-	44	-	-	3	25	3	25	0	0	0	0	40	44	44	43	L. vagus cut-no effect. R. vagus cut-release.	
24	19II	.1	4	30	27	28	28	0	28	-	-	-	-	45	45	45	2	30	2	30	0	30	0	30	28	28	45	-		
25	20I	.1	3	15	24	24	0	-	-	-	-	-	-	36	38	39	1	40	1	40	0	30	0	30	22	24	38	36	Second perfusion-no effect.	
26	20 ^{II} a	.01	6	0	27	28	28	28	28	0	-	-	-	55	52	54	5	15	5	15	0	0	3	40	7	27	53	52	L. vagus cut-no effect. Recovery phenomena only after cutting right vagus. Second inhibition total.	
	b	.01	6	50	26	26	26	11	-	8	8	-	-	53	58	56	1	55	6	0	0	0	0	15	24	28	52	52		
27	21a	.01	7	40	26	26	26	26	24	0	-	-	-	43	43	0	4	20	5	25	0	10	2	45	25	25	49	45	L. vagus cut-no release. Sinus beating regularly. Lat- er 15 min.perfusion-no effect.	
	b	.01	10	40	28	34	33	35	35	0	-	-	-	48	43	0	5	05	5	45	4	0	11	0	20	36	44	44		
28	Apr. 4I	.1	3	30	34	34	0	-	-	-	-	-	-	38	35	0	1	20	1	20	2	0	2	0	6	35	42	37	Sinus beating regularly. Escape partial, i.e. every third beat.	
29	4II	.05	11	40	43	43	43	43	43	43	43	42	-	47	46	43	6	40	10	0	0	0	0	0	40	43	33	45		

Peeler, J. V.
Physiology } Lab. of Mo.
Pharmacology }
Brain Perfusion
Digitalis-Turtle
0.01% - 2/20/14.



Record
b. in 10
seconds

Fig. I Exp. 26.

Showing inhibition of the heart with digitalin perfusing
the medulla- Cutting of L.vagus- Recovery with Ringers

Peeler #
Physiology Lab
Univ of Mo.
Head Perfusion
Cable - Dry 0/0

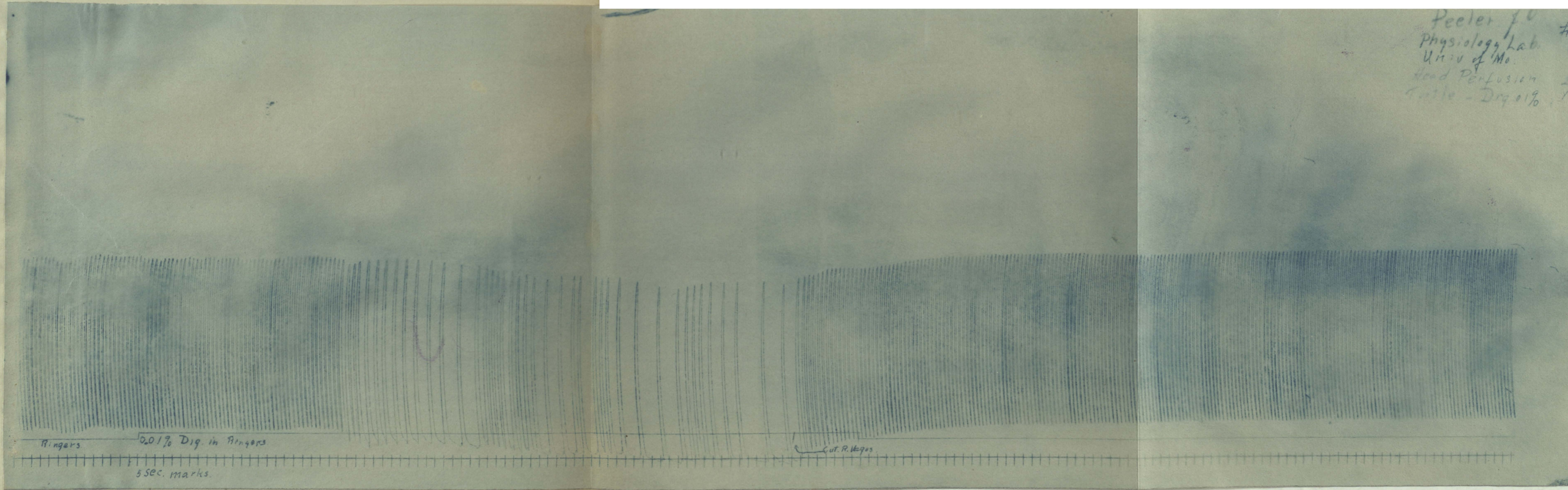


Fig. II Exp. 26 (cont.)

Showing effect of second perfusion with release upon cutting R. vagus.

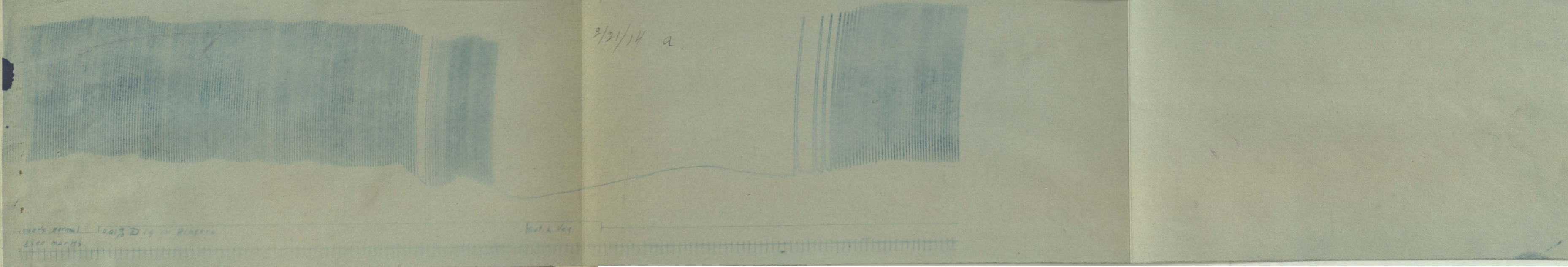
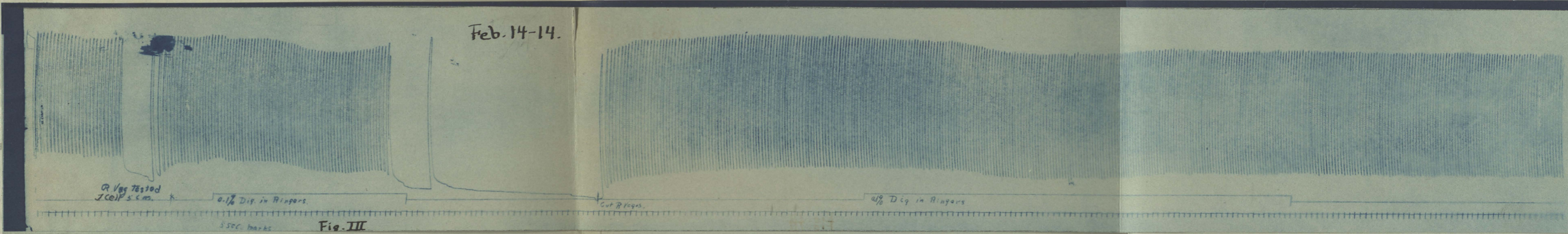


Fig. III, Exp. 20.

Showing effect of cutting R. vagus. Second perfusion gave no effect.

Fig. IV, Exp. 27

Showing effect of cutting L. vagus.-Recovery from inhibition with Ringers.

Dec. 6
Peeler, J. O.
Physiology Lab. V & A
Head Perfusion - decap
except Vagi, Carotid Cut & Juxta

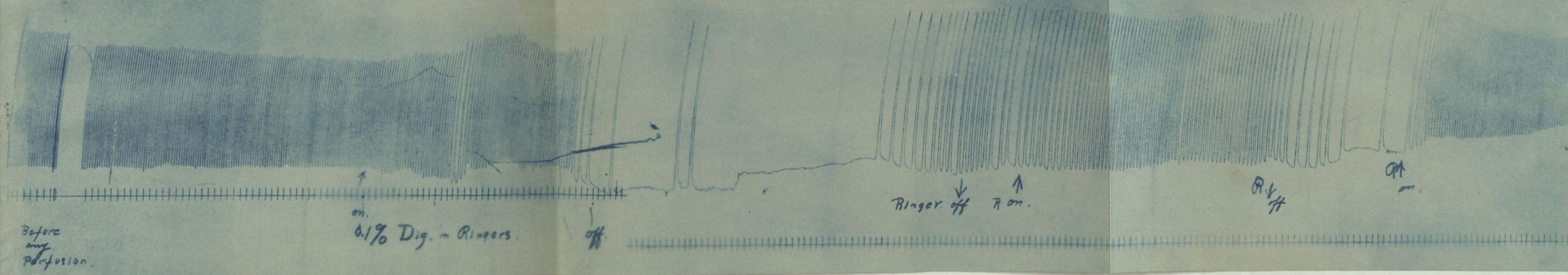


Fig. V. Exp. 6.

Showing the sinus beat during inhibition of the ventricle-
Recurrent inhibition when the Ringers is withheld.

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