PHYSIOLOGICAL AND PHARMACOLOGICAL
STUDIES ON CARDIAC TONICITY
IN MAMMALS

By

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SYNOPSIS

- Effects of Strychnin on Rate of Filling of the Ventricles - The Action of Strychnin on the Blood Pressure - Indications for Clinical Administration of Strychnin in Cardiac Therapy - Digitalis and Stramonium - Nitroglycerin - Calcium and Potassium - Effect of Sodium Citrate on the Heart - Calcium and Potassium following Atropin Sulphate - Effect of Asphyxiation on Cardiac Tonicity - Traube-Mering Curves - Injection of Air into a Vein - Formic Acid - Aconite - Summary and Conclusions -
Many of the advances, both physiologic and clinical, which have been made in the study of the heart since 1897 owe their existence to the suggestion of Engelmann that cardiac phenomena should be analyzed from the standpoint of the four primary properties of the heart muscle: rhythmicity, irritability, conductivity, and contractility; and most of the researches since then have been conducted with regard to these four properties. James Mackenzie in 1905, however, called attention to the fact that in pathologic conditions a fifth property of the heart muscle - that of tonicity - should be taken into account, and should also be studied analytically, and that investigations in which this was omitted must be to a certain extent regarded as incomplete. Although Mackenzie was perhaps the first boldly to class tonicity along with the four fundamental properties of Engelmann, its great importance had long been taught by the most advanced writers upon cardiac subjects, at least of the British school, particularly by Clifford Allbutt and C. A. Gibson.

Although the importance of considering the cardiac tone was thus established, little has been done toward the accurate study of the variations which take place in mammals and in man under physiologic and pathologic conditions, and under the influence of drugs. The present research was begun in hope of gaining some more accurate idea of these variations, and of establishing more
exact methods for their study. The drugs employed were strychnin sulphate, digitalis, strophanthus, calcium, potassium, nitroglycerin, adrenalin, ether, ammonium carbonate, formic acid, and aconite. The methods developed will be discussed in a subsequent section of the paper.

I take this opportunity of expressing my thanks to Professor L. F. Barker, in whose service the work was carried out, and to Dr. A. D. Hirschfelder, at whose suggestion and under whose guidance it was undertaken. My thanks are also due to Dr. Harvey Cushing and Dr. W. G. MacCallum for the privileges of the Hunterian Laboratory.
DEFINITION OF TONICITY.

The tonicity of the heart muscle may be defined as the property by which its fibers resist stretching when no active contraction is taking place - in other words during its diastole.
Under the heading of "Contraction remainder", it was first pointed out by Hermann in 1859 that a voluntary muscle (its contractions being recorded by a myograph and stimulated by rhythmic excitations, one or two per second, from an induction coil) frequently does not return after the first contraction to the same degree of extension which before existed, but remains somewhat shortened. Regarding the nature of this contraction, Tiegel found it only on direct stimulation with an induction current. Rossbach and Harteneck found it with direct and indirect induction currents, while Roy finds that it may occur independent of any external stimulation, that it is more or less evident in all ventricular curves and greatly increased by imperfect nutrition.

Roy goes on to state that this "contraction remainder" or "after-expansion" resembles the "idiomuscular" contraction in some respects, but differs in one very important particular, viz. that it is purely a passive phenomenon, presenting a close analogy to a well-known fundamental characteristic of the elasticity of organic substances in general. For example, a piece of silk thread or a piece of an artery stretched by a weight elongates rapidly for a certain distance and then very slowly, while when the weight
is removed it contracts rapidly until nearly its former length, then more slowly until it reaches a position of equilibrium. In 1878 Roy investigated tonicity, which he designated as "idio-muscular contraction", and made some interesting statements, borne out by tracings. In the characteristic form of this contraction, caused in this case by digitalis, the ventricle slowly contracts and again slowly expands. In the cases in which the dose has been large, the ventricle remains contracted and we have the "arrest in systole" of the digitalis heart. This slow contraction differs fundamentally from the ordinary systole of the ventricle, because ordinary contractions are often found superimposed upon it. That it is not tetanus is equally evident. It differs from contraction remainder in that the ventricle after each contraction expands rapidly, and often assumes at once a more dilated position than existed immediately before the systole. This form of contraction in the case of the digitalis heart seems to Roy to have more of a toxicologic than a therapeutic importance, since in frogs to which the drug has been administered gradually in small doses, so that death results from chronic poisoning, the ventricle is usually found relaxed. This relaxation has been attributed by Cushny and others to the lesser development of the central nervous system in frogs, and indicates paralysis of the vagus. He goes on to mention the drugs which cause this condition. They are as follows: digitalin, digitalein, digitoxin, alcohol, atropin, helleborein,
Rossbach observed the same condition independent of the action of drugs in the case of ventricles, which after having been allowed to contract for some time without renewal of their contents, were supplied with fresh diluted blood.

Roy also noted it three or four times under these conditions, and believed that in this condition its most probable explanation lay in the poisonous action of products of tissue change which had been accumulated in the ventricle, rather than in the stimulus of the fresh fluid which had been supplied immediately before its appearance. His reasons for this belief are that when the idiomuscular contraction results from the action of digitalis, it not infrequently first appears when the poisoned blood is replaced by fresh unpoisoned fluid; where the dose of poison is larger, this form of contraction shows itself while the drug is still contained in the cavity of the organ. During the time that this idiomuscular contraction is present, the elasticity equivalent of the ventricle wall varied, being increased with larger amounts of digitalis in the fluid supplied to the organ. With a small dose of the poison and the idiomuscular curve not very high, on raising the intraventricular pressure from 20 to 30 cm. (water) the resulting increase in capacity of the ventricle is greater than would be the case with the normal ventricle. In such instances, therefore, the elasticity is diminished as is the case with voluntary muscles in the contracted condition.
When the dose of poison has been relatively larger, and the arrest in systole has occurred, not infrequently an increase in the distending pressure by 10 cm. water - e.g., raising it from 20 to 30 cm. - may cause but a very slight increase in the ventricular organ. Here the elasticity is increased.

If, however, with a ventricle in this condition we go on gradually raising the intracardiac pressure, we finally arrive at a point where a given increase (10 cm. for example) of the distending force results in a very much greater distention than is given by the relaxed organ under corresponding conditions.

W. H. Gaskell in his research on the tonicity of the heart and blood vessels, found that in the case of the heart of the turtle the tonicity could be increased or decreased by perfusing the heart with dilute alkalies or dilute acids respectively. In the former case the dilute alkalies caused the expansion of the heart to lessen gradually until the ventricular cavity was totally occluded, and the heart became arrested in a condition of extreme tonicity - systolic or tonic standstill. Conversely, dilute acids caused a progressive dilatation until the ventricles became arrested in a condition of extreme atonicity - diastolic or atonic standstill. The arteries also reacted in the same manner. He likewise observed that the effect of the alkali could be neutralized and counteracted by the acid and vice versa, so that all the intermediate steps between tonic and atonic standstill could be
brought about in the same heart by interchange of the two solutions. The same reactions occur with digitalin, antiarin, and muscarin solutions; the digitalin acting in the same manner as dilute alkalies, increasing tonicity, while muscarin acts similarly to dilute acids, decreasing tonicity.

With regard to the evidence that the cardiac muscle possesses tonicity, we find from the article on tonicity in Professor Schäfer's text-book that it is in great part founded on these experiments of Gaskell. The reasoning is based by Leonard Hill on the fact that digitalin and muscarin alternately administered furnish precisely similar curves to those of alternate alkalies and acids, and that muscarin acts on the apex or on the whole ventricle in the opposite sense to digitalin, and, "therefore, as there is every reason to believe that digitalin acts on the muscle substance in a direction of bringing about a tonic condition of that muscle, muscarin must also act directly on the muscle in the opposite direction and produce its effect by bringing about an atonic condition of that muscle."

Goltz and Ewald have proved that tonus of any organ is not altogether dependent on the central nervous system, that tonus in any organ is dependent on efferent nerves, and there is evidence that the corresponding centers in the brain and cord are tonically stimulated, thus concluding that tonus is of mixed origin, and that whether the automatic or reflex factor is the more important is not known.
Cyon and Steinmann conclude that muscle tonus may be also of peripheral origin.

According to Tigerstedt tonus is often caused by direct stimulating influence of substances formed in the body (internal secretions) on peripheral organs, or on peripheral or central nerve cells.

Leonard Hill also says:

An alteration of tone in the two directions, due to an activity emanating from the ganglion cells of the two sets of nerves, is in accordance with the known facts of the function of the afferent vagrant ganglia, and the nerves emanating from them in other cases - e.g. the vasomotor and visceromotor ganglia and nerves - and that relaxation of tone by inhibitory nerves is closely connected with the relaxation phenomena brought about in a tonically contracted muscle by the passage of a constant current.

In the year 1903 Porter demonstrated several facts regarding tonus before the American Physiological Society, while in 1905 these findings, somewhat amplified, were published. These physiologic studies were made on the extirpated heart of the tortoise, and showed that as the tonus increases, conductivity diminishes; that the height of the tonus contraction is proportional to the strength of the stimulus and has no refractory period; that tonus contractions may be superposed, as contractions of skeletal muscle are superposed; and he records a tetanus of
tonus secured by rapidly repeated induction shocks resembling the tetanus curve of skeletal muscle. W. H. Schultz finds that the frog's heart poisoned with chloral hydrate at a certain stage of poisoning, being stimulated by two successive shocks, shows the phenomenon of summated contraction, and gives on repeated stimuli a curve resembling that of incomplete tetanus of skeletal muscle. Porter emphasizes the fact that only the tonus contraction may be summed up, the fundamental contractions not entering into this addition. Thus tetanus of the heart does occur, but is not a tetanus or fusion of the fundamental contractions, but is a tetanus of the tonus contractions.

Porter also states that the tonus of the ventricle is greatly increased at the onset of fibrillation and that coordinated beats do not return unless the extreme tone spasm is considerably lessened. Localized areas of tonic spasm break up the normal conduction of the contraction wave by blocking its passage, thus leaving the remaining muscle fibers dissociated and in confusion, namely in fibrillation.

From these facts Porter forms a hypothesis that tetanus is essentially the same in smooth cardiac and skeletal muscle, consisting in each of fused tonus contractions on which are placed the fundamental contractions, in some cases visible to the naked eye, in others not so, though often demonstrable by special means. According to this hypothesis tetanus is not produced by the
by the fusion of fundamental contractions (Helmholtz's fusion) but by the fusion of tonus contractions. This he calls tetanus of tone.

From the clinical standpoint, Clifford Allbutt has observed in functional disorders of the heart and arteries that tone is often signally deficient. In these cases he has often seen a temporary extension of the area of cardiac dulness, and points out in a later section that diminution or lack of tone is an important factor in the production of cardiac dilatation. This conclusion is also held by G. A. Gibson, and in 1904 was stated by Colbeck as the common origin of all forms of cardiac dilatation, this being confirmed in an article published by Mackenzie the following year pointing out in addition the inadequacy of the old belief that dilatation was due to thinning of the ventricular walls. He refers to cases noted also by Keith, in which the ventricular walls were greatly thinned but the heart not dilated, also alluding to the fallacy that increased intraventricular pressure invariably was a factor in the production of dilatation, as dilatation occurred in cases in which, due to a pure mitral stenosis, the diastolic filling force of the ventricle was diminished.

Tonicity determines and limits the tensile properties of the ventricular walls, and regulating the tension of the muscle walls it follows that to a large extent it regulates also the force of the contraction. As stated by Clifford Allbutt, tension and tone
have something like an inverse relation one to the other, being mutually provocative and antagonistic.

This function is also stated to be of paramount importance in the maintenance of diastolic distention of the heart when unimpaired, restraining undue diastolic distention, thus limiting the quantity of the residual blood in the ventricle at the end of systole, stimulating the ventricular wall to a more vigorous contraction and placing the ventricles at a mechanical advantage, inasmuch as the smaller the cavities of the ventricular chambers the greater their power, in accordance with the rule formulated by R. H. Woods that the blood pressure inside a contracting cardiac chamber varies inversely as the radius of the chamber.

Colbeck now contrasts this with cases in which there is diminution or loss of tone, pointing out that the conditions are reversed, that the diastolic distention is inadequately checked, the residual blood increased, the ventricle partially or wholly lacks the stimulus to more vigorous contraction, and moreover acts at a mechanical disadvantage in accordance with Woods' rule. Thus the consequences of loss of tone are indicated by him as stretching of the ventricular walls and dilatation of the cavities, a condition which tends to increase and become perpetuated. Furthermore Colbeck remarks that in dilatation (depression of tonicity) the function of contractility is able, until its reserve power gives out, to maintain the circulation more or less imperfectly for long periods of time apart from the restoration and reinforcement of the cardiac tonus.
by hypertrophy. The reason for this is that tonicity, being a more specialized and a later acquired attribute of muscular tissue than contractility, is therefore more readily and profoundly affected by any interference with function than is contractility.

He alludes to the importance of the nervous factor in cardiac dilatation with regard to its regulating and maintaining tonicity, pointing out that tone, though automatic, may be increased or decreased by the central nervous system, and describes fully the mechanism by which in aortic regurgitation and other valve lesions dilatation occurs, attributing the dilatation to a relative insufficiency of the tonicity of the ventricular muscle. Theoretically the force of the ventricular contraction may be increased either by diastolic distention of the ventricular cavity or by increasing tonicity through nervous influence. Also temporary dilatation of the heart occurs in apparently healthy individuals as a result of violent or protracted exercise, being due to a transient increase in blood pressure associated with largely increased diastolic distention of the ventricle.

In spite of the claims of Colbeck and Woods, the blood pressure and intraventricular pressure bear no essential relation to the tonicity. Thus, upon stimulating the vagus, the tonus of the muscle is diminished and the heart dilates in diastole, but the force of the contraction need not be impaired, and the intraventricular pressure may rise to the same height as before. It is certainly true, as these observers and Roy and Adami have pointed out,
that the total pressure on the ventricular walls during systole increases as the square of the radius of the cavity. But the studies of O. Frank and others have shown that this may, up to a certain point, serve as a stimulus rather than as an impediment to the contraction, the condition of the distended heart being analogous to that of the loaded muscle, while that of the undis-tended is more similar to the after-loaded muscle, a certain amount of load being conducive to the maximal contraction.

Both Colbeck and Mackenzie attribute the beneficial action in cardiac dilatation of cardiac tonics, as digitalis, to their power of increasing tonicity, and the depressing effect of drugs, as aconite, to depression of tonicity, thus producing dilatation.

Mackenzie goes a step further, arguing that on account of the peculiar arrangement of the muscle bundles in the heart, pointed out by Arthur Keith, and on the fact that from their location some bundles must have different functions to perform than others, then some require the function of tonicity in a high degree, as those muscle fibers pointed out by G. A. Gibson surrounding the infundibulum and supporting the pulmonary valves, while others require different functions such as contractility more than tonicity. That is to say, he assumes that the tonicity of the ventricular muscle varies according to the situation and function of the muscle fibers. Furthermore, he points out that the tonicity of one set of fibers may be affected alone, as the ventricles may generally be dilated, due to the loss of tone, without a corresponding want
of tonicity in the ring fibers of the pulmonary artery, thus producing a functional stricture and systolic murmur.

The same holds good with regard to the auricles and their venous orifices; while on the other hand the ring fibers may have lost their tone, allowing regurgitation into the veins or producing a functional insufficiency without the auricle or ventricle being dilated. Cases are quoted bearing out these statements, and in addition a case is quoted which indicates that certain drugs may direct their action to a special group of muscle fibers; thus, a mixture of alcohol and arsenic produced regurgitation of blood into the veins, which disappeared when the arsenic was removed from the alcohol, though the use of alcohol in excess was still continued. Then he classes the symptoms of depression of tonicity as dilatation of the heart, functional murmurs, and regurgitation into the veins; the causes of depression of tone as "failure of compensation", in cases of valvular disease dilatation being the main evidence, and exhaustion of the muscle playing the principal part in its production.

In 1906 Henderson pointed out that in the normal heart variations in the volume curve are mainly determined by rate of beat; that increased rate induces a "trappe", causing a more complete emptying of the ventricle, so that the amount of residual blood in a rapid heart is very small, the ventricular cavity being practically obliterated at the end of systole, while with the slow heart he estimates this discharge volume as two-thirds the diastolic volume,
the other third remaining in the ventricle as residual blood, while apparently both tonic and "trappe" at the onset and end of each beat respectively depend on the rate of the few preceding beats. That is, an increase of tonicity with an increase of rate up to the optimum rate diminishes the diastolic volume of the ventricles by amounts equal to or slightly greater than the coincident development of "trappe" diminishes the systolic volume.

Thus, as pointed out by Leonard Hill in Schäfer's text-book, one cannot attribute apparent increase in tonus to the administration of a drug, if this increase be accompanied by increase in frequency, since this allows a shorter time for the ventricle to expand in diastole. Thus it does not follow that the tonicity is increased.
DESCRIPTION OF APPARATUS

The Cardiometers. — Following the description given by Vandell and Henderson, these were constructed out of light rubber tennis-balls, ranging from 4.5 to 11.5 mm. in diameter. Out of the side of each ball a circular portion 0.7 mm. in diameter of the ball was removed. Over the opening was cemented light rubber dam, out of which was cut a central circular window 0.6 mm. in diameter of the ball. Over this a second layer with a slightly larger window was cemented. Into the opposite end of the ball a bent glass tube with a flange was inserted, and made air-tight by means of a rubber or cork washer and rubber cement. (While with a normal heart these dimensions were found satisfactory, sometimes with a large or dilated heart that cardiometer containing an aperture suitable for the auriculo-ventricular groove of the heart in question was found too small to contain the ventricles, while a cardiometer of the requisite size possessed too large an aperture. Therefore, over the diaphragm of a larger cardiometer was cemented a very thin sheet of rubber into which was cut when required an aperture of the right size.

This statement does not imply that the cardiometers were too small.

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A cardiometer to enclose the ventricles only has been described by R. Tigerstedt and Johansson (Skand. Arch. f. Physiol., ) to whom belongs the credit of priority. This instrument differed from that of Henderson in being constructed of tin with a very thin rubber diaphragm, which was covered with wax after adjustment of the instrument. Also it was adapted either to enclose the auricles and ventricles or the latter alone. This instrument was employed to confirm some of the work of Roy and Adami.
to allow of full dilatation of the heart, but that there was a gap in the gradation of available rubber balls, which had to be filled in the manner described.)

The cardiometer was connected with the recording tambour by means of a rubber tube (105 cm. long and 5 mm. internal diameter). Into this system was inserted a glass T-tube, its third limb terminating in a short piece of rubber tubing which, after the adjustment of the cardiometer to the heart, was clamped as near to the end of systole as could be estimated. (Fig. 1).

**Recording Tambours.**—The cardiac tambour was constructed out of an oil-can more or less conical in shape, its greatest diameter being 3 3/4 inches and its height 2 3/4 inches. Its base was removed and replaced by a sheet of thin rubber dam cemented firmly round the edges of the can. A stem was provided in the form of a brass tube and was firmly soldered to the side of the can. A bent wire bracket, one end of which allowed of adjustment by sliding on the stem, possessed at its other end a hinge from which came off the recording lever of aluminum wire. Movements of the tambour were communicated to this by an aluminum upright, the base of which was cemented to the rubber diaphragm, while its blunt apex was split in two, and each of these parts twisted on itself so that the flat surfaces faced each other. Through these a small hole was bored, a short piece of fine aluminum wire passed through, between the two uprights taking a turn round the recording lever. Thus a pivot
the joint was formed. Later on, an aluminum lever was cut off beyond the joint and replaced by one constructed out of straw with a writing point of celluloid.

In Experiments XIII, XIX, XX, and XXI, a small Marey tambour was employed, and in Experiment XVII a large flat Marey tambour. These were found to possess no special advantages. A small Marey tambour 3.5 cm. was used to record the limb volume, being connected with the limb plethysmograph by rubber tubing (length 193 cm. and 5 mm. internal diameter).

The apparatus was tested frequently for leaks by blowing smoke through it, sometimes also by inflating till the lever was at a known height and then clamping and leaving the apparatus for some time. There was a little fling with the aluminum levers, which disappeared after the substitution of straw.

From the sixth experiment onward the cardiac tambour was employed upside down, primarily because of the greater ease thus obtained in getting its record above that of the arterial pressure, its bulk combined with the projecting limbs of the Hürthle manometer rendering its application right side up difficult in the extreme. In this position upstrokes represent cardiac contraction, downstrokes cardiac dilatation.

__Graduation of the Cardiograph. —__ After each experiment the apparatus was graduated by being connected with a bottle containing an air-space roughly corresponding to that of the cardiometer employed. This space was estimated after the death of the animal.
by filling the cardiometer with water and then inserting the ventricles. The water remaining represented the air-space. The bottle was fitted with a cork, and all joints made air-tight with sealing-wax. Through the cork passed two glass tubes, one nearly to the bottom of the bottle, the other ending flush with the cork on its lower side. On the short tube was slipped the rubber tube leading to the tambour, while on the other was slipped a rubber tube fitted with a clamp and leading from a burette graduated in cubic centimeters and filled with water. (Fig. 1). Thus the bottle being previously partially filled with water in such a manner as to leave an air-space corresponding to that of the cardiometer by running in water from the burette at a time, the corresponding excursions of the lever marked a scale on the tracing paper.

For determining maximum, mean, and minimum blood pressures simultaneously, and for registering the arterial pulse with a Härthle membrane manometer, the arrangement shown in Figure 2 was used. As usual the medium of transmission was 5 per cent sodium citrate solution supplied by a pressure bottle raised about eight feet above the apparatus. Out of this bottle (A) the solution proceeds by means of a lead tube (B) to a T-tube (C), one arm of which (D) provided with a clamp forms the inflow to the minimal manometer. The other arm of the T-tube leads to a glass T-tube (E), in the center of which is a glass three-way stop-cock. On the neck of this stop-cock was fixed a wire pointer showing the direction of the third way. The arm (F) connects by lead tubing with the
carotid artery, the lead tubing ending in a brass tube divided mesially by a partition - one side being the inflow and the other the outflow opening into another lead tube passing through a tap to the common outflow. The arm (G) also by lead tubing connects with the manometer system and the Hürthle. Thus when the pointer of the stop-cock is directed toward F the solution flows into the carotid wash-out cannula; when toward I the solution in the carotid tube will be in connection with the mercurial manometers and with the Hürthle, while the pressure bottle supply is shut off. The lead tube from G passes to another glass T-tube with three-way stop-cock and wire pointer as the former, the solution entering by the limb H either to the Hürthle or to the mercurial manometers according to the position of the stop-cock (the pointer turned toward H for the Hürthle, to I for the manometers.) Through K the solution passes to another T-tube, one arm of which leads to the minimal valve through which the solution passes to the minimal manometer. The other arm leads to yet another T-tube through one arm of which the solution passes through the maximal valve to the maximal manometer, through the other arm passing to the mean manometer. On this tube is a screw clamp (L) by which the pulsations of the mercury manometer are damped down, thereby recording the mean arterial pressure as shown by Howell and Brush.

The manometers themselves are glass U-tubes of the usual type, from the upper end of each of which, on the same arm as the pressure tubes, are led off stout rubber tubes all opening into a common
outlet tube, and each tube provided with a clamp. The tube from
the minimal manometer also serves as an inflow. Into the common
cut flow tube also opens the outflow from the carotid wash-out
cannula, passing through a tap on its way.

Behind each simple limb of the manometer is fixed a scale
graduated in millimeters of mercury. The carotid cannulae were of
varying sizes and each consisted of a short brass cylinder into
which fitted tightly the brass carotid tube. This cylinder was
connected by short rubber tubing with a glass nozzle (M) tapering
abruptly with an obliquely ground aperture about the size of the
internal diameter of the artery, and having close to its point a
constriction so that it might be firmly tied into the carotid.
The lever of the Härthle membrane manometer was clamped to cut out any
fling.

Catchline: Insert Fig. 2 about here

The limb plethysmograph was kindly lent to me by the Physiolo-
gical Department of the Johns Hopkins University. It consisted
of a glass cylinder open at one end around which was an india-
rubber jacket which fitted closely round the shaved limb, and was
made tight by a thick coating of petrolatum and held in place by
a bandage. In its upper surface was a circular aperture into which
fitted a tight cork pierced by two glass tubes, one ending in a short
piece of rubber tubing with a clamp for filling the instrument with
warm water, the other leading by a piece of rubber tubing (195 cm.
long by 5 mm. internal diameter) to a tambour 3.5 cm. in diameter.
METHOD OF EXPERIMENTATION

In all of the experiments dogs were used. Each received a moderate dose of morphin, 1/4 grain, after which they were anesthetized with ether, and the etherization kept up by a Woulff's bottle connected with a trachéal cannula. Artificial respiration was administered by a bellows worked by an electric motor. The amount of air entering the lungs, and how much of it passed directly over the ether first, could be easily regulated by mechanical devices, care being taken to prevent shock by limiting the excursion of the lung.

One of the hind limbs was carefully shaved and the limb plethysmograph applied, the rubber sleeve made tight at first with petrolatum and a bandage, while later on axle-grease was substituted for the petrolatum with marked benefit. The instrument was now filled with warm water and connected with its recording tambour.

The chest was opened under artificial respiration after ligating the internal mammary, care being taken to remove a large extent of the chest wall on either side of the midline. The pericardium was opened and the cardiometer - as described by Henderson - slipped over the ventricles till the rubber dam fitted into the auriculo-ventricular groove. When adjusted and connected with its tambour, the short piece of the T-tube was clamped with a pair of artery forceps at or near the end of systole. The carotid cannula was now tied into the artery and connected with the manometer system. Time was recorded in seconds of fifths by a Jaquet's chronograph.
The tracings were taken on smoked paper worked on double drums capable of variations in speed.

**ADMINISTRATION OF DRUGS**

These were injected intravenously, mainly into the external jugular, at other times into the superior vena cava or femoral vein as noted.
In working out the action of drugs on animals, several factors require to be taken into consideration. The conditions under which the experiments are performed, the state of the animal, accidents happening to apparatus, all tend, unless carefully watched for, to give results foreign to that of the drug under investigation.

Let us consider first the seat of injection. That most generally chosen is the jugular vein, to which objections are sometimes raised, because, being so near the heart, the injected drug has but little time to become absorbed by the blood and body fluids, so that nearly its full force must be exerted on the heart. But in these experiments that is anything but a disadvantage, as we are studying the effect on the heart and not on other organs. On its way to the left heart it has to pass through only one organ, viz. the lungs, in which solid particles, if any, are liable to be arrested. Care must be taken to see that the drug is injected into the vein and not into the surrounding tissues. Hill and Barnard consider it very important to follow the injection of a drug by the injection of a little normal saline to ensure its being washed into the circulation. This was done several times with strychnin without modifying the subsequent result.

Then occasionally it was necessary to refill the ether bottle, a manipulation which involved a temporary stoppage of the artificial respiration. Thus there was produced a disturbance of the tracings
which entirely negatived any further conclusions as to the action of any drug previously administered, and on account of rise in tonicity following the cessation of the period of asphyxia, it was necessary to wait a variable time till the conditions had settled down before proceeding to inject the drug again.

Another source of error showed itself in association with the manometer system. Here the medium of conduction, 5 per cent sodium citrate solution, in order to minimize the chance of the blood passing into the metal tubes and clotting, was generally run a little way into the artery. This fluid is also very nearly at the blood pressure. Now with any temporary weakening of the arterial pressure, this solution was liable to pass down into the heart, where by precipitating the calcium salts great interference (depending on the amount reaching the heart) resulted. In fact several dogs were killed and it was some little time before the reason for this was detected, and the defect located in a defective clamp, which when the blood pressure was turned into the manometers, the inflow now not being completely shut off, caused the fluid to spurt into the artery. This effect is easily recognizable on the cardiac tracing, and has been excluded whenever inferences are drawn as to the effect of the drugs tested.

Any movement of the ventricles in or out of the cardiometer has naturally to be avoided. This is best effected by the careful adjustment of the instrument and the regulation of the lung expansion.
Henderson has recently pointed out that this regulation of the artificial respiration is of great importance, excessive filling of the lungs being a fertile cause of shock. In this series of experiments, however, the lungs were rarely fully inflated - the rough rule followed being if possible to fill the lungs to such an extent as appeared normal for the thorax in question, and if this amount of filling interfered with the cardiometer to cut the respiration down still further.

Changes in the volume of blood in the coronary arteries also furnish a slight source of error.

Care must be taken that the cardiometer does not rest on the inferior vena cava, that its septum remains practically flat, that it does not hinder free dilatation of the heart, and that it does not exert too much pressure on the auriculo-ventricular groove. It goes without saying that the system must be air-tight.

The limb plethysmograph may render incorrect results by leakage, or as happened on one occasion the close proximity of the heating arrangement. In the case of strychnin, gradual arterial contraction may be masked by increased outflow of lymph produced by the drug.

The effects of the anesthetic, viz. ether, do not come very much into prominence (Briggs and Cook) except after refilling the bottle.

Shock and collapse were undoubtedly manifested several times, and Crile points out that in shock strychnin produces no rise in blood pressure. Under light anesthesia any reflex movements are apt to cause disturbance of the blood pressure.
Increase of tone means decrease of ventricular volume. Now this diminution in volume may be due to three factors:

1. Diminution in the amount of residual blood.
2. Diminution in the coronary blood.
3. Diminution in lymph in cardiac muscle.

But diminution in volume can only represent increase in tone whichever of these factors is most affected. Hence from the standpoint of increase of tonicity, these items present no source of error.

**MEASUREMENT OF TONICITY**

In the curves thus obtained the upstrokes represent contractions, down strokes dilatations. The vertical distance from the crest to the base of the volume curve for each beat represents the systolic output. Tonicity is indicated by the level occupied by the curve at the very end of diastole, the distance being measured from an arbitrary base line. The changes in volume which correspond to changes in tonicity are recorded in cubic centimeters. Other things being equal, a rise in the lower edge of the curve indicates increased tonicity, a fall indicates decreased tonicity.

Insert Figs. 3 & 4 about here
In the curves thus obtained the upstrokes represent contractions, downstrokes dilatations. The vertical distance from the crest to the base of the volume curve for each beat represents the systolic output. Tonicity is indicated by the level occupied by the curve at the very end of diastole, the distance being measured from an arbitrary base line. The changes in volume which correspond to changes in tonicity are recorded in cubic centimeters (Fig. 3). Other things being equal a rise in the lower edge of the curve indicates increased tonicity, a fall indicates decreased tonicity (Fig. 4).
That part of the cardiac cycle in which tonicity has reached its greatest expression and at which the measurement is most satisfactory lies just before the following systole, and in addition this is the only practically non-variable point in diastasis available for this purpose, it being influenced by two factors only: (1) change in tonicity; (2) venous pressure, which becomes evident chiefly with a slow rate of beat and with extreme cardiac weakness. In the portions of these experiments on which conclusions are based, these factors were reduced as far as possible to the minimum.

For ease of comparison, these changes are all expressed in cubic centimeters of ventricular volume, and are measured from an arbitrary base line in each experiment (Fig. 4). These figures furnish relative though not absolute measurements of tonicity, but express in figures the changes occurring throughout the individual experiment. In some of the experiments it will be noted that changes have been expressed in parts of 1 cc., the reason being that in the most marked cases, owing to a different recording tambour, the excursion produced by 1 cc. was very large, thus allowing the ready appreciation of small variations.

Systolic output is also expressed in cubic centimeters, measured on the same scale as tonicity. Velocity of flow is calculated by multiplying the systolic output by the rate per unit of time.
PHYSIOLOGIC AND PATHOLOGIC VARIATIONS IN TONICITY

Under this heading are considered some of the variations which may occur more or less physiologically and pathologically, and mostly apart from the influence of drugs. These changes are grouped as follows:

Changes in tonicity due to accompanying change in frequency.

The influence of vagus stimulation, of atropin, and the result of dividing the vagi.

Increase of arterial pressure, produced by clamping the thoracic aorta. It is convenient at this section to consider also the influence of adrenalin, seeing that its main action lies in the increase of arterial pressure.

Changes produced by hemorrhage, and the result of subsequent saline infusions are also referred to.

Catchline: Insert Fig. 5 and Table 1 about here

Experiment I. — Figure 5 shows a spontaneous increase of frequency from 70 to 110, accompanied by increase in tonicity, diminution of systolic output, increase of velocity of flow. Systolic pressure falls from 88 to 84; diastolic pressure rises from 58 to 64 mm. Hg.; pulse pressure is therefore diminished from 30 to 20 mm.

The amount of residual blood is appreciably diminished, inducing the phenomenon of "trappe," and in spite of the diminution in systolic output the velocity of flow is markedly increased.

The decrease in pulse pressure corresponds with the diminution in systolic output.

This tracing, therefore, shows very well that, as pointed out by Henderson (l.c.), the level of the tonicity curve in the normal heart is determined by the frequency of the few preceding beats, the tonicity increasing with the frequency as shown in the figure.
Vagus stimulation, as has been pointed out by Henderson, Stewart, and others, acts conversely to vagus division and to increase in frequency. The frequency is greatly diminished, thus decreasing the blood pressure. The period of filling, also that of diastasis, is prolonged; the heart expels more blood at each systole thereby increasing the pulse pressure. Roy and Adami attributed the great distention entirely to the increased intraventricular pressure during diastole, not to any change in elasticity of the relaxed ventricular wall.

On withdrawing the stimulation the tonicity curve rapidly ascends with accompanying increase in rate and increase in blood pressure, the systolic output with the increased rapidity of beat being smaller than with the excessive slowing, while the tonicity gradually returns practically to the same level as before the interference.

Catchline: Insert Fig. 6 about here

Experiment II. — The curve shown in Figure 6 (introduced for the sake of completing this section) shows in a marked degree the well-known series of changes following vagus stimulation. In the middle of the period of depression produced by stimulation, note a slight further fall due possibly to the tonicity wearing off, as demonstrated by Henderson. The tonicity is diminished 5 c.c.; the rate falls from 112 to 34, the systolic output increases 3.3 c.c.

On ceasing to stimulate, the rate returns toward the normal; the ventricle has less time to fill in diastole, so the tonicity increases, also the blood pressure.
In this case the rise in blood pressure is due to the heart, and therefore the tonicity also increases at the same time, the change in tonicity varying directly and not inversely with the change in blood pressure. If, however, without an accompanying increase in strength or in frequency of the heart, the mean arterial pressure be increased, as for instance by contraction of the peripheral vessels or by compressing the aorta, then the tonicity will vary inversely with the blood pressure, as will be pointed out in the experiments on increasing blood pressure. The heart is then overloaded and its contraction corresponds to that given by Frank (Fig. 16).

Stimulation of the central end of the vagus, on the other hand, increases cardiac tonicity. This effect may be produced either by first cutting the nerve or by introducing atropin sulphate, thereby paralyzing the peripheral ends in the heart, and then stimulating. An example of the latter is shown in Fig. 7 under the heading of "Atropin", which is considered here mainly for the purpose of showing the effects of this stimulation, this drug possessing more of a physiologic than a clinical interest.

Atropin.

Under certain conditions, as when the heart is beating fairly rapidly, an administration of atropin by removing vagus control does not cause any increment of rate, then the effects of atropin on the cardiac tonicity are as shown in the next experiment (Fig. 7).
Experimient III. - Atropin sulphate 1/60 grain (1/780 grain per pound) injected into external jugular vein (Fig. 7). At F, five and three-fourths minutes after injection the tonicity has decreased 1.8 c.c., the systolic output has very slightly diminished, the frequency has diminished 7 beats per minute. Arterial pressure is somewhat lower.

At S5 seven minutes later, tonicity is slightly increasing, and systolic output and rate further diminished. Blood pressure is practically unchanged.

At the arrow mark eleven minutes, five seconds later, tonicity has markedly increased, being higher than at the commencement, the rate had decreased 10 per minute, the systolic output is larger than at first, though still irregular.

At the three portions marked S. V, where the uncut vagus was stimulated, the changes are all similar in kind, corresponding to stimulation of the central end of the nerve. The changes consist of an increase in tonicity rendering the systolic output regular. "Treppe" is also present, as shown by the greater height reached by the upper part of the curve, and indicates a more thorough emptying of the ventricles, thus lessening the amount of residual blood. The frequency is lessened during these periods of stimulation.

The systolic output is lessened inasmuch as it becomes regular; the periodic variations in tonicity, as shown by the different levels of the starting positions of the upstroke or systole during preceding beats, have now become standardized. The carotid tracing shows at these periods a diminution in all factors including pulse pressure.

Atropin, therefore, after a primary depression causes an increase in tonicity, an increase which has no connection with changes in frequency of beat and which is capable of further augmentation by stimulation of the central end of the vagus. As already mentioned, stimulation of the central end of the vagus apart from atropin causes increase in tonicity.
Experiment IV. - In this experiment the vagi were divided one at a time at an interval of five and one-half minutes (Fig. 8). It will be noted that for a certain time the changes resemble those shown in Figure 5, where a spontaneous increase in frequency had occurred, but differ markedly in the fact that these changes are not maintained for any length of time.

Dividing one vagus nerve causes marked increase in frequency with accompanying increase of tone. Systolic output diminishes. Frequency goes on increasing, tonus remaining unchanged and systolic output decreasing further; later it increases, with a fall in tonicity and in rate. Blood pressure, tonus, systolic output and rate progressively diminish. Division of the vagi, therefore, increases frequency, and therefore tonicity decreases the systolic output and blood pressure; pulse pressure is also decreased.

This increase in tonicity is undoubtedly mainly due to the increase in frequency, permitting less time for the ventricles to fill during the diastole. That it is purely a case of removing the inhibition and not one of increasing any stimulus to tone change is fairly evident.

Comparisons with Figure 8, A 1 (S₅) seventeen and three-fourths minutes before division of the right vagus shows a much higher level of tonicity than was present immediately before division; also it is much higher than any position reached after division though its frequency is less. The tonicity falls in association with slight slowing, the systolic output and velocity of flow are increased; blood pressure falls markedly even though the velocity of flow is actually increased. Division of the other vagus produced the same changes but to a much less marked extent. In a short period of time the tonicity, systolic output, and rate all diminish, causing a very marked fall in the blood pressure.

Henderson points out that on vagus section the amplitude of beat is diminished more than would be the case coincident to the same increase in rate prior to section, and states that "the sudden withdrawal of this factor upsets the balance of influences normally maintaining the 'all or none' character of beat, allowing only of variations in rhythm." He also states that these factors become readjusted in one hour, because the amplitude of beat again becomes...
maximal. It is evident from a glance at Table 3 that the heart has been slowly dilating, owing to a progressive diminution of its tonicity most probably going hand in hand with progressive general weakening of the dog after the operation.

Effect of Bleeding on Cardiac Tonicity.

The results of hemorrhage depend, generally speaking, on the diminution of the blood in the vessels, resulting, therefore, in lessened arterial pressure and in the delivery of a less quantity of blood through the great veins into the heart. Thus the output is lessened, the ventricle not expanding as far in diastole as when it is receiving its normal quota of fluid. Just before death from hemorrhage, however, a terminal dilatation sets in, indicating that the tonicity is really diminished. Roy and Adami attributed the diminution in strength of the heart to the decreased flow through the coronaries. It is well known that this loss of blood is readily readjusted, especially in the young subject. This factor does not, however, enter into account in the experiment next considered (Figs. 9, 10, 11, 12, 13). Saline administered intravenously and the addition of strychnin are also considered here.

Catchline: Insert Table 4 about here
Experiment V. - In all 90 c.c. of blood were removed. The first (Fig. 9) from the femoral vein progressed too slowly to have much effect apart from the blood pressure, so the femoral artery was opened (Fig. 10) with the result that the tonicity apparently increased with diminution of systolic output and no change in frequency. 

Limb volume was not much affected. Blood pressure fell. As pointed out previously, the changes are to be referred to the lessening of the blood supply to the heart.

Figure 11 shows the condition of affairs in twelve and one-half minutes. The tonicity curve is high, the systolic output small, and there is a very slight increase in frequency. The blood pressure is lower by 16, 5, 4, 4 mm. Hg. maximum, mean, and minimum respectively. Pulse pressure is reduced. The greatest amount of change is in the systolic pressure.

Figure 12 shows two injections into the femoral vein, each of 20 c.c. normal saline. The change is the same in both - being a primary dilatation of the heart, with an increase in the systolic output, and in frequency. The blood pressure shows a transient rise. It is noteworthy that saline infusions in none of my experiments have given a rise of tone much, if any, beyond that present before the primary dilatation. These changes are probably more passive than active, and are more in the nature of an accommodation of the heart to the increased blood supply. This action is the converse of bleeding and the changes are to be regarded as the same in character.

The next tracing (Fig. 13) should come under the heading of "Strychnin": but it is preferable to introduce it here for the reason that it is a continuation of the same experiment and shows that where the salines did not produce more than a transient increase of tonicity, two injections of strychnin sulphate 1/250 gr. (1/2500 gr. per pound) at S8, followed by 1/100 gr. (1/1000 gr. per pound) at S9 increased the tonicity and the systolic output. The blood pressure shows no alteration. The carotid tracing shows variations which are due to the unequal and bad adjustment of the lever.
Changes in Tonicity due to Appreciable Changes in Arterial Pressure.

Adrenalin Chlorid.

Figure 14 and the tracings following demonstrate the resemblance between the action of this drug and raising arterial pressure by compressing the aorta, with the difference that the reflex mechanism which regulates and accommodates the conditions to high pressure apparently cannot be utilized in the case of adrenalin as it is in compression of the aorta.

Experiment VI demonstrates the effect of a small dose; Experiment VII that of an overdose, also showing the subsequent modification induced by nitroglycerin.

Catchline: Fig. 14 about here
: Table 5 about here

Experiment VI. - Figure 14 is an example of the result produced by 1 min of adrenalin chlorid solution (1:1000) injected into the superior vena cava. The primary depression of tonicity was produced by the mechanical disturbance of the vena cava and great vessels in introducing the drug.

The theory that vascular constriction is the cause of the increased pressure is in accord with the well-known action of adrenalin; further proof of this is afforded here by the fact that the velocity of flow at the time of greatest blood pressure is greatly diminished. The diminution in frequency may be attributed to the increased pressure.

As the blood pressure falls there is no decrease in tonicity, but the tonus keeps on increasing, the systolic output increases with slowing of rate.

Three minutes, forty seconds after injection, the arterial pressure is lower than at commencement, while the systolic output and frequency are practically the same.
The fact that the tonicity commences to decrease before the arterial pressure is affected suggests that the primary action on the heart of adrenalin is in the direction of decreasing tonicity. The later rise in tonicity may be due to increased intraventricular pressure caused by the vasoconstriction. Further rise may be attributed to dilatation of the coronary vessels flushing the heart muscle with blood, and thus increasing its nutriment. The coronary vessels are said to be exceptions to the general rule that adrenalin constricts all the arteries of the body.

Catchline: Fig. 15 about here
Table 6 about here

Experiment VII. - Adrenalin chlorid 5 minims (solution 1 - 1000) was injected into the superior vena cava (Fig. 15).

The first change occurs fifty seconds after injection and consists of a depression of tonicity accompanied by a lengthening of the periods of diastole and diastasis, thereby producing marked slowing. Corresponding changes are visible in the carotid tracing. The systolic output gradually increases in spite of which the velocity of flow is reduced. The blood pressure is kept up undoubtedly by the vascular constriction. Slight further increase occurs in the pressure with increase in velocity of flow. The tonicity is unchanged.

Following the mark 9, both blood pressure and tonicity increased slightly, with slight increase in frequency. Then suddenly the heart passed into delirium with great irregularity in systolic output and a corresponding blood pressure which maintained a fairly high level.

On removing the cardiometer, all the coronary vessels were found greatly dilated, the heart was flushed with blood and was beating very irregularly and forcibly, mainly in a condition of extreme tonicity.

The cardiometer being replaced, injection of 1/50 grain nitroglycerin into the superior vena cava was followed in about fifty seconds by a fall in blood pressure and in tonicity, while the condition of delirium passed off leaving a slow rate of beat with a large systolic output. The velocity of flow was small, and it is evident that the vascular constriction had not passed off to any very great extent. The improvement lasted two minutes, when the heart again went into delirium.
From the fact that nitroglycerin diminished tonicity in contrast to its usual action, the heart must, therefore, have been very much weakened at this stage. The heart was undoubtedly in a condition of extreme tonicity attributable to the tremendous flushing of the coronaries. Nitroglycerin, by unlocking the spasm of the systemic arteries, would diminish the flushing of the coronaries by diminishing aortic pressure. Thus for two reasons the tonicity would decrease: first, intraventricular pressure is lessened; secondly, there is less blood in the coronary vessels; conditions approaching more to the normal and naturally as the effect of the nitroglycerin passed off the former state of affairs returned.

Compressing the Aorta.

The mechanism called into force during this procedure is increase in the intraventricular pressure. The heart, corresponding as it does to an afterloaded muscle, experiences an increase in that load and reacts accordingly. An increase in the load is beneficial, calling forth increase in contractile force and in the tonicity up to a certain degree of loading, beyond which the reverse occurs (See Frank's curves, Fig. 16).

Roy and Adami believed that increased intraventricular pressure, resulting from increased arterial pressure, tended to dilate the ventricle, but that this tendency was counteracted by the greater flushing of the coronary vessels.

It is impossible to state whether the depression of tonicity was due to the extreme slowing, or the slowing was due to the decrease in tonicity.
In these experiments the intraventricular pressure was raised by clamping the thoracic aorta immediately above the diaphragm. Raising the aortic pressure increases the strength of the heart. This was worked out by Roy and Adami who attributed it to flushing of the coronaries with blood.

Otto Frank determined the isotonic and isometric curves of the heart muscle, pointing out that the isometric curve increases with filling up to a certain point, then decreases; or in other words, the work of the heart increases with the load up to a certain point, when it begins to decrease (Fig. 16). He thinks that the heart contraction within the body may be regarded as an afterloaded isotonic curve with pressure equal to arterial pressure. The maximum contraction is at the end of systole, whereas in the isometric curve the maximum contraction is in the middle of systole, and in its first part the contraction is a pure isometric curve, the larger the higher the pressure (Anspannungs-Zeit). During outflow the curve is not exactly isotonic owing to variations in velocity. Hence it follows that the cardiac reaction to increased pressure will depend on the degree of loading; obviously a weakened heart cannot withstand a high pressure as can a strong heart. Figure 17 shows a condition in which the extra load was productive of increased strength and tonicity of the heart, while Figure 18 presents an example in which evidently the loading was somewhat excessive.
Experiment VIII. - Clamping the thoracic aorta.

The tracing (Fig. 17) demonstrates that the primary effect is a marked rise in arterial pressure associated with an equally marked dilatation of the ventricle due to overloading. Following this primary alteration, both curves tend upwards. Tonus, blood pressure, and systolic output increase, with no change in frequency. The heart has now accommodated to the load.

On unclamping the aorta, there is a marked fall in blood pressure associated with a more or less corresponding further rise in tonicity, which, however, is only temporary. The systolic output is diminished, but increases further as the tonicity diminishes.

The pulse pressure corresponds with the increased systolic output, but is not demonstrated correctly on the tracing owing to a clot in the carotid cannula.

This experiment demonstrates the relation of changes in tonicity to appreciable changes in arterial pressure in the case of a weakened heart.

Catchline: Insert Fig. 18 and Table 8 about here.

Experiment IX. - Clamping thoracic aorta; weak heart; loading excessive (Fig. 18).

On clamping the thoracic aorta, one obtains a simultaneous alteration in both cardiac and carotid tracings. The rise in blood pressure goes hand in hand with an increasing dilatation of the ventricles, accompanied by a diminution in the systolic output and an increase in the rate of beat. This primary change attains its maximum in five seconds, when the reverse occurs - the blood pressure falling again, tonicity and systolic output increasing, the frequency decreasing, in eleven and one-half seconds; after which a similar change goes on, but much slower, as twenty-three seconds later the tonicity has increased 0.7 c.c., the systolic output and rate remaining unchanged, while the carotid tracing shows that the systolic pressure has fallen slightly. Twelve seconds later the tonus, systolic output, and frequency remain practically the same.

The drum was now revolved at a slow speed. One minute, twenty-nine seconds later, the tonus has fallen 1 c.c., the systolic output increased 0.5 c.c., the frequency remaining practically unchanged. The arterial pressure shows a corresponding rise.

During the next three minutes, thirty-five seconds, this change proceeds, though to a less extent. After five minutes compression in all, the aorta was unclamped, resulting in an immediate increase of tonicity, diminution of the systolic output, slowing of two beats per second, and a just appreciable slow diminution in arterial pressure.
It is of the utmost importance to realize that the reactions of
tonicity to increased blood pressure in a strong as compared with
a weakened heart are diametrically opposite. In a strong heart
following the primary dilatation caused by the overwhelming resistance,
the ventricles stimulated by the increase of intraventricular press-
ure respond by an increase of tonicity, the tonicity going hand in
hand with the rise in arterial pressure, corresponding to Frank's
curves 1, 2, and 3. But with a weak heart the type of the primary
alteration in the form of inverse reaction of tonicity to arterial
pressure, tends to persist, further increase in pressure being ac-
companied by decrease in tonicity and vice versa.

The curve corresponds to the curve of after-loaded muscle
where the load is excessive(Fig. 16, Curve 4), though not necessarily
so in toto, as the function of contractility may be stimulated
by the increased intraventricular pressure, yet the tonicity be
reduced. There is, therefore, a dissociation of the functions of
tonicity and contractility, tonicity, the later acquired and more
specialized function, being the first to be diminished (Colbeck).

It is therefore evident that whether a given heart will recover
from or succumb to a certain strain depends in a large measure on
its tonicity, and the question naturally arises in how far we can
influence cardiac tonicity by the administration of drugs.

Clinically, the drug most frequently administered in condi-
tions in which the tonus of the heart muscle is supposed to be low,
but the systolic output sufficient to maintain compensation, is
strychnine. The belief that the favorable action of this drug is due to its effect on cardiac tone has long been held and expressed by clinicians; whereas most pharmacologists have stated that it acted only on the peripheral circulation, and have either denied or failed to mention that it had any action whatever on the heart itself.
LITERATURE ON STRYCHNIN

Strychnin was discovered by Pettelier and Caventon in the year 1818, and in the form of upas poison its action was first investigated in the classical experiments of Magendie. Since his time an enormous amount of literature on this subject has accumulated; but little of the literature, however, and that little varied, deals with the circulatory system.

With therapeutic doses it has generally been held that the blood pressure is increased, mainly by the action of the drug on the peripheral arterioles. Cushny holds to this statement, quoting exceptional cases, however, in which the slowing of the heart is so great as to counteract the contraction of the arterioles. Doubts have, however, arisen regarding the truth of this statement mainly due to Cabot's conclusions that in patients with fevers to whom the strychnin was administered both orally and hypodermically in dosage usually employed, this drug has but little influence on the blood pressure as measured by the instruments at present in use. (Here 5000 estimations are reported by Cabot.)

Crile's experimental research on the value of strychnin in shock, in which he points out that in forty-eight carefully observed measurements of blood pressure in normal animals with small doses no noteworthy change occurred until sufficient had been administered to cause increased excitability of the spinal cord, as evidenced by increase in reflexes and in muscular tone, when a rise in blood pressure resulted.
Oushny states in his text-book that therapeutic doses of strychnin generally slow the pulse and that the artery feels less compressible, the blood pressure is raised, except in the exceptional cases quoted above in which the slowing of the heart is so great as to counteract the contraction of the arterioles.

Brunton classed strychnin with the cardiac tonics, defining this group in the following words: "These are drugs which have no perceptible immediate action on the heart, but when given for a little while render its beat much more powerful though usually much slower." Its action on the circulation is to increase the blood pressure, stimulating the vasomotor center directly, or else greatly increasing its excitability to the ordinary stimuli it receives even when the dose is too small to produce convulsions. When these occur, other factors help to increase the pressure, as indirect stimulation of the vasomotor center by carbon dioxide; and the violent muscular contractions during the convulsions increase the resistance to the flow of blood through the arteries and capillaries. Also the vasomotor center has its excitability increased so much that on section of the cord that part of the vasomotor center in the cord becomes able to take on to a great extent the normal functions of the whole center.

It is pointed out by Cushny that the "constriction seems to affect mainly the internal vessels, while those of the skin and perhaps of the muscles are dilated, and that the blood current is therefore deflected largely from the internal organs to the skin and limbs."
Sollman states that its direct effect on the heart is extremely small. A small dose slows and increases the force of the excised mammalian heart. Larger doses cause slight quickening with increased force. He concludes that these effects are probably too small to be of therapeutic importance. Very large doses paralyze the heart.

The reason for the belief that strychnin stimulates the heart is attributed to the improvement of the pulse - a result of the rise of blood pressure.

Briggs and Cook tested the action of strychnin on the blood pressure in seven cases of shock, the smallest dose employed being 1/60 grain, the largest 1/10 grain hypodermically. In two cases (20 per cent of their observations in shock) there was no response on the part of the vasomotor center, as shown by a rise of blood pressure to large doses of strychnin and digitalis.

Under the heading of "Comparative Study of General Stimulant Measures" some interesting results with strychnin are quoted. The dose employed ranged from 1/60 to 1/10 grain hypodermically. They found that the onset of rise in pressure was delayed as compared with the rise following alcohol given by the mouth. The increase in pressure was not so abrupt and was maintained from one to four hours. In every case the rise in blood pressure was associated
with improvement in the patient's condition. When a routine administration was continued for eight or ten doses, then individual doses often failed to produce any marked immediate rise in systolic blood pressure; but if one or two doses were omitted, and the pressure carefully followed in the interval, they found a progressive fall. The previous level was again restored by now repeating the drug. Their conclusion is that "on the whole strychnin is by far the most satisfactory cardiovascular stimulant for long-continued routine administration, the maintenance of a satisfactory blood-pressure level free from intervals of depression being most easily accomplished by its use in appropriate doses. When in the absence of any previous stimulation, or when general stimulatory treatment has been inadequate, it is desired to quickly raise a markedly lowered blood pressure, strychnin often has a most dramatic effect. Here large doses are required; 1/10 or 1/20 gr. soon repeated are not excessive for hypodermic administration in adults. The gain is not transient, but endures for one hour or more if the patient is not moribund. When the pressure begins to decline, a much smaller dose suffices to check further fall. Then regular small doses, with digitalin if necessary, will maintain a safe level. Strychnin fails to raise blood pressure in moderate and large doses in moribund, hopeless cases, and in cases which are not in need of stimulation, where the heart and vessels possess a normal tone. Between these extremes lie the cases in which strychnin is of the utmost service." Their charts unfortunately were taken from a
very few of their cases, and no tabulations are given to indicate the number of exceptions to their rules.

R. Heinz states that rise in blood pressure appears in a curarized animal, but not after cutting the cervical cord. Later vasomotor effects appear which are then due to the stimulation of vasomotor centers in the cord and are small. In the curarized animal the pulse rate either slows or is unchanged, otherwise quickening occurs.

Schmiedeberg found strychnin had no action on the heart. Hedbom found that on the isolated heart strychnin acted only when in high concentration.

**GENERAL EFFECTS OF STRYCHNI N**

The results of these experiments may be summarized in the statement that strychnin in large or small doses tends to increase cardiac tonicity, except when the slowing of the heart may be so great as to counteract this effect, or when this slowing is associated with an increased blood pressure, or when the increase in blood pressure alone is sufficient to counteract the tendency to increased tonicity, this latter depending on the condition of the heart. The blood pressure with small doses is not affected to any marked degree; with large doses, as shown by increased reflexes, the blood pressure may rise unless the animal is in a condition of profound shock. The systolic output is generally diminished, except with a slow rate
of beat where it is increased. The period of ventricular filling appears to be slightly prolonged. Medicinal doses produce slight slowing of the heart almost invariably, as do toxic doses. The limb volume tends to increase rather than diminish.

Apparently a definite change in tonicity does not occur after the administration of strychnin until the dose has reached the amount of 1/150 to 1/100 grain (1/1500 - 1/1000 grain per pound weight approximately). The action of strychnin on the ventricles shows itself generally in from one to two minutes, being characterized by gradual increase in tonicity, diminution of the systolic output, slowing of rate, generally an increase in the limb volume, and if the dosage be moderate no change in arterial pressure. On the other hand, large doses increase the blood pressure as a general rule, unless the animal be in a condition of shock.

The experiments are arranged in order of ascending doses in grains per pound weight of the animal.

Experiment X (33 A). - This showed the effect of a small dose of strychnin, viz. 1/120 grain (1/1680 grain per pound weight), injected into the external jugular vein, causing no change in tonicity but increase in diastolic pressure, limb volume and systolic output, while the frequency is diminished (Fig. 19).

During eleven minutes this produced absolutely no increase in tonicity, but on the other hand the rate fell from 64 to 52. The systolic output increased and the limb plethysmograph shows an increase in volume.

The heart rate is in this case rather a slow one for a dog, and it is worth while noting that although the frequency decreases the tonus does not. While the tonicity does not appreciably increase,
it does not diminish. The tendency of strychnine to increase tonicity is probably counterbalanced by the decrease in frequency, and it must be remembered that the dosage in this example was small. Also, being the first injection, the factor of accumulative effect is eliminated. The diastolic pressure has slightly increased, which increase cannot be attributed to the fall in pulse rate, as that produces normally the opposite effect, but must be referred to constriction of some vascular area other than that of the limb, as the limb volume has increased instead of diminishing. The reason for increased systolic output with slow rate of beat is indicated under the heading of "Effect of Strychnine on Rate of Filling of the Ventricles", where it is pointed out that the period of diastole is prolonged, by which in the rapid heart the ensuing systole shortens the diastole, while with a slow heart this prolongation of diastole shortens the period of diastasis or rest, not the ensuing systole.

Henderson divides the ventricular cycle into three periods: systole or period of discharge, diastole or period of filling, and diastasis or period of rest; pointing out that the filling occurs immediately after the emptying, being practically as rapid, then with a slow heart the period of rest ensues, which is interrupted only immediately before the following systole by the auricular discharge which, however, propels but a very small quantity of blood into the ventricles. These are well shown in the first portion of Figure 19.

The flatness of the summit of the curves is rather out of the way. It is not due to the personal equation, as both Dr. Hirschfelder and Dr. Stewart on adjusting the cardiometer obtained the same result. This flattening occurred in the cases of small dogs which were used mainly throughout these experiments. With large dogs the ordinary Henderson curve was obtained, also in some small dogs when using relatively large cardiometers.
Experiment XI demonstrates one of the most common results produced by strychnin.

Experiment XI (39 A). — Figure 20 shows tracings two and one-half minutes before injection of the first dose of 1/90 grain strychnin sulphate into the external jugular vein (1/1170 grain per pound). Figure 21, fourteen minutes after injection, shows the slight increase in tonicity and absence of change in arterial pressure.

The increase in tonicity has been maintained at the same level seven and three-fourths minutes.

The blood pressure readings show no material variation. Rate is the same in both tracings. Systolic output is diminished.

Catchline: Insert Figs. 20 and 21 and Table 10 about here

Figures 20 and 21 present a fairly typical picture of the effect of a moderate dose of strychnin sulphate. They demonstrate admirably the lack of change in the blood pressure, the increase of tonicity, and the decrease of systolic output. There is no change in frequency. The systolic output has decreased in such a manner that the amount of residual blood in the ventricles remains unchanged.

This illustrates a fact which has manifested quite uniformly throughout the experiments that an increase in tonicity may occur without any accompanying change in maximal, minimal, or mean pressure or in pulse rate, and which is in absolute harmony with the clinical observation that strychnin has a good effect in cases of dilated heart even when the sphygmomanometer shows no changes whatever.

The following experiment demonstrates that tonicity may increase with a fall in blood pressure.

Catchline: Insert Fig. 32 and Table 11 about here
Experiment XII (12 F). - Strychnin sulphate, 1/100 grain, or 1/1000 grain per pound, was injected into the external jugular vein followed by 15 minims normal saline at S. S. (Fig. 22).

At 20, one and one half minutes later, tonicity has increased 0.5 c.c., the systolic output has diminished 0.25 c.c., and the frequency decreased 2 beats per minute. Blood pressure is decreasing. Limb volume shows little change.

At 21, five minutes after injection, tonus increased in all 0.75 c.c. Systolic output unchanged. Frequency further decreased, also velocity of flow. Blood pressure, systolic, fallen 5 mm. Limb volume no change.

At 22, eight minutes after injection, tonus increased in all 1 c.c. Systolic output decreased 1 c.c. Frequency increased 3 since 21. Systolic and diastolic blood pressures fallen.

At 23, eleven minutes after injection, tonus increased 1.25 c.c. Frequency unchanged (limb plethysmograph lever raised by hand here).

Sixteen and one-half minutes after injection, tonus increased .25 c.c. has remained the same five and one-half minutes. Frequency has decreased 10 beats per second. Blood pressure has decreased 4, 2, and 3 mm. Maximum, mean and minimum respectively.

This shows, therefore, a general decrease in blood pressure accompanied by an increase in tonicity, a diminution in the systolic output and rate. The pulse pressure also decreases. The period of ventricular filling is alternately shortened and prolonged.

This dog has received in all 1/500, 1/250, two injections of 1/100 and one of 1/50. Hence the dog has received a large amount of strychnin previous to this dose, in spite of which the blood pressure has not increased, the changes being shown in the gradual increase of tonicity, diminution of systolic output, and slight slowing of rate. This presents no evidence of accumulation of the drug. The fall of blood pressure is explainable by the decrease in frequency and systolic output. The velocity of flow, found by multiplying the systolic output by the rate, is decreased, thus a less amount of blood is being discharged into the aorta per unit of time. The
diastolic pressure does not fall in the same ratio, and as the
diastolic pressure is kept up by the contraction of the peripheral
vessels, this indicates a contraction of some vascular area, though
not that of the limbs. Slowing of the rate in this case is not due
to stimulation of the vagus center by heightened blood pressure,
but is more probably due to a direct stimulation of the center by
strychnin. The increase of tonicity depends at least partly on the
action of the vagus, as after it is atropinized rise of tonicity
only occurs after very large doses, due then to its direct action
on the heart muscle, which is apparently slight.

The next experiment shows but little change in the cardiac
tracing with two injections, one small, one large, but exhibits a
well-marked increase in both diastolic and mean blood pressures.
The frequency, though excessively slow at the beginning, is still
further decreased.

Catchline: Insert Fig. 23 and Table 12 about here

Experiment XIII (33 D - E). - Strychnin sulphate, 1/150 grain,
(1/2100 gr. per pound weight), injected into the external jugular
(Fig. 23) at D. Four minutes ten seconds later, tonus has in-
creased 0.1 c.c.; systolic output and rate practically unchanged.

Seven minutes twenty seconds later, no change; therefore in-
jected at E, 1/60 grain strychnin sulphate into the external jugular.
Three minutes ten seconds later, blood pressure unchanged, tonicity
increased 0.1 c.c.; frequency decreased 4. Hereafter tonicity
increases definitely with slight decrease in systolic output. No
change in rate. Marked increase in diastolic and mean pressures,
systolic unchanged. The frequency and systolic output have hardly
changed, explaining the sustenance of the systolic pressure. The
tonicity has slightly increased, vagus action is profound as
evidenced by the very slow rate.
Therefore in this example the change in tonicity, though slight, is very well sustained considering the remarkably slow rate of beat. This increase in diastolic and mean pressures appears to be the rule with sufficient dosage.

A well-marked increase in tonicity occurs when the drug has been pushed to the physiologic limit as shown in the following experiment.

Catchline: Insert Fig. 24 and Table 13 about here

**Experiment XIV (39 S10).** - Strychnin sulphate, 1/45 grain (1/583 gr. per pound) injected into the superior vena cava (Fig. 24).

In three and one-half minutes the dog showed irritability to mechanical stimulation. Tonus increased 1.25 cc., systolic output irregular. Frequency decreased 5 per minute. Diastolic pressure definitely increased.

The diastolic and mean pressures are increasing, also the tonicity, while the frequency and systolic output are decreasing.

Catchline: Insert Fig. 25 and Table 14 about here

**Experiment XV (30 C).** - Strychnin, 1/50 grain (1/450 gr. per pound) injected into the external jugular (Fig. 25). Latent period 140 seconds.

At S11, four and three-fourths minutes later, tonicity has increased 0.75 cc. Systolic output diminished 0.5 cc. Frequency unchanged. Diastolic blood pressure increased 2 mm. Limb plethysmograph has risen.

At S12, nine and one-fourth minutes later, tonus increased 1.5 cc. Systolic output diminished 0.75 cc. Frequency diminished 8 per minute. Blood pressure unchanged. Limb plethysmograph has fallen.

This experiment shows a very slight increase in diastolic blood pressure, the limb volume after a primary rise has decreased. As the tonus increased, the systolic output and rate decreased. There is a distinct rise in the carotid tracing immediately before the mark S. This is not due to a contraction of the limb vessels as the limb volume is increasing.

At the mark S12 the carotid tracing indicates that the blood pressure is much the same as before the rise.

This rise of pressure appears to have been but temporary as it is not corroborated altogether by the manometer reading taken within three-quarters of one minute. This shows, however, that
the diastolic pressure was increased, which may be attributed, 
though not with certainty, to the limb constriction which the limb 
plethysmograph shows occurred during stoppage.

The tracing reproduced in Figure 26 shows the marked cardiac 
dilatation occurring during a strychnin convulsion.

Catchline: Insert Fig. 26 and Table 15 about here

**Experiment XVI** (39 S13). - Strychnin sulphate, 1/30 gr. (Fig. 26); 
Irregularities appeared. The addition of 1/20 grain (1/390 gr. 
per pound) caused a marked convulsion lasting one minute and fifty 
seconds, during which the heart dilated and frequently dimin-
ishd markedly, while the systolic output increased. Blood pressure 
immediately after the rigor showed the systolic practically un-
changed, with a marked fall in diastolic and mean. The marked 
dilatation was probably due to the squeezing of the blood out of 
the muscles into the great vessels. Following the convulsion the 
tonicity, systolic output and rate became very irregular, all, 
however, returning gradually toward their former condition. The 
mean and diastolic pressures increased. Closing the air outlet 
of the tracheal cannula caused the irritability to pass off, most 
probably by the concentration of the ether thus produced.

The following experiment is a continuation of the preceding one 
and shows return of irritability with another injection:

**Catchline**: Insert Fig. 27 and Table 16 about here

**Experiment XVII** (39 S18). - Strychnin sulphate, 1/30 grain, 
(1/390 gr. per pound) injected into the superior cava.

Although the concentration of the ether abolished the reflex 
irritability of the skeletal muscles, this injection brought it 
back again. The systolic pressure had fallen markedly before the 
 injection, with increase in diastolic and mean. This is possibly 
due to decrease in the velocity of flow, while the diastolic and 
mean rise may be attributed to the vessels regaining their toniciry. 
The cardiac tonus is also increasing.

These experiments clearly demonstrate the great tendency of 
strychnin, when given in sufficient dosage, to increase cardiac 
tonicity.
A rise in the systolic blood pressure occurs under certain conditions, viz. fairly slow rate and efficient dosage, as shown in the following experiment.

Catchline: Insert Figs. 27, 28 and 29 and Table 17 about here

Experiment XVIII (12 H). - Strychnin sulphate 1/30 grain (1/300 gr. per pound), followed by 15 minims saline solution, injected into the external jugular vein (Figs. 27, 28, and 29).

The animal has up to and including this injection received 0.4 grain strychnin sulphate.

In twenty seconds the limb plethysmograph rises distinctly, gradually falling to its former level in two and one-half minutes.

In one and one-half minutes the systolic output has increased 1 c.c. with no change in frequency or tonicity. The blood pressure is commencing to rise.

In Figure 28, twenty-four minutes after injection, the tonicity remains practically unchanged; the systolic output has increased 3.2 c.c., the frequency practically unchanged. The velocity of flow is much increased.

The systolic pressure has increased 9 mm., the mean 8 mm., and the diastolic has fallen 3 mm. Pulse pressure has, therefore, risen from 28 to 40.

In thirty and one-half minutes (Fig. 29) the condition remains practically unchanged with the exception of an increase in tonicity of 0.7 c.c. Frequency is further diminished and systolic output slightly diminished.

Between Figures 28 and 29 the level of the limb plethysmograph was raised. It is now falling slightly, indicating the possibility of a constriction of the limb vessels, or, on the other hand, improved lymph absorption.

This experiment, therefore, demonstrates increase in the systolic pressure with a large dosage. Increase in the systolic output is in accordance with the slow rate of beat, and is directly responsible for this rise of pressure.
EFFECT OF STRYCHNIN ON RATE OF FILLING OF THE VENTRICLES.

The curves shown in Figure 30 show the effect of strychnin on the phases of emptying and filling of the ventricles. In this example the strychnin has caused, as shown by the curve B, a slow rate of beat and an increase of systolic output. The curves correspond closely to Frank's curves (Fig. 16), showing an increase in loading.

The period of emptying or systole and the slow portion of diastole are totally unaffected after strychnin, as they occupy the same period of time in both curves. The uniformity of the systolic discharge cannot be altogether depended on, as pointed out by Henderson. The main change occurs during the rapid portion of diastole and during diastasis.

Comparing the rapid portions of diastole, one finds, as the drum was revolving at the same rate during both curves, that if the total period from the beginning of systole to the beginning of the next systole be measured in millimeters, the rapidity of filling in the first curve may be expressed as 8/61, the same portion in the second curve as 14/75; reducing those to the same common denominator gives 600/4575 to 854/4575, that is, the rapid portion of filling in the first curve is to the second curve as 600 is to 854. Thus the period of filling is lengthened. But in the normal heart
Henderson points out that alterations in frequency up to a certain rate are produced by altering the duration of the period of rest or diastasis, while it is not until this rate is exceeded that diastasis is affected. Considering that the volume curve for each normal heart is identical as far as the rate allows time for its development, this prolongation of the period of filling must be attributed to the strychnin.

These curves, therefore, show that slowing is caused by lengthening the period of filling as well as that of diastasis. Therefore, depending on the frequency of beat, one may have a diminution or increase of the systolic output. With faster rates of beat where there is no period of diastasis, following an injection of strychnin, the period of diastole or filling being longer drawn out, the ensuing systole will occur before the ventricle is totally filled, thus delivering a smaller charge of blood and diminishing the systolic output. With greatly increased slowing as in the example, this shortening of the systolic output will not occur, except the diastole be so extremely prolonged as to do away with the period of diastasis. In such a case any further prolongation would diminish the output. This explains the increase of systolic output found in the case of a slow heart, also indicating the reason that in the great majority of these experiments the systolic output is definitely decreased.
The three following experiments demonstrate the fact that atropin sulphate prevents strychnin from producing its customary effect on tonicity:

**Catchline**: Insert Fig. 31 and Table 18 about here

**Experiment XIX** (38 B). - Vagus paralyzed by atropin. Strychnin sulphate, 1/90 grain (1/655 gr. per pound), injected into the external jugular (Fig. 31). Latent period one minute.

**Catchline**: Insert Table 19 about here

**Experiment XX** (38 D). - Atropin sulphate previously administered, 1/90 grain strychnin sulphate (1/655 gr. per pound) injected into the external jugular (Fig. 33). Diminution in tonicity, increase in systolic output, slowing of rate. Blood pressure: systolic fall, diastolic rise, mean fall and rise again. No change in tonicity, very slight slowing of rate. Systolic output practically unchanged. Blood pressure - mean and diastolic-falls.

**Catchline**: Insert Table 20 about here

**Experiment XXI** (38 E). - Vagus paralyzed with atropin. Strychnin sulphate, 1/45 grain (1/427 gr. per pound), injected into external jugular.

This experiment shows hardly any change except a slight increase in the systolic output, evidently due to the action of strychnin on the cardiac muscle. Changes in blood pressure and rate are practically negligible.

These tracings show when the influence of the vagus has been removed, the effect of strychnin is to decrease tonicity though increasing the systolic output. The blood pressure is not appreciably affected. The frequency is somewhat less, and later may account for the diminution in tonicity. The heart's action has been certainly rendered more forcible. This result, therefore, corresponds closely with that of digitalis under the same circumstances, showing
that both these drugs increase tonicity through their action upon
certain fibers of the vagus.

Figure 32 demonstrates the effect of a large amount of strychnin
and the changes induced by clamping the descending aorta.

Catchline: Insert Fig. 32 and Table 21 about here

Experiment XXII (48 F). - Strychnin sulphate, 1/15 grain (1/202
gr. per pound), injected into the superior vena cava (Fig. 32).
The heart being well under the influence of strychnin, the
aorta was clamped toward the end of the experiment, at G, the dog
being in a condition of shock.
The changes are much as usual; first, the primary dilatation
with little change in systolic output, due to overloading; slowing
of rate, which is contrary to what occurred apart from drugs. The
systolic output and tonicity increase for a short period, when the
load evidently proving excessive, tonus and systolic output again
diminished with a slight increase in frequency. The blood pressure
at first rises smartly, the systolic maintains a certain level to
which the diastolic gradually approaches, thus diminishing pulse
pressure.

On unclamping, the tonicity momentarily increased with shortening
of the systolic output. The frequency slightly decreased, the
blood pressure falls, but the carotid lever fails to write.

On comparison with Experiment VIII (Fig. 17) in which the
aorta was compressed before strychnin, the most striking difference
lies in the behavior of the carotid tracing. Then it rises with
the rise in tonicity, but the aorta had been clamped before, in
which case the carotid tracing rapidly assumed a higher level and
maintained that level, though the tonicity progressively increased.
Thus this divergence is not peculiar to the strychnin effect. Most
probably the dog is in a condition of shock produced by the rapidly
following large doses of strychnin sulphate, as according to Crile,
the repetition of large doses of this drug is perhaps the most ready
method of inducing this condition. The tracing corresponds closely with Frank's curves showing the reaction to loading, which is later on excessive for the heart as evidenced by the diminution in systolic output and tonicity. It was first thought that the method of clamping the descending aorta suggested by Romberg as a test of cardiac endurance, might be applicable to the changes in strength resulting from injections of strychnin, but experience showed that this criterion was too severe and subject to too many variations.
THE ACTION OF STRYCHNIN ON BLOOD PRESSURE.

With moderate dosage a systolic rise of pressure was found present in two or three experiments, occurring only with the first two or three injections of very insufficient dosage, and in every case the pressure was rising before any injection at all was made. This gradual rise went on without apparently being influenced by the strychnin, which was certainly not causative. On the other hand, diastolic and mean pressures are frequently increased by this drug.

Herein lies the cause for much disagreement among clinicians, most of whom, expecting from the statements of pharmacologists that a rise of blood pressure should take place, find evidence for the latter. Among this group of writers are chiefly those who have not followed their doses with exact blood pressure estimations. On the other hand, those observers who base their statements on instrumental determinations (Cabot, Hirschfelder, Drayer) find little or no change of blood pressure (never more than a transitory rise of 10 mm. Hg.). The reason for this discrepancy is evident. The clinicians base their findings on determinations of the maximal (systolic) pressure by some modification of Riva-Rocci's method and find little change. The pharmacologists all used the mercury manometer, which recorded only the mean pressure and showed a uniform rise. When, however, in animals, we determine not only the

Personal communication.
mean but the maximum and minimum pressures with appropriate manometers, we find that in therapeutic doses there is rarely any change in the maximum, just as holds for the maximum pressure in man according to the above mentioned observers, while the minimum and mean pressures rise just as has been found by most pharmacologists. But the orthodox physician whose finger has followed blindly the teaching of the text-books, has perceived that which was in many cases not present, and has misinterpreted his findings. Nowadays with the excellent instruments of Erlanger and G. A. Gibson, both of which take into account the minimum as well as the maximum or systolic pressures, probably this reaction could be followed and many apparent and unsuspected discrepancies could be detected and explained.

The following experiment shows the modification in the action of potassium induced by strychnin, which evidently prevents tone being diminished as readily as it is diminished by potassium in the normal heart.

Catchline: Insert Fig. 33 and Table 22 about here

Experiment XXII (37 M - N). Two injections each of 1 c.c. potassium chlorid solution into the superior vena cava (preceded six minutes and thirteen and one-fourth minutes before by injections of strychnin sulphate 1/15 and 1/30 grain respectively) showed none of the characteristic depression of tonicity (Fig. 33). This tracing shows no depression of the tonicity but a slight increase, the systolic output diminishes slightly, also the frequency. Stimulation of the vagus produced slowing and depression of tonicity soon recovered from. Blood pressure fell.

This is not by any means an isolated example; it has been found several times that after strychnin had been administered a following dose of potassium, unless large enough to overwhelm the effect of
the strychnin, does not produce its characteristic effect (depression of tonicity). Some experiments were also made bearing directly on this point. One exception occurred, in which case 1/100 grain of strychnin sulphate was injected into the femoral vein producing in three minutes and twenty-three seconds, a marked increase of tonicity, 10.25 c.c. in all. An injection of 22 minims of potassium chloride (6.31 per cent) eleven minutes later also into the femoral vein, after a long latent period of five minutes and twenty seconds, was followed by a sudden fall in tone of 18 c.c. in fifteen seconds. No change in frequency. The systolic output increased with the strychnin, decreased a little more than its former increment with the potassium.

It was suggested by Professor Barker that possibly the sulphate ion in the strychnin played some part in the production of tone changes. It was found that injection of sodium sulphate produced no appreciable effect on the cardiac tracing. After lapse of a considerable period of time the tonicity diminished. This diminution could not be attributed to the sulphate and as the change seemed in the opposite direction to that of strychnin, it is obvious that the sulphate portion can influence the results but slightly if at all.
The large amount of evidence that has accumulated during this research, of which a few examples have been shown in the preceding section, firmly re-establish strychnin in the group of cardiac tonics, where it had been placed by Brunton and others of the older observers. Its value in cardiac therapy must be undoubted, sustaining and increasing as it does that all important function of the cardiac muscle, that inherent power of the heart to withstand stress and avert strain, viz. its tonicity. The failure to increase systolic blood pressure cannot be taken as a criterion of the value of the drug. Not every drug that increases blood pressure as a whole is to be regarded as of value in cardiac therapy for the reasons which have been demonstrated in the section on "Asphyxia" and elsewhere, that the blood pressure is already too high and that an increase in the pressure may not stimulate the ventricle to increased tonicity and increased systolic output, but may act in the very reverse direction (overloading).

What is the indication for the administration of strychnin? Obviously the indication lies not in a low systolic pressure but may be summed up in one phrase - dilatation of the heart without failure of compensation. Such dilatation as occurs in anemia and chlorosis offers perhaps the best opportunity for its beneficial
action. There is no occasion to push the drug to extreme doses, 1/30 to 1/20 grain subcutaneously being probably quite efficient. Injected subcutaneously the action will be in all probability better sustained, though its action on tonicity from the series of experiments appears to be maintained for a considerable time, not being in the nature of a transitory change as is any effect which may be produced on the systolic blood pressure. The transitory and small variations in the systolic pressure are apparently not attributable to the strychnin itself, and offer absolutely no indication of its action upon tonicity at least within the limits of therapeutic dosage.
Digitalis and the digitalis group in medicinal doses react on the circulatory system by slowing the rate, increasing the force of contraction, constricting the peripheral vessels, and raising the blood pressure. Opinion differs as to which factor is most efficacious in bringing about the improvement noted clinically.

Of late years Colbeck and Mackenzie have pointed out that in cases of cardiac dilatation the improvement may be attributed to the action of the drug on cardiac tonicity, referring to the experiments of Gaskell on the excised heart of the tortoise, and to the fact that perhaps the most marked action of this drug is in the direction of increasing that function.

Cushny divides the action of digitalis into two stages; the first characterized by marked inhibitory action together with modification of the cardiac muscle, while in the second the inhibitory action is less marked and the muscular action becomes the more prominent feature. According to the same observer, the inhibitory action is due to direct stimulation of the pneumogastric center in the medulla oblongata and of the terminal fibers in the heart. In small quantities muscular action is evidenced by a tendency to increased contraction, and in some cases to a less degree of relaxation in diastole, while in large quantities the irritability of the cardiac muscle is increased very considerably and the independent rhythm of the ventricles therefore becomes developed.
Hence he attributes slowing, more complete contraction of the ventricle, and increased diastolic relaxation - though this latter factor may be unchanged or lessened - to the interaction in the first stage of the two factors of vagus stimulation and irritation of the cardiac muscle. He publishes some cardiometer records obtained with Roy's instrument, but in which, as the auricles are also included, no conclusions as to tone changes of the ventricles can be drawn.

Cushny attributes the benefit of digitalis in dilatation of the heart to two causes: first, he believes that the increased contraction lessens the large amount of residual blood, and second, he inclines to the opinion that the muscular overcomes the inhibitory action and actually lessens the dilatation.

Strophanthus differs in its action from digitalis in producing no constriction of the peripheral vessels, thus exerting its action on the heart alone. (Peripheral constriction has been experimentally demonstrated recently with strophanthus.) In addition its action manifests itself clinically more rapidly than does that of digitalis, especially when injected intravenously in the form of strophanthin. That this lack of peripheral constriction is in favor of strophanthus is apparently readily proved by the fact that a combination of digitalis and nitroglycerin, by doing away with the peripheral constriction, has proved of much benefit in practical experience. In this paper, however, it will be shown that another explanation...
may possibly be added to this, for we are combining two drugs, each of which produces experimentally increased tonicity.

As the action of the digitalis group has been so often worked out experimentally with great care and thoroughness and is very well known, it was thought of interest to try a few injections so as to be able to compare the definite results of these drugs with the action of strychnine.

The action of digitalis differs considerably from that of strychnine. Even very small doses raise the blood pressure and show a greater tendency to increase the systolic output, though this latter action does not always occur. The limb plethysmograph indicates a well-marked constriction of the peripheral vessels, which gradually passes off. The effect of digitalis on tonicity is clearly shown in the following experiment.

**Experiment XXIV**

- A solution of the fluid extract of digitalis, 1 in 40 water, was employed. An injection of 5 minims of the solution into the external jugular vein was followed by a gradual regular increase in tonicity - the systolic output remaining practically unchanged - showing that there was an accompanying lessening in the amount of residual blood (Fig. 34). The frequency remained unchanged seven minutes; eleven minutes, later had decreased 4 beats per minute, a change of no significance. The blood pressure increased slightly accompanied by a diminution in the limb volume.

When the solution is injected into the external jugular vein, the latent period is apparently very short, the tonicity curve rises gradually and regularly. With this first dose there is no change in frequency, hardly any in the systolic output, the rise in pressure being mainly due to the vascular constriction.

Figure 35 shows the effect of a second injection of digitalis, same quantity and strength as before.
This tracing shows in particular the fall in the limb plethysmograph, denoting constriction of the peripheral vessels. This is accompanied by an increase in blood pressure and in tonicity. While the systolic output diminishes, the frequency increases from 120 to 124 per minute.

The peripheral constriction commences to pass off in four and one-half minutes, the tonicity remaining unchanged.

At $S_4$ after a stop of five minutes, the constriction of the limb vessels has passed off to a larger extent, the blood pressure tracing has fallen slightly, the tonicity increased, while the systolic output and frequency remained unchanged.

This, the second injection, shows a gradual increase in tonicity and a rise in systolic blood pressure. This rise must be attributed to the increase in systolic output and the change in frequency.

A slightly larger dosage demonstrates a close resemblance to the reaction commonly produced by strychnin.

Catchline: Insert Table 25 about here

Experiment XXV (37 B). — Digitalis solution, 10 minims, injected into the external jugular.

A slight gradual increase in tonicity, increase in diastolic and mean pressures, slight decrease in systolic output, and no change in frequency. Amount of residual blood remains practically unchanged.

These tracings demonstrate exactly the same gradual rise in tonicity; here the diastolic and mean pressures are increased, the systolic pressure is unchanged, the systolic output is slightly diminished, frequency practically unchanged.

Following atropin sulphate tone changes are more difficult to elucidate, as shown in the following example.

Catchline: Insert Figs. 36, 37 and 38 and Table 26 about here

Experiment XXVI (27 B). — Very irregular heart. Atropin sulphate previously administered, vagus paralyzed. Digitalis, 5 minims and 4 minims (sol. 1 in 40) injected into the external jugular vein (Figs. 36 and 37).

The first injection of 5 minims had no effect in the direction of increasing tonicity or the systolic output.
On the other hand, at the end of nineteen minutes the tonicity has diminished 1%., the systolic output has also diminished, but the frequency increased from 108 to 120 beats per minute. The limb plethysmograph shows a constriction of the limb vessels. The diastolic blood pressure has increased 8 mm. Hg., the systolic and mean remaining practically unchanged, thus furnishing a decrease in pulse pressure.

Ten minims of digitalis solution were injected into the external jugular nineteen and three-fourths minutes later, and the injection was followed in eleven and one-half minutes by an increase in tonicity, systolic output, and rate. Blood pressure is increased.

The inferences to be drawn from these tracings are that the first injection was too small to have any direct action on the heart muscle itself, and that the effect usually obtained through the vagus was entirely prevented by atropin. Apparently, increase in tone due to increase in rate depends on the integrity of the vagus nerve or of its fibers in the heart, as in this case with increase in frequency the tonicity has diminished.

The second injection, however, produces increase in tonicity and in systolic output; the frequency has increased with the increase of tonicity. But after the effects of atropin increases and decreases in rate do not apparently bear any well-defined relation to tonicity. Also it is noticeable that the frequency with the rise in tonicity at the mark $S_1$ is precisely the same as at the time of injection when the tonicity was lower.

An increase in frequency does not explain the increase in systolic output which is very irregular.

There is a vascular constriction, as evidenced by the limb plethysmograph and the heightened diastolic pressure. Hence the systolic output increase is due to the action on the muscle tissue, also it is more than probable that the increase of tonicity is in part due to the same action.

The irregularity, which later on becomes very marked, depends on the irritation of the muscle produced by the drug.

An important clinical deduction to be drawn from this experiment is that the combination of digitalis and atropin suggested by A. W. Hewlett is apparently contraindicated from the standpoint of tonicity, at least for pharmacologic doses. Otherwise we might assume that there are two different varieties of tonicity: one produced by nervous influences, which appears first with drugs;
the other produced by direct action on the muscle itself and which, the vagus being eliminated by atropin, requires a large quantity of the drug for its elucidation.

The following experiment (Fig. 39) points out the resemblance between digitalis and strophanthus in increasing tonicity and blood pressure - the systolic output is in this instance diminished, as it may be with digitalis, while the frequency is decreased. The difference lies in the absence of peripheral constriction under the influence of strophanthus. The pulse pressure at first increases, later returning to its former dimensions.

Catchline: Insert Fig. 39 and Table 27 about here

Experiment XXVII. - Tincture strophanthus, 1/2 minims injected into the superior vena cava, showing probably increase in tonicity, blood pressure, pulse pressure, and rate for nine minutes; four minutes after which the diastolic blood pressure only increases, thereby diminishing the pulse pressure (Fig. 39).

The tonicity increases in spite of a diminution in frequency. The systolic output is slightly decreased.

Increase in blood pressure is explainable by the increase in frequency. The limb plethysmograph shows no constriction of the peripheral vessels. The tonicity increases gradually and definitely, but the increased frequency may in this case explain the rise.

The following experiment is of interest in showing the effects of an overdose of tincture of strophanthus.

Experiment XXVIII (18 D). - An overdose tincture strophanthus (U.S.P.) 2 1/2 minims injected into the external jugular vein (Fig. 40).

After about twenty seconds the blood pressure rises, followed by a rise in tonicity, increase in systolic output and limb volume. The rate is slowed 8 per minute.

One and one-half minutes later, the blood pressure begins to fall, limb volume to decrease. Toncity is sustained, until affected by
the extreme slowing it decreases accompanied by an increase in systolic output and rise in blood pressure. Limb volume still decreasing, until in two minutes fifty seconds, at S13 the frequency has decreased 34 per minute.

At S14, three and one half minutes later, is shown a secondary rise in tonicity associated with a fall in blood pressure. Limb volume still decreasing, frequency has increased 8.

This rise in tonicity and frequency is very transient. The systolic output, tone, blood pressure and frequency decrease markedly. Heart very irregular, resembling delirium cordis.

At S15, five minutes fifty seconds later, is shown a rate of 2.1/2 beats per minute with a large systolic output, very low blood pressure, and progressive decrease in limb volume.

A large dose of strophanthus markedly increases blood pressure, tonicity, and systolic output, slowing the rate. The limb volume increases with the rise in tonicity, then commenced to decrease, the decrease being largely attributable to the slowing.

The blood pressure commences to fall, the rate becomes irregular, and with further slowing the systolic output increased, with increase in blood pressure.

A secondary rise in tonicity occurred associated with increase in frequency. The blood pressure varies directly with the systolic output, the height of the tonicity curve having no influence on it. Systolic output and tone now diminished with consequent fall in blood pressure and slowing. Then for a short time the heart passed into a condition of delirium.

The rate after this shows excessive slowing associated with diminished tonicity and large systolic output. The blood pressure has fallen very low owing to the slow rate. The limb plethysmographe shows a remarkable fall, but this may be regarded as terminal.

The question now arises, What is the role of digitalis and strophanthus in cardiac disease? Considering that the signal for their use is broken compensation, and that the choice of digitalis or strophanthus is decided by the height of the blood pressure and the rapidity with which it is desired to get the patient under the influence of the drug, strophanthus being employed in preference to digitalis where a speedy result is indicated, and also where the pressure is high, when a combination of digitalis with nitro-
glycerin may be substituted, it follows that the resulting action apart from these points is practically the same.

The whole matter hinges on the amount of residual blood in the ventricles, and this to a very large extent depends on the tonicity. Contractility, it is hardly necessary to state, is also an important factor, determining the amount of residual blood and depending to a great extent for its effect in this direction on the degree of tonicity which may be present. As has been shown, the effect of these drugs is to increase the function of cardiac tonicity. Thus the cavities are rendered smaller, they do not expand to such an extent during the period of filling, withstanding better any high degree of venous pressure; while the systolic output, sometimes increased, never much diminished, is, as it were, "bolstered up" by the increased tonicity, thus inducing a "trapped" and reducing the residual blood. Therefore up to a certain point, a point possibly never overstepped with pharmacological dosage, improvement in the condition of the heart must be produced.

In aortic incompetence it has been demonstrated experimentally by Stewart that no appreciable quantity of blood regurgitates into the ventricles until the muscular toms has been diminished. Hence one readily appreciates why drugs of the digitalis group frequently give excellent results in these cases.
Nitroglycerin has been employed chiefly for its effect on the vascular system - relieving spasmodic contraction of the vessels, and by its vasodilator effect, lowering the arterial pressure. Thus one of the chief indications for its employment is high blood pressure as found typically in chronic Bright's disease. In addition to the decrease in blood pressure, the tonicity of the ventricular muscle and the pulse pressure are increased. These points are indicated in the following experiment.

Insert Fig. 41 and Table 29 about here

**Experiment XXIX (46 G).** - Nitroglycerin, 1/100 grain (1/1200 gr. per pound) injected into the superior vena cava (Fig. 41).

In seven seconds there is a marked fall of blood pressure accompanied by an increase in tonicity, diminution in the systolic output and rate.

With the following increase in blood pressure tonicity diminishes slightly.

The systolic output remains smaller and the rate goes on decreasing.

The amount of residual blood slightly decreases in the first two minutes; then remains remarkably constant.

In this tracing there is no change in the amount of residual blood until the blood pressure has been steadily falling fifteen seconds. Then with the further fall of blood pressure, the residual blood is decreased with the increase of tonicity. The heart evidently has less work to do, and accommodates itself by shortening in the systolic output and diminution in rate, thus reducing the velocity of flow. The following rise in pressure must be attributed to the passing off of the vascular dilatation, as the cardiac tracing shows a much further slowing with no change in the systolic output, the velocity of flow, therefore, being diminished.

Contrary to the usual rule the fall in pressure did not cause an increase in frequency. The decrease must be attributed to stimulation of the vagus by the strophanthus previously administered.
The following experiment shows the effect of a much smaller injection of nitroglycerin.

Catchline: Insert Figs. 42, 43 and 44 and Table 30 about here

Experiment XXX (30 F) - Nitroglycerin, 1/300 grain (1/2700 gr. per pound), injected into the external jugular (Figs. 42, 43 and 44). Strychnin and digitalis previously administered. Latent period was 124 seconds.

At 9, in three minutes, fall in diastolic and mean pressures with increase in tonicity 0.9 c.c. No change in systolic output or rate. This fall must be due to vascular dilatation.

At 10, in four and one-half minutes, a general fall in blood pressures, tonus diminished, systolic output and rate increased.

At 11, in seven minutes, increase in diastolic and mean pressures, with a further diminution of tonicity, increase in limb volume, and diminished systolic output and rate. The change in rate so far has been negligible.

At 11, in eleven minutes, tonus has regained its former height, and limb volume same as at start. Systolic output and rate are diminished.

At 11, in fifteen minutes, associated with a rise in blood pressure, tonus markedly diminishes, systolic output increases, and rate still slower.

(The cardiac tracing was raised artificially so as not to interfere with the carotid.)

At 12, in twenty-one minutes, blood pressure not appreciably changing.

A sudden variation in tonus now occurred resembling Traube-Hering waves. There is a very definite increase in tonicity, an increase in the systolic output, the quantity of residual blood is decreased. On the carotid tracing this change shows as a marked sudden increase in blood pressure, which gradually falls with the diminution in tonicity and systolic output. There is no change in frequency. This change in the carotid tracing is synchronous with and depends directly on the heart.

This change is of interest as it is really the opposite of Traube-Hering curves, in which the systolic output and tonicity vary inversely and not directly with the blood pressure.

Nitroglycerin, in the following case of a slowly beating heart, does not cause a fall of blood pressure, but increases tonicity and
systolic output.

Catchline: Insert Figs. 45 and 46 and Table 31 about here

**Experiment XXXI (12 I).** - Nitroglycerin 1/100 grain (1/1000 gr. per pound), injected into the external jugular (Figs. 45 and 46).

In this experiment no fall of blood pressure occurred and there is not sufficient increase in frequency or in velocity of flow to account for the want of depression. The conclusion must be that either the nitroglycerin injected was without effect on the vascular system, or that it was not properly injected into the vein, but passed into the tissues, and that absorption was not sufficiently active to carry it into the circulation. Nevertheless it has shown its action on tonicity.

These tracings demonstrate the beneficial action on cardiac tonicity produced by nitroglycerin, and indicate the value of a combination of digitalis with this drug, both of these having a strong tendency to increase this attribute of the ventricular muscle; and the additional effect of the latter in doing away with the peripheral resistance points to this as an ideal drug treatment in bad cases of cardiac dilatation.

The clinical effects on blood pressure of digitalis and nitroglycerin are well shown in the figures from one of Dr. Hirschfelder's series of cases which he kindly put at my disposal.

Summarized, the action of digitalis alone is to increase both systolic and diastolic pressures, thus not altering the pulse pressure greatly. Nitroglycerin alone produces fall in both systolic and diastolic pressures with but little change in the pulse pressure. But a combination of the two secures the increase of the systolic pressure due to digitalis, and the decrease of the diastolic, and especially the mean pressure attributed to the nitroglycerin,
thus resulting in a greater increase of pulse pressure than would be obtained by either drug alone. The patient's condition varied with the pulse pressure, being better when the pulse pressure was large, worse when it was small.

Following are the notes of the case (observations by Dr. A.D. Hirschfelder):

George G. admitted to Prof. J. O. Hirschfelder's service in the City and County Hospital, San Francisco, April 26, 1905.

Max. pressure 115
Min. " 80
Pulse rate 108
P.P. x P.R. = 35 x 108 = 3780
Fluidextract digitalis, m. v, t.i.d.

April 29. Max. pressure 145
Min. " 120 - 125
Pulse " 22.5
P.P. x P.R. = 2250
Nitroglycerin, gr. 1/25, half-hourly, increasing by gr. 1/100 at each dose.

No symptoms by 7.10 p.m. Feels better.

Max. pressure 140
Min. " 95
Pulse " 45
Pulse rate 96
P.P. x P.R. = 4320
Discontinue digitalis.

April 30. Has been delirious.
Max. pressure 130
Min. " 97.5
Pulse " 32.5
Pulse rate 88
P.P. x P.R. = 2860
Resume digitalis. Discontinue nitroglycerin.

May 1. Max. pressure 150 - 160
Min. " 115
Pulse " 35
Pulse rate 90
P.P. x P.R. = 3150
Orthopnea, pulse small and weak. Resume nitroglycerin.
May 6. Feels about the same.
Max. pressure  150
Min. "  105
Pulse "  45
Pulse rate  72
P.P. x P.R. = 3240
Calcium and potassium are important chemical constituents of
the heart muscle, the former at least playing a large part in the
maintenance of its beat. They also largely influence cardiac
tonicity. With regard to the function of tonicity they are antago-
nistic - calcium increasing, potassium decreasing, the one solu-
tion neutralizing the action of the other.

In his book on "Dynamics of Living Matter", J. Loeb states:

"In order to start the heart beat a pure sodium chlorid
solution or a pure solution of a sodium salt is required, but if
the heart remains permanently in a pure sodium chlorid solution it
stops beating. The pure solution of sodium chlorid acts like a
poison. If, however, a small amount of calcium chlorid be added
to the sodium chlorid solution after the heart beats have once
started, the beats can go on for a long time. They can also con-
tinue in serum after they are once started in a pure sodium chlorid
solution. The addition of the calcium, therefore, acts antago-
nistically to the injurious action of the pure sodium chlorid
solution. Calcium cannot start rhythmical contractions in the
ventricle, but it is necessary to sustain the rhythmical action
once started by sodium chlorid."

W. H. Howell in 1902 pointed out that a strip of terrapin
ventricle immersed in sodium chlorid solution shows a continuous
loss of tone during the latent period and throughout the whole
series of beats, and that this loss of tone is one of the most
distinct effects of the solution. Calcium, on the other hand,
produces first loss of tone, but subsequently increases this

53 Experiments proving these points made by Dr. Lingle on the
heart of tortoise and published in the Am. Jour. Physiol., 1900,
iv, 265, and 1902, vii, 75.
function, the rapidity of the rise depending on the amount of calcium present. In addition it is of interest to note his finding that if the solution be changed to a Ringer's solution before the tone change became too marked, beats occur; while if the tone rise were too rapid both Ringer's and sodium chlorid solutions had no effect.

The effects of intravenous injections of calcium salts on the intact animal are, however, much more transitory than on the excised heart, since the excess of calcium is rapidly dissipated among the tissues, and, on the other hand, the potassium is probably rapidly increased in the blood until equilibrium is established. The effect of such an injection is seen in the following experiment.

Catchline: Insert Fig. 47 and Table 32 about here

Experiment XXXII (34 D).—At D 1 c.c. calcium chlorid (sol. 2.316 per cent) was injected into the external jugular vein (Fig. 60). Two and one fourth minutes later systolic output has increased and rate decreased, resulting, however, in increased velocity of flow. In four and one-half minutes tonus has increased, rate further decreased, systolic output remaining unchanged, velocity of flow still slightly increased. In six minutes mean and diastolic pressures, tonus, systolic output and rate are suddenly decreased. In ten minutes further considerable decrease has occurred in all factors and the excursion of the carotid lever gradually diminished.

Therefore in this experiment the change was very transitory though marked. The animal apparently was very susceptible to calcium. From the standpoint of this experiment, the transitory nature of the changes produced are not very encouraging to the administration of this drug clinically for the purpose of increasing tonicity,
though found of service in sustaining the heart in pneumonia by Brunton.

The next experiment, in which a much larger amount was injected, shows changes in the same direction, which are decidedly better sustained.

Catchline: Insert Fig. 48 and Table 33 about here

Experiment XXXIII (37 F). - Calcium chloride, 5 c.c. (2.316 per cent sol.) injected into the superior vena cava (Fig. 48).

After a latent period of two minutes the tonicity gradually increases. This increase is associated with a diminution in limb volume as shown by the plethysmograph.

At 12, three and one-half minutes later the tonicity is very slightly increased, the systolic output has increased 0.5 c.c., and the frequency increased 4 per minute.

Four minutes and fifteen seconds later the tonicity is increasing more rapidly, associated with a marked decrease in limb volume. The amount of residual blood is lessened, the frequency is not changed, systolic output is slightly increased.

At 13, seven minutes later, systolic output and rate practically unchanged. Diastolic pressure is slightly less. Pulse pressure slightly decreased.

The primary disturbance, consisting of an increase in tonicity with corresponding reduction in the amount of residual blood, as is indicated by the elevation of the upper border of the cardiometer tracing and accompanied by a corresponding decrease in the pulse pressure, is due to interference with the superior cava in injecting the drug.

Hence from the clinical standpoint this evidence is of a much more encouraging nature, demonstrating as it does the marked benefit derived from the injection of a sufficient quantity of calcium into the system. A quantity evidently greatly overbalancing the potassium salts, as is indicated in the next experiment where an injection of potassium chloride produces but a transient disturbance, being apparently rapidly neutralized by the excess of calcium and
an equilibrium established. It therefore seems quite possible that calcium might be of value in increasing tone clinically without producing changes in blood pressure or in any other way giving external evidence of its action, except possibly improvement in the patient's condition and diminution in the size of the heart as seems to be frequently the case with strychnine. On the other hand, there is not as yet sufficient clinical evidence to warrant ranking it among the heart stimulants.

The important factor to bear in mind with calcium is its tendency to increase the coagulability of the blood; hence large doses cannot be safely continued for any length of time as it may bring about thrombosis. Whether a patient requires a large or a small amount will depend to a certain extent on the relative amounts of potassium and calcium already present in the system; in other words whether there is an equilibrium or a deficiency in the calcium supply. If it is given by mouth one cannot expect such a marked action on the heart as when injected intravenously, it being obvious that a more even distribution of the drug will occur, so that the cardiac action will probably be more sustained though later in appearing and less marked.

The next experiment, a continuation of the last, demonstrates the action of potassium in decreasing tonicity and the modification induced by the large amount of calcium present in the system.

Catchline: Insert Fig. 49 and Table 34 about here
Experiment XXXIV (37 G). - Potassium chloride, 1 c.c. (6.31 per cent) injected into the superior vena cava thirteen and a quarter minutes after 5 c.c. calcium chloride (Fig. 49).

(The primary disturbance in the cardiac tracing, is due to the interference with the superior vena cava during injection of the drug. This has been proved by injecting a small quantity of normal saline, the resulting interference being the same and being only transient not interfering with the further tracing.)

Following this is a temporary diminution in blood pressure occurring in fourteen seconds and associated with a decrease in the systolic output and an increase in frequency. Then occurs a rapid dilatation of the heart with decrease in the systolic output and further increase in frequency. The velocity of flow is decreased about 40 per cent. The blood pressure readings show but little change. Thus far the change is characteristic of potassium. The systolic output commences to increase before the lowest level of tonicity is reached, and finally both systolic output and tonicity gradually and regularly increase again with a slowing in rate and a fall in the carotid tracing, slight but corroborated by the manometer reading. The tonicity curve reaches a higher level than it occupied at the time of injection, but the systolic output remained somewhat diminished. The velocity of flow, however, is increased.

Two and three-fourths minutes later, though the tonicity curve is slightly higher, the velocity of flow is less than at the time of injection, the frequency is exactly the same. The blood pressure underwent no material change, being maintained by the increase in frequency.

At 16, three and one-half minutes after injection the tonicity is higher by 0.4 than before injection. The systolic output is less by 0.6 and the frequency is exactly the same.

At 24, in six and one-fourth minutes the tonicity is greater by 0.5 c.c., the systolic output less by 0.7, the frequency unchanged, the blood pressure not materially altered.

The limb plethysmograph showed an increase in limb volume during the fall in tonus and a decrease during the increase of tonicity. This is in accord with the variations in frequency.

In this case the recovery is much more rapid than it is typically after potassium. The reason for this probably lies in the fact that 5 c.c. calcium chloride had been injected thirteen and one-fourth minutes previously. (It was calculated from the work of Howell and Duke that this amount would be sufficient to neutralize 1 c.c. of potassium chloride in the solutions used in this laboratory.)
The facts in favor of the supposition are that calcium and potassium possess an opposite action, being capable of neutralizing each other's effects. Also calcium chlorid is very readily stored up in the tissues and is as readily liberated.
EFFECT OF SODIUM CITRATE ON THE HEART

Catchline: Insert Fig. 50 about here

Experiment XXXV. - Figure 50 shows effect produced by the entry of a sodium citrate solution, 5 per cent, into the carotid artery. The letters a, b, c, d, on the cardiometer tracing correspond with the letters a, b, c, d, on the carotid tracing. At the mark "art" the Härthle membrane manometer was artificially lowered so that its tracing might not interfere with that of the cardiometer.

While determining the blood pressure reading at the mark 4, the solution entered the artery showing its effect primarily by an increase in tonicity very transient in nature. The blood pressure is apparently higher. The heart then rapidly dilates with accompanying diminution of systolic output, which, however, begins to increase before the tonicity has reached its lowest level.

The carotid tracing shows a secondary rise, then gradually falls as the tonicity increases, at first with increase in systolic output, later with decrease.

At the marks S2, S3, and S4, the tonicity evidently varies inversely with the blood pressure.

Following S4, 30 c.c. normal saline solution was transfused into the femoral vein, resulting in increased systolic output and pulse pressure. The diastolic expansion of the heart is more complete, residual blood slightly lessened, rate not appreciably changed.

Contrast the gradual return to normal with the return in the next experiment, in which calcium chlorid was injected.

Catchline: Insert Fig. 51 and Table 35 about here

Experiment XXXVI. - As soon as noted that the sodium citrate solution was entering the carotid artery, the artery was clamped. As the heart continued to dilate the drum was stopped, calcium chlorid injected into the superior vena cava, and the drum restarted at a slower speed (Fig. 51).

The tonus has increased definitely, but as further increase failed to occur, the same dose of calcium was repeated, resulting after a latent period of twenty seconds in a sudden rise in tonicity occupying six seconds. The systolic output, which had increased as a result of the sodium citrate solution, returns toward the normal, and the frequency is lessened.
Thus the second injection at A was apparently given after an equilibrium was established, and as soon as the injection reached the heart it very rapidly produced its effect, after which equilibrium was again established.

This experiment is of interest in showing the marked benefit resulting from replacing the calcium salts in the heart which had accidentally been precipitated by the sodium citrate solution, 5 per cent, from the manometer. The action of the sodium citrate largely resembles that of potassium, causing marked decrease in tonicity associated with marked dilatation of the heart, as a rule recovered from gradually if too large an amount has not entered the heart.

In this example it is shown that the calcium readjusts conditions, and following the mark A one notes the very sudden rise in tonicity produced apparently almost synchronously with the entry of the calcium salt into the left ventricle.

Catchline: Insert about here Figs. 52, 53, and 54 and Table 36

Figures 52, 53, and 54 show a series of tracings in which the vagus nerve had previously been paralyzed by atropin sulphate.

As a result of two injections of calcium chloride, each 1 c.c., separated by four minute intervals, one observes that the most characteristic effect of calcium, namely increase of tonicity, is absent. The tonicity remains practically unchanged, the effect of the drug showing as a slight increase of the systolic output. The frequency of beat and blood pressure vary very little. The systolic output shows no change until four minutes have elapsed from the first injection.

Experiment XXXVII (38 F and G). - After the vagus nerve and its fibers in the heart had been paralyzed by means of atropin sulphate, the administration of two doses of calcium chloride (each 1 c.c. = 2.316 per cent sol.), separated by an interval of four minutes, had no effect on the tonicity (Fig. 52). The arterial pressure and systolic output remained practically unchanged. Four minutes after the first injection the velocity of flow was increased, owing to an increase of 4 beats per minute in the rate. After the
second injection the systolic output remaining the same, the rate in one and one-half minutes dropped 4 beats, remained the same three and one-half minutes, while five minutes later it increased 4, two minutes after which it increased 12 beats per minute (Fig. 53). The volume flow, therefore, varied with the frequency, first decreasing, then remaining steady, then increasing.

The blood pressure ten minutes after the second injection shows a slight fall of systolic with a corresponding rise in the diastolic pressure (Fig. 54). Mean pressure has slightly fallen.

Figures 55 and 56 show comparatively the same change occurring with potassium after atropin, indicating that this drug depends for its depressing effect on tonicity on the integrity of the vagus nerve, even as calcium depends on the vagus for its characteristic increase of tonicity. The results following atropin with calcium and potassium are discussed together, following the tracings.

Catchline: Insert Figs. 55 and 56 and Table 37 about here.

Experiment XXXVIII (38 H). -- Vagus nerve previously paralyzed with atropin. The injection of 1 c.c. potassium chlorid into the superior vena cava after the vagus nerve has been put out of action by atropin sulphate, gives a tracing showing a diametrically opposite result to that obtained by calcium chlorid under the same circumstances (Fig. 55). Here the great characteristic of the action of potassium, namely the depression of tonicity, is absent. The opposite effect is shown - an increase in tonicity - brought about at the expense of the systolic output, which is markedly diminished, indicating an increase in the quantity of residual blood and a less thorough expansion of the ventricle during diastole in addition to the less perfect contraction. These changes are accompanied by a decrease in frequency. The arterial pressure is at first little affected; later the diastolic and systolic pressures increase and decrease respectively in accord with the change in the systolic output (Fig. 56).
In view of the results obtained in the intact animal after paralysis of the vagus and vagus ends in the heart by atropin in which calcium and potassium respectively did not increase or decrease tonicity as they do under normal conditions, but showed their effects as a change in the systolic output, the former increasing, the latter decreasing it, this being obviously their action on the muscle itself, and from the fact that a fair dose of digitalis did increase tonicity, evidently by its action on the muscle, it seems probable that not only is cardiac tonicity to a certain extent affected by nervous influences, but certain drugs, for instance calcium and potassium, apparently increase and decrease tonicity by their action on this nervous apparatus, while digitalis in large doses is able to increase tonicity independently of any nervous influences through the vagus. This is in accord with the well-known action of digitalis on the heart muscle.

* - This apparent discrepancy between the marked effect of calcium and potassium on the tone of strips of cardiac muscle in the excised heart, and the apparent absence of direct effect on the muscle in the intact animal is probably simply a question of dosage, it being much more difficult to maintain an excess of one or the other ion in the circulation. The nerve centers, being more sensitive to such slight changes than is the cardiac muscle, therefore respond to them when the latter does not.
EFFECT OF ASPHYXIA ON CARDIAC TONICITY

Asphyxia must be borne in mind as an additional factor in failure of compensation, since in cardiac failure the blood becomes over-loaded with carbon dioxide. We are dealing more or less with a condition of chronic asphyxia. It is therefore of great importance to study as carefully as possible the changes due to asphyxia setting in acutely.

Roy and Adami point out that asphyxia increases the systolic output mainly if not entirely by the slowing; they say:

"The first effect on the heart is to produce vagus action due to excitation of the vagus center in the medulla, as its appearance can be prevented by section of the vagosympathetics. There is also produced a progressive weakening of the auricular and ventricular contractions, due presumably to the imperfect supply of oxygenated blood to the heart muscle. The output of blood would presumably be increased in non-curarized animals owing to the high venous pressure, which would probably more than counterbalance the diminution of the output that could be brought about by vagus action alone. It need hardly be added that owing to the contraction of the vessels in certain vascular areas, the blood pressure in the systemic arteries is raised."

These effects are well shown in the following experiment.

Catchline: Insert Fig. 57 about here

Experiment XXXIX. Artificial respiration turned off (Fig. 57). In four seconds the first change occurred, consisting of a slight increase in the excursion of the carotid lever, diastolic blood pressure falling, systolic rising. Tonicity has decreased 0.5 cc.

In twenty-four seconds, tonus decreases regularly, the systolic output increases, while the carotid tracing correspondingly shows the diastolic pressure unchanged, while the mean and systolic are greatly increased, the heart is slowing.

Now the heart slows more markedly with a further fall in tonicity and further increase in systolic output. In the carotid tracing
all pressures now begin to fall, but not in the same ratio - the diastolic falling more than either the mean or systolic. The tracing also shows a regular rhythmical increase and decrease in the systolic output.

From a study of the cardiometer record it appears that the tone which had at first diminished steadily, is now diminishing here and there by steps and stairs - the tonus remains steady while the systolic output is diminishing, that is in each beat the amount of residual blood left in the heart is decreasing till a certain period when the tone again diminishes and the process is repeated, each time leaving more residual blood in the heart.

Summarized, asphyxia causes diminution of tonicity, increase in systolic output, slowing in rate, while the arterial pressure shows increase of systolic and mean pressures, and it is not until the tonicity has diminished considerably that the diastolic along with the mean and systolic falls appreciably.

Catchline: Insert Fig. 58 about here

Experiment XI. - Figure 58 demonstrates extremely well the effects of asphyxia in increasing the blood pressure and diminishing the cardiac tonicity. During a period of forty seconds between the two marks on the margin (resembling the Greek letter phi) partial asphyxia was produced by cutting down the respiratory movement with the result that tonicity decreased markedly, the carotid tracing reaching a higher level. Following the second mark the respiration was again increased, but the blood pressure and tonicity continued to maintain a high and a lower level respectively. The frequency does not decrease, indicating, therefore, probably a true tone diminution, while the limb plethysmograph demonstrates a peripheral constriction passing off later with an increase in respiration. No change occurs in the systolic output. Compare with Figure 59 in which is shown the opposite effect.

Catchline: Insert Fig. 59 about here

Again numerous examples of the result of asphyxia were obtained on refilling the ether bottle.

Experiment XLI. - An example of this in which the vagus was paralyzed by atropin is shown in figure 59. Here, tonicity is also
affected before blood pressure. At first we notice a slight increase of tonicity with diminution of the systolic output. Then at the same time as the blood pressure increases the tonus decreases, the systolic output increasing in such a manner that the residual blood remains practically unchanged. The frequency, which had remained at 100 per minute for more than 12 minutes, remained the same during the small increase in tonicity and became 96 when the tonus had fallen. As the blood pressure fell again the tonicity increased, though not in the same ratio; the systolic output varied but slightly.

The frequency slowed still further to 84 three and one-half minutes later, while the blood pressure still fell, though very slightly. The arterial pressure readings two and one-half minutes before and three and one-half minutes afterwards are respectively 104, 71, 59, 103, 68, 49; and this blood pressure continues to fall in spite of two injections of strychnin, 1/90 and 1/45 gr., to 100, 59, 47 in sixteen minutes. During this time the tonicity remained unchanged, and the systolic output varied but little. The frequency (helped probably by the strychnin) has become 80 per minute.

Therefore the effect of the carbon dioxide accumulation is to poison the heart muscle, thereby increasing the systolic output and decreasing the tonicity, or, on the other hand, the dilatation of the heart may be regarded as a passive accommodation to the increased blood pressure. Which of the two factors, the diminution of tonicity or the increase of blood pressure, is the more important it is impossible to state.

During broken compensation the condition of asphyxia due to deficient aeration and overloading of the blood with carbon dioxide causes the maintenance of a high blood pressure. One of the first signs of compensation being reestablished is a fall in pressure. Changes corresponding closely to those observed clinically during recovery in such cases are demonstrated by Figure 60.

Catchline: Insert Fig. 60 and Table 38 about here
Experiment XLII. - In this example the respiration had been cut down too much, with the result that the lungs were not filling well. There was produced a condition analogous to slight cardiac failure. The effect of a larger air supply was followed by a fall in blood pressure, increase in tonicity, diminution of the systolic output and rate. The rate does not immediately change with the rise in tonicity, the slowing appearing only after the tonus had apparently established an equilibrium, and this being directly the opposite change to what one would expect after partial asphyxiation, when, as Roy and Adami and others have demonstrated, the frequency is slowed, the slowing occurring in this case must be referred to the previous injection of tincture of strophanthus.

It is of interest to note that the strophanthus during the period of asphyxiation produced no increase in tonicity. The change which did occur was a depression attributed to the excess of carbon dioxide in the system which showed its presence by the high blood pressure and the increase in the systolic output, part but not all of which may be attributed to the strophanthus. The limb plethysmograph shows no marked change (Fig. 60).

Hence the factor of asphyxia, coming into force as it so frequently does in cardiac cases under treatment, deserves full recognition. In failure of the circulation we have the following conditions: failure of the circulation leads by the diminished flow through the lungs directly to excess of carbon dioxide in the blood. Thus we have the starting point of a vicious circle. The carbon dioxide, being in excess stimulates the heart to a greater but slower contraction, increases the peripheral resistance, but decreases the cardiac tonicity. Sooner or later the tonus becomes so diminished that the systolic contraction, large as it may be, does not empty the heart to the same extent as formerly; the amount of residual blood increases. Still less blood goes to the lungs, the carbon dioxide further accumulates, resulting in a progressive diminution of tonicity and a further increase of carbon dioxide. This is the picture in cyanotic conditions generally, perhaps also coming into
play in cardiac irregularities. This dual role of asphyxia in bringing about increase in peripheral resistance, increased blood pressure, but decreased tone, is one of the few conditions in which increased blood pressure goes hand in hand with decrease in tonicity.

Figure 61 shows Traube Hering curves, produced evidently by partial asphyxiation, as they disappeared after increasing the supply of air to the lungs. Their cause in this example, therefore, lies in a rhythmical stimulation of the nerve centers by carbon dioxide. The cardiac and carotid changes correspond exactly, indicating that the blood pressure changes are in all probability directly dependent upon the heart. There is practically no change in frequency. The tonicity varies indirectly, the systolic output directly with the blood pressure. That is to say, there has been produced a negatively inotropic without a negatively chromotropic effect, probably through reflex stimulation of the vagus.
INJECTION OF AIR INTO A VEIN

Experiment XLIII. - Figure 62 demonstrates the dilatation produced by the injection of 1 minim of air along with 1/250 grain (1/2562 gr. per pound) strychnin sulphate into the external jugular vein.

The first change occurs in seventeen seconds in the shape of an extrasystole. With no change in the level of the blood pressure the heart dilates. Counting the extrasystoles, which are evidently auricular, the rate increases, the systolic output is at first diminished, later increased. Finally the extrasystoles become larger until at 53 they have about regained the normal dimension, but some irregularity still remains and the frequency is increased. The diastolic and mean pressures are now higher and the limb plethysmograph demonstrates a reduction in limb volume.
Gaskell pointed out the fact that acids diminish cardiac tonicity, in spite of which formic acid was at one time recommended for the very purpose of increasing tonicity, and in fact clinically proved itself beneficial as far as could be ascertained. Experimentally however, dilatation occurs.

Catchline: Insert Fig. 63 and Table 40 about here

Experiment XLIV. - March 24, 1908, fox terrier weighing 12 pounds.

Dilatation occurs which, with the first injection at A of 4 minims 10 per cent solution, an amount roughly corresponding to that employed therapeutically, was well marked reaching its limit in approximately ten seconds, after which a gradual recovery ensued, until in twenty-one minutes the tonicity was exactly the same as at the commencement. Likewise systolic output, rate, and blood pressure are not appreciably changed.

The second injection at B of a slightly larger amount (1 1/2 minims 50 per cent solution) produced a similar change in tonicity, consisting of fairly rapid diminution though not quite so marked as the first injection. Now, however, the blood pressure and systolic output increase with a decrease in frequency.

At C, in seventeen minutes, the tonicity has reached a much higher level than it occupied at the commencement (A).

The third injection at C, of a much larger quantity (5 minims 50 per cent solution) almost immediately produced a very marked diminution in tonicity, associated with a diminution in systolic output, increase in frequency, and fall in blood pressure.

The systolic output shortly begins to increase in size and the tonicity to recover when a second depression of tone occurs, the blood pressure is rising and the systolic output increasing.

Following the dilatation the tonus gradually and regularly increases and the systolic output gradually diminishes, until twenty-six minutes later the tonus is greater than it had been at any previous occasion and the systolic output much smaller. The blood pressure is also appreciably increased, as is the frequency. The majority of the increase in tonicity cannot be attributed to an increase in frequency.

At D injection of 1 minim tincture aconite did not prevent a further increase in tonicity, with which the frequency decreased, the systolic output remaining practically unchanged. The diastolic and mean pressures increase, not the systolic.
In short, therefore, formic acid tends in therapeutic doses to decrease tonicity for a short period of time. All pressures, systolic, mean and diastolic, tend to be increased and increased appreciably. The systolic output is also increased, while the frequency diminishes.

Toxic doses cause in the first place decrease in tonicity, systolic output, and blood pressure, with a secondary increase in all. Rate increases at first, later decreases.

**Catchline:** Insert Fig. 64 and Table 41 about here

**Experiment KLV (51 F).** - Two injections of tincture aconite (1 minim and 5 minims) into the superior vena cava.

Figure 64 evidences the only dilatation produced by aconite in the few estimations made.

The carotid artery was clamped because of a slight suspicion of hemorrhage into the manometer system. It was thought at the time that the unexpected slight increase in tonicity might be due to a fault in the manometer; so it being of more importance to register the action on the volume of the heart than on the blood pressure, the carotid artery was clamped.

Dilatation having occurred, the carotid cannula was washed out, producing the irregular markings on the tracing, and as the dilatation was passing off, the carotid was unclamped and a blood pressure reading taken, then the artery was again clamped.

The injection at E (1 minim tincture aconite) produced slight slowing with but little change in systolic output or tonicity.

At F, 5 minims tincture aconite, a very large dose for a dog of thirteen and one-half pounds, produced after a latent period of forty-two seconds further slowing with increased diastolic expansion and increase in systolic output. The amount of residual blood is but little increased.

The diastolic and mean pressures are higher than at the last reading fifteen minutes, five seconds previously. At the time of the reading the tonus is again increasing, the systolic output decreasing, and the rate remaining the same. The tonicity keeps on increasing until it reaches a higher level than at the commencement; the systolic output is increased; the rate is increasing but is still below what it was at the mark 8.
This experiment shows that the action of aconite is that of vagus stimulation, but is peculiar in the large amount of the drug necessary to produce effect. In another experiment with a slower rate of beat, in the same way 1 minim tincture aconite produced no dilatation, corresponding to the injection E in this experiment.
SUMMARY AND CONCLUSIONS

1. The level of the tonicity curve in the normal heart is determined by the frequency of the few preceding beats as stated by Henderson; tonicity increasing with the frequency.

2. Vagus stimulation reacts conversely to increase in frequency and to vagus division. The heart dilates, blood pressure falls, depending on the degree of slowing. During recovery the rise in blood pressure is due to the heart, hence tonicity increases directly with the blood pressure.

3. Atropin sulphate produces diminution, then increase in tonicity. Stimulation of the uncut vagus produces changes similar to stimulation of the central end of the unatropinized nerve, viz. increased tone, an induced treppe, and by regulating the level of the tonicity curve it regulates the systolic output. Blood and pulse pressures decrease.

4. Division of each vagus produces changes similar to those occurring with increase in frequency but not well sustained. They are the converse of vagus stimulation and are attributed purely to removal of vagus inhibition.

5. Hemorrhage is followed by apparent increase in tonicity, depending on the lessened supply of blood to the ventricular cavities. Systolic output and blood pressure are diminished.
6. Normal saline solution, administered intravenously, produces a passive change in the opposite direction, i.e., a transient elevation of blood pressure with an equally transient dilatation and increase in systolic output. Tonicity is subsequently increased little or none. All these findings confirm the previous work of Roy and Adami and Henderson.

7. Adrenalin increases blood pressure and dilates the heart, the changes being complementary and inverse. The increased intraventricular pressure stimulates the systole to a greater effort, but tone changes are sometimes masked by the slowing induced by the heightened pressure. A large dosage produces partly the same series of changes: slowing, dilatation, increase in systolic output and residual blood, followed however by an apparent marked increase in tonicity associated with extreme frequency resembling paroxysmal tachycardia. The systolic output is small and variable, the tonicity curve is very irregular, and the carotid tracing shows similar changes. The addition of nitroglycerin, by lowering the blood pressure and thus probably reducing the pressure in the coronaries, produced slowing with resulting increase in systolic output and corresponding changes in blood pressure. The improvement was but temporary, the frequency again increased with a resulting return of the paroxysm.
8. Compressing the aorta induces changes apparently depending on the degree of loading, whether or not it is excessive for the heart in question. The primary effect is in all cases marked increase in pressure with resulting dilatation of the heart, which shortly passes off. The subsequent course of the tonicity curve lies in one of two directions. It may tend upward (increase of tonicity) owing to the stimulation of the increased intraventricular pressure, or if the pressure be excessive, the tonicity will diminish as the blood pressure rises. On unclamping, the blood pressure falls with a corresponding temporary increase in tonicity. On the other hand if the aorta has been clamped a considerable time, occasionally the blood pressure and tonicity have so regulated themselves that but little change occurs on unclamping.

9. Strychnin in large and small doses increases tonicity mainly through the vagi. The increase may be masked by progressive slowing of rate. Increased tonicity may be produced without any change in blood pressure, systolic output, or rate. Herein lies the reason for improvement in the condition of the heart without objective change in the patient. Small doses do not appreciably affect blood pressure. Moderate doses tend to increase the diastolic and mean pressures, while large doses may increase the systolic pressure unless shock be profound. Hence, the difference of opinion between clinicians and pharmacologists which occurred after the Riva-Rocci machine had been introduced into
general use is explained on the basis that clinicians are estimating systolic pressure, pharmacologists are estimating mean pressure; therefore the systolic being unchanged and the mean increased, using the term blood pressure loosely without designating which blood pressure is meant leads to diametrically opposite statements. The value of the educated finger in estimating blood pressure is called into question. Strychnin prolongs the period of filling. The systolic output may be either increased or decreased, depending to a certain extent on the rate of beat. Increase occurs with a slow heart, attributed to the prolongation of diastole into diastasis, not into the following systole. With a rapid heart rate diastole is prolonged at the expense of the ensuing systole, shortening, therefore, the systolic output. Medicinal and toxic doses produce slowing of rate almost invariably. The limb volume tends to be increased. There is evidence that with very large dosage the systolic output may cease before the end of systole as pointed out by Hurthle. Regarding the degree and character of the tone changes induced, potassium chlorid does not readily produce cardiac dilatation after strychnin administration until an overwhelming quantity has been injected. Compression of the descending aorta has given but little information regarding the tonicity induced by strychnin. The indication for strychnin is not a low blood pressure but cardiac dilatation without failure of compensation. Dilatation is remedied in two ways: (1) by an increase in tonicity preventing
excessive filling between beats, and also inducing a "trappe" which reduces the amount of residual blood; (2) by an increase in the systolic output decreasing the residual blood, as it were bailing out the heart. The degree of treppe induced by the increase in systolic output must obviously depend on the tonicity.

10. Digitalis and strophanthus increase tonicity and blood pressure, differing in the marked peripheral constriction noted with the former as compared with the latter. The systolic output is generally but not always increased. In cardiac disease these drugs produce their beneficial results largely by reduction of the residual blood. This reduction being brought about by the increased tonicity inducing a "trappe" or by lessened relaxation between beats, or on the other hand, by increase in the systolic output. In aortic regurgitation the action depends on the restoration of the ventricular tonicity limiting the amount of regurgitation. Following atropin the tonus does not increase until the amount of the drug is sufficient to act directly on the cardiac muscle. The combination of atropin with digitalis is considered contraindicated, as after atropin large doses of digitalis are necessary to increase tonicity. An example of an overdose of strophanthus is given, showing marked variations in tonus until excessive slowing caused dilatation and death.
11. Nitroglycerin increases tonicity and pulse pressure, decreases the blood pressure. The inverse reaction of tonicity to blood pressure may be considered in the light of a passive change in the heart. The cardiac change resembles to a certain extent that following a hemorrhage, less blood being delivered to the heart and less work requiring to be done decreasing its size. A clinical case is quoted in which the patient's condition varied with his pulse pressure, the larger the pressure the better the patient. These results were produced by a combination of digitalis with nitroglycerin. This drug combination is regarded as one of great value in cardiac dilatation. Improvement is attributed to increased cardiac tonicity as well as lessened peripheral resistance.

12. Calcium and potassium react inversely and antagonistically, the former increasing, the latter decreasing tonicity and systolic output. Tonicity decreases with calcium, increases with potassium. In the case of both drugs following atropin, tonicity is unchanged or changed in the opposite direction according to the changes in systolic output which remain the same. The effect of potassium may be largely modified by previous administration of calcium, the diminished tonicity rapidly regaining its former level. From this and other data is drawn the inference that the utility of calcium depends on the calcium potassium equilibrium, or on which of the two elements is present in excess. On this must be founded the amount of dosage. Attention is recalled to the pos-
sible danger of thrombosis with the conclusion that as yet there is not sufficient evidence to firmly establish calcium as a cardiac stimulant. Two experiments in which sodium citrate caused dilatation of the heart are shown to contrast the mode of recovery in the second in which calcium was administered with the more gradual recovery apart from calcium. It is apparent that immediately the calcium entered the heart it instantly found its place, rapidly increasing to tonicity until equilibrium was again established.

13. From the few experiments made with aconite apparently therapeutic doses do not readily cause diminution in tonicity. Large doses were required to produce this effect.

14. Intravenous injection of ether produced dilatation of the heart as has been described by Hill and Barnard.

15. Asphyxia leads to diminution of tonicity and dilatation of the heart by the direct action of the carbon dioxide on the heart muscle as well as on the vagi. The ensuing changes set up a vicious cycle.

16. Formic acid diminishes cardiac tonicity, thus proving itself no exception to Gaskell's rule that dilute acids decrease tonicity.
Clinically tonicity cannot be estimated, as increase and decrease in this function occur, having no well defined relation to any of the estimable factors. It is an inherent property of the muscular wall and bears no apparent relation to blood pressure, pulse pressure, pulse rate, energy of heart, or peripheral resistance. Thus the table of Erlanger and Hooker can be of no service in estimating its change.

Percussion is entirely too fallible a method to detect the slight changes which occur. Possibly the only available indication could be obtained by the use of the orthodiagraph using Moeritz's scheme of a square of cardiac dulness. This I hope to investigate clinically at some future time.
Fig. 1. - Device for graduating cardiograph.

Fig. 2. - Arrangement for determining maximum, mean and minimum blood pressures simultaneously, and for registering the arterial pulse with a Härthle membrane manometer.

Fig. 3. - Diagrammatic representation of a tracing taken on a slow drum and showing an increase in tonicity. The upstroke represents systole, the downstroke diastole. The distance from the base line to the lower border of the tracing measured on the scale represents the tonicity. The length of the heavy upstroke measured perpendicularly gives the systolic output. In the diagram the tonicity and systolic output are calculated at two different periods, the lines being projected on the scale so as to give the measurements.

Fig. 4. - Diagram to illustrate the different conditions under which the ventricles may contract. The curves represent a cardiogram indicating the same amount of systolic discharge in each. The degree of tonus, the degree of distention, the systolic output, and the amount of residual blood are graphically represented. In Condition 2 there is a diminution of tonicity, increased distention, and an increase in the amount of residual blood. In Condition 3
there is an increase in tonicity, a diminution in the degree of distention, and the amount of residual blood is decreased.

Fig. 5. - Experiment I: spontaneous increase in frequency.

All tracings are to be read from left to right. The upstroke represents systole, the downstroke diastole.

From below upward in order are:

1. Time in seconds. In fifths only in very fast tracings when it will be plainly called attention to.

2. Abscissa of the Wrathle membrane manometer which serves as an abscissa for the cardiac tracing also, with the exception of Figure 19, Experiment XX, Figure 23, Experiment XIII, Figure 39 and 40; Experiment XXIV, and Figure 43, Experiment XXVIII, in which an extra abscissa was introduced directly under the carotid tracing.

3. The tracing from the carotid artery.

4. The cardiometer tracing from the heart, of which in every example upstroke represents systole, downstroke diastole.

5. The tracing from the limb plethysmograph which is represented sometimes as a straight line, at other times showing pulsations, depending on the condition of the animal and the adjustment. This is not represented in all tracings.

Marks. - A fairly definite system of marking was adhered to (see tables). Injections of drugs are denoted by capital letters underneath the time-tracing, space permitting. The carotid tracing shows here and there spaces which are numbered. These indicate manometer readings. Under the time-tracing the marks $S_1$, $S_2$, etc., denote that the drum was stopped. In the tables figures opposite these marks are calculated for the period just before the mark to which the time refers.
The tracings shown are referred to as Figs. 5, 6, 7, etc. The number and letter within the brackets indicate the experiment and maneuver.

Fig. 6. - Experiment II; changes following vagus stimulation.

Fig. 7. - Experiment III; injection of atropin sulphate into external jugular vein.

Fig. 8. - Experiment IV; division of the vagi.

Fig. 9. - Experiment V; bleeding from the femoral vein.

Fig. 10. - Experiment V; bleeding from the femoral vein and artery.

Fig. 11. - Experiment V; after twelve and a half minutes' bleeding.

Fig. 12 - Experiment V; two injections each of 20 c.c. normal saline into the femoral vein.

Fig. 13. - Experiment V; two injections of strychnin sulphate (1/250 gr.).

Fig. 14. - Experiment VI; injection of 1 minim of adrenalin chlorid  
(1/1000) into the superior vena cava.

Fig. 15. - Experiment VII; injection of 5 minims of adrenalin chlorid  
(1/1000) into the superior vena cava.

Fig. 16. - Effect of increasing the load on the isometric contraction and relaxation of the frog's heart (after O. Frank). The load is increased progressively in curves 1, 2, 3, 4. Both strength of contraction and tonus (diastolic shortening) increase progressively in curves 1, 2, and 3, and decrease in 4 when the load has become excessive.

Fig. 17. - Experiment VIII; clamping the thoracic aorta.
Fig. 18. - Experiment IX; weak heart, loading excessive. The rise in tonicity carried the lever above the top of the tracing. The time marker was not writing.

Fig. 19. - Experiment X; small dose of strychnin (1/120 grain, or 1/1680 grain per pound weight) injected into the external jugular vein.

Fig. 20. - Experiment XI; tracings two and a half minutes before injection of dose of 1/90 grain of strychnin sulphate into the external jugular vein.

Fig. 21. - Experiment XI concluded; tracings fourteen minutes after injection. T = Tonus; S.O. = Systolic Output.

Fig. 22. - Experiment XII; strychnin sulphate 1/100 grain (1/1000 gr. per pound) followed by 15 minims normal saline injected into the external jugular vein.

Fig. 23. - Experiment XIII; strychnin sulphate 1/150 grain (1/2100 gr. per pound) injected into the external jugular.

Fig. 24. - Experiment XIV; strychnin sulphate 1/45 grain (1/583 gr. per pound) injected into the superior vena cava.

Fig. 25. - Experiment XV; strychnin 1/50 grain (1/450 gr. per pound) injected into the external jugular vein.

Fig. 26. - Experiment XVI; strychnin sulphate 1/30 grain injected into the external jugular vein.

Fig. 27. - Experiment XVII; strychnin sulphate 1/30 grain (1/300 gr. per pound) injected into the external jugular vein.

Fig. 28. - Experiment XVIII continued; twenty-four minutes after injection.
Fig. 29. - Experiment XVIII concluded; thirty and a half minutes after injection.

Fig. 30. - Curves showing effect of strychnin on the phases of emptying and filling of the ventricles.

Fig. 31. - Experiment XIX; vagus paralyzed by atropin; strychnin sulphate 1/90 grain (1/855 gr. per pound) injected into the external jugular.

Fig. 32. - Experiment XXII concluded; aorta clamped after strychnin sulphate 1/15 had been injected into the superior vena cava.

Fig. 33. - Experiment XXIII; strychnin sulphate previously administered; two injections each 1 c.c. potassium chlorid into the superior vena cava.

Fig. 34. - Experiment XXIV; fluidextract of digitalis 5 minims (sol. 1 in 40 water) injected into the external jugular vein.

Fig. 35. - Experiment XXIV concluded; second injection of digitalis, same quantity and strength.

Fig. 36. - Experiment XXVI; atropin sulphate previously administered; vagus paralyzed; digitalis 5 minims (sol. 1 in 40) injected into the external jugular vein.

Fig. 37. - Experiment XXVI continued; second injection of digitalis (10 minims).

Fig. 38. - Experiment XXVI concluded.

Fig. 39. - Experiment XXVII; tincture strophanthus 1/2 minim injected into the superior vena cava.

Fig. 40. - Experiment XXVIII; tincture strophanthus 2 1/2 minims injected into the external jugular vein.
Fig. 41. - Experiment XXIX; nitroglycerin 1/100 grain (1/1200 gr. per pound) injected into the superior vena cava. Corresponding points are marked in the tracing by two short vertical arrow-heads. The primary elevation of the carotid tracing is due to mechanical interference with the superior cava.

Fig. 42. - Experiment XXX; nitroglycerin 1/300 grain (1/2700 gr. per pound) injected into the external jugular.

Fig. 43. - Experiment XXX continued.

Fig. 44. - Experiment XXX concluded.

Fig. 45. - Experiment XXXI; nitroglycerin 1/100 grain (1/1000 gr. per pound) injected into the superior vena cava.

Fig. 46. - Experiment XXXI concluded.

Fig. 47. - Experiment XXXII; calcium chloride 1 c.c. (sol. 2.316 per cent) injected into the external jugular vein.

Fig. 48. - Experiment XXXIII; calcium chloride 5 c.c. (2.316 per cent sol.) injected into the superior vena cava.

Fig. 49. - Experiment XXXIV; potassium chloride 1 c.c. (6.31 per cent) injected into the superior vena cava.

Fig. 50. - Experiment XXXV; effect produced by the entry of 5 per cent sodium citrate solution into the carotid artery.

Fig. 51. - Experiment XXXVI; calcium chloride injected into the external jugular vein and superior vena cava, following sodium citrate.

Fig. 52. - Experiment XXXVII; vagus primarily paralyzed with atropin; 1 c.c. calcium chloride injected into the external jugular vein.
Fig. 53. - Experiment XXXVII continued; 1 c.c. calcium injected into the superior vena cava.

Fig. 54. - Experiment XXXVII concluded.

Fig. 55. - Experiment XXXVIII; vagus nerve previously paralyzed with atropin sulphate; 1 c.c. potassium chlorid injected into the superior vena cava. Primary disturbance of tracing due to interference with the superior vena cava in injecting.

Fig. 56. - Experiment XXXVIII concluded.

Fig. 57. - Experiment XXXIX; effect of asphyxia on cardiac tonicity.

Fig. 58. - Experiment XL; effect of asphyxia in increasing the blood-pressure and diminishing the cardiac tonicity.

Fig. 59. - Experiment XLI; effect of asphyxia; vagus previously paralyzed with atropin.

Fig. 60. - Experiment XLII; effect of increased respiration.

Fig. 61. - Traube-Hering curves, produced evidently by partial asphyxiation, as they disappeared after an increase of the supply of air in the lungs.

Fig. 62. - Experiment XLIII; dilatation produced by injection of 1 minim of air along with 1/250 grain (1/2562 gr. per pound) strychnin sulphate into the external jugular.

Fig. 63. - Experiment XLIV; three injections of formic acid (4 minims 10 per cent, 1 1/2 minims 50 per cent, 5 minims 50 per cent) followed by 1 minim tincture of aconite, into the superior vena cava.

Fig. 64. - Experiment XLV; latent period 42 seconds; two injections of tincture of aconite (at E, 1 minim; at F, 5 minims) into the superior vena cava.
Table 1 - Experiment I, Shown in Figure 5.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Syst.</td>
<td>Diast.</td>
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<tr>
<td>-10</td>
<td>10</td>
<td>70</td>
<td>88</td>
<td>58</td>
<td>30</td>
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<td>- 6 1/2</td>
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<td>64</td>
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<td>-1 1/2</td>
<td>+ 40</td>
<td>- 4</td>
<td>+ 6</td>
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*In the tables the following headings of columns are used:

Mark refers to the mark on the tracing indicating the time and the maneuver. Capital letters indicate drug injection or such like. Numbers indicate manometer readings.

Blood Pressure column indicates, in three divisions, systolic or maximum, mean, diastolic or minimum respectively.

Pulse Pressure column indicates difference between systolic and diastolic.

Tonus indicates level of tonicity curve in °, above or below an arbitrary point; above expressed by the plus sign, below by the minus sign. Therefore with +, increase in number indicates increase in tonicity and vice versa. With -, decrease in number indicates increase in tonicity and vice versa.

Pleth. means plethysmograph. Its height is expressed in millimeter measurement above base line.

S. O. indicates systolic output in cubic centimeters.

Rate is always expressed in beats per minute.

Velocity of flow, sometimes added, is found by multiplying the rate per minute by the systolic output, giving, therefore, output in cubic centimeters per minute.
Table 2. - Experiment III, Shown in Figure 7.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>min:sec</td>
<td></td>
<td>Exp.</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>min. m.</td>
<td></td>
<td></td>
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<tr>
<td>4:43:30</td>
<td>A</td>
<td></td>
<td></td>
<td>+7</td>
<td></td>
<td>100</td>
<td>9.2</td>
</tr>
<tr>
<td>4:44</td>
<td>S4</td>
<td></td>
<td></td>
<td>+7</td>
<td></td>
<td>100</td>
<td>9.5</td>
</tr>
<tr>
<td>4:49:15</td>
<td>F</td>
<td></td>
<td></td>
<td>+5.2</td>
<td></td>
<td>8.2</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Stimulated vagus</td>
<td></td>
<td></td>
<td>+7 regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:50:30</td>
<td>S5</td>
<td></td>
<td>123:90:75</td>
<td>48</td>
<td></td>
<td>98</td>
<td>8</td>
</tr>
<tr>
<td>4:53:30</td>
<td></td>
<td></td>
<td></td>
<td>+5.6</td>
<td></td>
<td>10</td>
<td>102</td>
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<tr>
<td>4:54:35</td>
<td></td>
<td></td>
<td></td>
<td>+8</td>
<td></td>
<td>10</td>
<td>102</td>
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<tr>
<td>4:54:54</td>
<td>S.V.</td>
<td></td>
<td></td>
<td>+11</td>
<td></td>
<td>8.7</td>
<td>96</td>
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<tr>
<td>5:10</td>
<td></td>
<td></td>
<td>106:81:68</td>
<td>38</td>
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</table>
Table 3. - Experiment IV, Shown in Figure 8. Division of the Vagi.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
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<td>3:46 P.M.</td>
<td>S5</td>
<td>131:121:71</td>
<td>+ 9.25</td>
<td>9</td>
<td>81</td>
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<tr>
<td>3:59:45</td>
<td>S10</td>
<td></td>
<td>+ 5.25</td>
<td>8</td>
<td>77</td>
</tr>
<tr>
<td>4:3:15</td>
<td>A</td>
<td></td>
<td>+ 8 1/2</td>
<td>6.5</td>
<td>108</td>
</tr>
<tr>
<td>4:3:21</td>
<td></td>
<td></td>
<td>+ 8</td>
<td>5.7</td>
<td>119</td>
</tr>
<tr>
<td>4:6:40</td>
<td>S11</td>
<td></td>
<td>+ 8</td>
<td>5.5</td>
<td>120</td>
</tr>
<tr>
<td>4:8:15</td>
<td>B</td>
<td></td>
<td>+ 4 1/2</td>
<td>6</td>
<td>115</td>
</tr>
<tr>
<td>4:8:37</td>
<td></td>
<td></td>
<td>+ 5.25</td>
<td>5.25</td>
<td>120</td>
</tr>
<tr>
<td>4:9</td>
<td>S12</td>
<td>marked fall</td>
<td>+ 4.75</td>
<td>5.75</td>
<td>120</td>
</tr>
<tr>
<td>4:16</td>
<td>S13</td>
<td></td>
<td>+ 2.6</td>
<td>4.75</td>
<td>47</td>
</tr>
<tr>
<td>4:20:30</td>
<td></td>
<td></td>
<td>- 2.25</td>
<td>4.75</td>
<td>33</td>
</tr>
</tbody>
</table>

Cut right vagus
Cut left vagus
Table 1. - Experiment V. Shown in Figures 9, 10, 11, 12, and 13. Bleeding and Salines (Figures at beginning and end of saline injections are bracketed).

<table>
<thead>
<tr>
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</thead>
<tbody>
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<td>40</td>
<td>81:59:51</td>
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<td>3:38</td>
<td>Bl.1</td>
<td>81:59:51</td>
<td>31</td>
<td>+4</td>
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<td>8</td>
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<td>3:39:30</td>
<td>41</td>
<td>76:62:47</td>
<td>18</td>
<td>+4.2</td>
<td>-5</td>
<td>8</td>
<td>60</td>
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<td>3:43</td>
<td>42</td>
<td>68:59:50</td>
<td>18</td>
<td>+7</td>
<td>-3.5</td>
<td>6</td>
<td>62</td>
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<td>3:46</td>
<td>43</td>
<td>65:56:47</td>
<td>18</td>
<td>-7.7</td>
<td>-4</td>
<td>5.5</td>
<td>60</td>
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<td>3:50:30</td>
<td>44</td>
<td>65:54:47</td>
<td>18</td>
<td>+6.7</td>
<td>-3</td>
<td>4.2</td>
<td>64</td>
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<tr>
<td>3:59:30</td>
<td>45</td>
<td>62:53:41</td>
<td>21</td>
<td>+7.5</td>
<td>-5</td>
<td>3.5</td>
<td>60</td>
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<td></td>
<td></td>
<td>Saline 20 c.c. fem.vein</td>
<td>+5.7</td>
<td>-4</td>
<td>3.2</td>
<td>68</td>
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<tr>
<td>4:3</td>
<td>46</td>
<td>56:45:37</td>
<td>19</td>
<td>+5.7</td>
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<td>4.7</td>
<td>60</td>
</tr>
<tr>
<td></td>
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<td>Saline 20 c.c.</td>
<td>+5.7</td>
<td>-2.5</td>
<td>5.5</td>
<td>66</td>
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<tr>
<td>4:3:30</td>
<td>S3</td>
<td>62:47:37</td>
<td>25</td>
<td>+4.2</td>
<td>-3</td>
<td>6.7</td>
<td>56</td>
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<tr>
<td>4:5:30</td>
<td>S4</td>
<td>62:47:37</td>
<td>25</td>
<td>+4.2</td>
<td>-3</td>
<td>6.7</td>
<td>56</td>
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<td>4:6</td>
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<td>20 c.c. Saline</td>
<td>+3.7</td>
<td>-3.5</td>
<td>6.5</td>
<td>60</td>
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<tr>
<td>4:18</td>
<td>S8</td>
<td>56:41:31</td>
<td>25</td>
<td>-1.2</td>
<td>7</td>
<td>48</td>
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<td>Strych. Sul. 1/250</td>
<td>-1.2</td>
<td>7</td>
<td>48</td>
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<td></td>
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<td>S9</td>
<td>56:41:31</td>
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<td>-0.2</td>
<td>6</td>
<td>47</td>
<td></td>
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<td>4:22</td>
<td>S10</td>
<td>56:41:31</td>
<td>22</td>
<td>+1</td>
<td>9.2</td>
<td>39</td>
<td></td>
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<tr>
<td>4:25</td>
<td>S11</td>
<td>56:41:31</td>
<td>22</td>
<td>+2</td>
<td>8.5</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>4:28:45</td>
<td>S12</td>
<td>56:41:31</td>
<td>22</td>
<td>+2.7</td>
<td>8.7</td>
<td>44</td>
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<tr>
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<td>S13</td>
<td>56:41:31</td>
<td>22</td>
<td>+4.7</td>
<td>6.5</td>
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Table 5. - Experiment VI (46 L) Shown in Figure 14.
Adrenalin Chlorid 1 minim Injected into the Superior Vena Cava.
Latent Period Twelve Seconds.

<table>
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<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
<th>Veloc. of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:5</td>
<td>L</td>
<td>71:70:67</td>
<td>-8.4</td>
<td>2.4</td>
<td>96</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>2:6:55</td>
<td>L</td>
<td></td>
<td>-6.5</td>
<td>2.3</td>
<td>102</td>
<td>234</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonocity commences to fall before much change in blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:8</td>
<td></td>
<td>increased</td>
<td>-11</td>
<td>1.5</td>
<td>114</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>2:8:35</td>
<td>S6</td>
<td>diminishing</td>
<td>-9.4</td>
<td>2</td>
<td>90</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>2:10:35</td>
<td>S7</td>
<td>diminishing</td>
<td>-8</td>
<td>2.4</td>
<td>96</td>
<td>230</td>
<td></td>
</tr>
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5 2/2 5 2
Table 6. - Experiment VII, Shown in Figure 15. Adrenalin Chlorid 5 minims Injected into the Superior Vena Cava.

<table>
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<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
<th>Veloc. of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:58:30</td>
<td>E</td>
<td></td>
<td>-8</td>
<td>2.7</td>
<td>40</td>
<td>108</td>
</tr>
<tr>
<td>3:0:20</td>
<td>↑</td>
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<td>-15</td>
<td>5.2</td>
<td>15</td>
<td>78</td>
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<tr>
<td>3:3</td>
<td>9</td>
<td>62:56:47</td>
<td>-15</td>
<td>4.5</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>3:7:30</td>
<td>S17</td>
<td></td>
<td>-8.7</td>
<td>1.7</td>
<td>66</td>
<td>112</td>
</tr>
</tbody>
</table>

Cardiometer removed and replaced

3:15 Nitroglycerin 1/50 gr. - 2

3:18:40 S18

- 9 2.5 15 37
Table 7. - Experiment VIII, Shown in Figure 17. Clamping the Thoracic Aorta.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
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<tbody>
<tr>
<td>5:59</td>
<td>B2</td>
<td>78</td>
<td>+16.7</td>
<td>5.7</td>
<td>108</td>
</tr>
<tr>
<td>5:59:15</td>
<td>a</td>
<td>93</td>
<td>+12</td>
<td>5.7</td>
<td>108</td>
</tr>
<tr>
<td>6:2:2</td>
<td>b</td>
<td>138</td>
<td>+24</td>
<td>6.7</td>
<td>108</td>
</tr>
<tr>
<td>6:2:3</td>
<td>c</td>
<td>unclamped</td>
<td></td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>6:2:5</td>
<td>d</td>
<td>75</td>
<td>+15.5</td>
<td>11</td>
<td>72</td>
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Table 8. - Experiment IX, Shown in Figure 13. Clamping Thoracic Aorta. Weak Heart. Loading excessive.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>max.</td>
<td>min.</td>
<td></td>
<td>cc.</td>
<td></td>
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<tr>
<td>4:09:51</td>
<td>A</td>
<td>105</td>
<td>82</td>
<td>23</td>
<td>-11.7</td>
<td>6.7</td>
</tr>
<tr>
<td>4:09:55</td>
<td>a</td>
<td>151</td>
<td>124</td>
<td>27</td>
<td>-14.6</td>
<td>5.2</td>
</tr>
<tr>
<td>4:10:12</td>
<td>b</td>
<td>115</td>
<td>75</td>
<td>40</td>
<td>-1.1</td>
<td>6</td>
</tr>
<tr>
<td>4:10:35</td>
<td>c</td>
<td>118</td>
<td>71</td>
<td>47</td>
<td>-10.3</td>
<td>6</td>
</tr>
<tr>
<td>4:10:47</td>
<td>d</td>
<td>103</td>
<td>73</td>
<td>30</td>
<td>-10.3</td>
<td>6</td>
</tr>
<tr>
<td>4:11:16</td>
<td>e</td>
<td>114</td>
<td>84</td>
<td>30</td>
<td>-11.3</td>
<td>6.5</td>
</tr>
<tr>
<td>4:14:55</td>
<td>f</td>
<td>117</td>
<td>87</td>
<td>30</td>
<td>-12</td>
<td>7</td>
</tr>
<tr>
<td>4:14:58</td>
<td>g</td>
<td>110</td>
<td>84</td>
<td>26</td>
<td>-10.3</td>
<td>6.3</td>
</tr>
<tr>
<td>4:18:30</td>
<td>l</td>
<td>123</td>
<td>100</td>
<td>41</td>
<td>-10.5</td>
<td>6.8</td>
</tr>
</tbody>
</table>

- Aorta clamped
- Aorta unclamped
Table 9. - Experiment X, Shown in Figure 19. Strychnin Sulphate 1/120 grain (1/1680 gr. per pound). Injected into external jugular vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>min. mean. mea.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:25</td>
<td>A</td>
<td>75:53:39</td>
<td>36</td>
<td>+0.6</td>
<td>835</td>
<td>3.2</td>
<td>64</td>
</tr>
<tr>
<td>2:41</td>
<td>S6</td>
<td>Strychnin gr. 1/120</td>
<td>+0.6</td>
<td>835</td>
<td>3.2</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2:43</td>
<td>S7</td>
<td>75:47:44</td>
<td>31</td>
<td>+0.6</td>
<td>860</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>2:52:50</td>
<td>S8</td>
<td>+0.6</td>
<td>870</td>
<td>3.5</td>
<td>52</td>
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Table 10. - Experiment XI, Shown in Figures 20 and 21. Injection of 1/300 Streptomycin Sulphate into the External Jugular Vein.

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<th></th>
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<tbody>
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<td>1:17</td>
<td>2</td>
<td>124:110:100</td>
<td>24</td>
<td>-3.5</td>
<td>93</td>
<td>4.2</td>
<td>112</td>
</tr>
<tr>
<td>1:19:30</td>
<td>A</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1:33:30</td>
<td>3</td>
<td>124:108:100</td>
<td>24</td>
<td>-2.9</td>
<td>96</td>
<td>3.5</td>
<td>112</td>
</tr>
<tr>
<td>1:36</td>
<td></td>
<td>124:108:100</td>
<td>24</td>
<td>-2.7</td>
<td>96</td>
<td>3.5</td>
<td>112</td>
</tr>
</tbody>
</table>

Inj:

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Table 10. - Experiment XI, Shown in Figures 20 and 21. Injection of 1/300 Streptomycin Sulphate into the External Jugular Vein.

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<th></th>
<th></th>
</tr>
</thead>
<tbody>
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<td>1:17</td>
<td>2</td>
<td>124:110:100</td>
<td>24</td>
<td>-3.5</td>
<td>93</td>
<td>4.2</td>
<td>112</td>
</tr>
<tr>
<td>1:19:30</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:33:30</td>
<td>3</td>
<td>124:108:100</td>
<td>24</td>
<td>-2.9</td>
<td>96</td>
<td>3.5</td>
<td>112</td>
</tr>
<tr>
<td>1:36</td>
<td></td>
<td>124:108:100</td>
<td>24</td>
<td>-2.7</td>
<td>96</td>
<td>3.5</td>
<td>112</td>
</tr>
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</table>

Inj:
Table II. - Experiment XII, Shown in Figure 22. Strychnin Sulphate Grain 1/100 (1/1000 gr. per pound; followed by normal saline 15 minims) Injected into the External Jugular Vein.

<table>
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<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
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<td>1:31 P.M.</td>
<td>F</td>
<td>84:65:54</td>
<td>30</td>
<td>+1.25</td>
<td>0</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>1:32:30</td>
<td>20</td>
<td>84:62:53</td>
<td>31</td>
<td>+1.75</td>
<td></td>
<td>11.75</td>
<td>68</td>
</tr>
<tr>
<td>1:36</td>
<td>21</td>
<td>76:62:53</td>
<td>23</td>
<td>+2</td>
<td></td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>1:39</td>
<td>22</td>
<td>75:62:50</td>
<td>25</td>
<td>+2.25</td>
<td></td>
<td>11</td>
<td>66</td>
</tr>
<tr>
<td>1:42</td>
<td>23</td>
<td>75:62:50</td>
<td>25</td>
<td>+2.5</td>
<td></td>
<td>11</td>
<td>63</td>
</tr>
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</table>

5 1 1 6 2 3 7 14
Table 12. - Experiment XIII, Shown in Figure 23. Strychnin Sulphate 1/150 Grain Followed in Seven Minutes, Twenty Seconds by 1/60 Grain, Both into the External Jugular (1/2100 and 1/840 grs. per pound respectively).

<table>
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<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.m.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:32:30</td>
<td>5</td>
<td>76:34:23</td>
<td>53</td>
<td>+0.6</td>
<td>3.6</td>
<td>34</td>
</tr>
<tr>
<td>3:33:30</td>
<td>9</td>
<td>Strych. 1/150 gr.</td>
<td>+0.6</td>
<td>3.6</td>
<td>34</td>
<td></td>
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<tr>
<td>3:37:40</td>
<td>S17</td>
<td></td>
<td></td>
<td>+0.7</td>
<td>3.5</td>
<td>32</td>
</tr>
<tr>
<td>3:40:50</td>
<td>E</td>
<td>Strych. 1/60 gr.</td>
<td>+0.6</td>
<td>3.6</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>3:44</td>
<td>6</td>
<td>75:28:23</td>
<td>52</td>
<td>+0.7</td>
<td>3.6</td>
<td>28</td>
</tr>
<tr>
<td>3:45:30</td>
<td>S18</td>
<td></td>
<td></td>
<td>+0.7</td>
<td>3.5</td>
<td>28</td>
</tr>
<tr>
<td>3:50:30</td>
<td>7</td>
<td>75:44:39</td>
<td>36</td>
<td>+0.9</td>
<td>3.5</td>
<td>27</td>
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</table>

<table>
<thead>
<tr>
<th>Tonic</th>
<th>Rate</th>
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Table 13. - Experiment XIV, Shown in Figure 24. Strychnin Sulphate 1/45 Grain (1/583 gr. per pound) Injected into the Superior Vena Cava.

<table>
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<tr>
<th>Time</th>
<th>Mark</th>
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<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:42:45</td>
<td>12</td>
<td>115:102:90</td>
<td>25</td>
<td>-2.6</td>
<td>5.75</td>
<td>85</td>
</tr>
<tr>
<td>2:44</td>
<td></td>
<td></td>
<td>-2.6</td>
<td>5.75</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>2:44:30</td>
<td>S10</td>
<td>Strych. sulph. 1/45 gr. S.V.C.</td>
<td>-1.4</td>
<td>5.75</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>2:48</td>
<td>S11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:10:15</td>
<td>S12</td>
<td>115:105:96</td>
<td>19</td>
<td>-0.75</td>
<td>4.5</td>
<td>73</td>
</tr>
</tbody>
</table>

The numbers at the bottom of the table represent the total death count.
Table 14. - Experiment XV, Shown in Figure 25. Strychnin 1/50 Grain (1/450 gr. per pound) Injected into External Jugular

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse</th>
<th>Tomis</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:54:45</td>
<td>C</td>
<td>100:84:75</td>
<td>25</td>
<td>-1</td>
<td>100</td>
<td>6.5</td>
<td>128</td>
</tr>
<tr>
<td>2:59:30</td>
<td>S_{11}</td>
<td>Strychn. sulph. gr. 1/50</td>
<td>-0.25</td>
<td>102</td>
<td>6</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>3:0:15</td>
<td>S_{12}</td>
<td>100:84:78</td>
<td>22</td>
<td>+0.5</td>
<td>98</td>
<td>5.75</td>
<td>120</td>
</tr>
</tbody>
</table>


Table 15. - Experiment XVI, Shown in Figure 26. Strychnin Sulphate 1/30.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus cc.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Step. Mean. Max.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:14:45</td>
<td>S13</td>
<td>117:108:98</td>
<td>19</td>
<td>-1.1</td>
<td>5.2</td>
<td>73</td>
</tr>
<tr>
<td>3:17:15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:19:20</td>
<td></td>
<td></td>
<td></td>
<td>-11.5</td>
<td>11</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Convulsion lasting till 3:20 3/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:20:30</td>
<td></td>
<td>118:87:65</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:23:15</td>
<td>S14</td>
<td></td>
<td></td>
<td>-3.5</td>
<td>8.7</td>
<td>30</td>
</tr>
<tr>
<td>3:27:15</td>
<td>13</td>
<td>118:87:44</td>
<td>74</td>
<td>-4.7</td>
<td>8.2</td>
<td>59</td>
</tr>
<tr>
<td>3:28:15</td>
<td>S15</td>
<td></td>
<td></td>
<td>-4.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 16. - Experiment XVII. Strychnin sulphate 1/30 grain (1/390 gr. grain per pound) Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Torus S. O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:25</td>
<td>S18</td>
<td>All irregular</td>
<td>-2.4</td>
<td>7.5</td>
<td>90</td>
</tr>
<tr>
<td>3:38</td>
<td></td>
<td></td>
<td>102:107:101</td>
<td>Irritability has passed off with more ether, jaw is stiff</td>
<td></td>
</tr>
<tr>
<td>3:38:10</td>
<td>Strych. sulph. 1/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:40:30</td>
<td>S19</td>
<td></td>
<td>-0.8</td>
<td>6.3</td>
<td>61</td>
</tr>
<tr>
<td>3:42:10</td>
<td>S20</td>
<td></td>
<td></td>
<td>Increase of muscular irritability</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 17. - Experiment XVIII, Shown in Figures 27, 28, and 29.
Strychnin Sulphate 1/30 Grain (1/300 gr. per pound) followed by 15 minims saline solution into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:52</td>
<td>26</td>
<td>81:62:53</td>
<td>28</td>
<td>+2</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1:53</td>
<td>H</td>
<td>81:62:53</td>
<td>28</td>
<td>+2</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1:54:30</td>
<td>27</td>
<td>81:62:53</td>
<td>28</td>
<td>+2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>1:55</td>
<td>28</td>
<td>81:64:53</td>
<td>29</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:55:30</td>
<td>29</td>
<td>82:65:53</td>
<td>28</td>
<td>+1/2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:17</td>
<td>28</td>
<td>90:70:50</td>
<td>40</td>
<td>+1.7</td>
<td>0</td>
<td>15.2</td>
</tr>
<tr>
<td>2:23:30</td>
<td>29</td>
<td>39</td>
<td>+2.7</td>
<td>0</td>
<td>15</td>
<td>56</td>
</tr>
</tbody>
</table>

Note: All times are in minutes.
Table 18. - Experiment XIX, Shown in Figure 31. Vagus paralyzed by Atropin. Strychnin Sulphate 1/90 Grain (1/855 gr. per pound) Injected into the External Jugular.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press</th>
<th>Pulse Press</th>
<th>Tonus</th>
<th>S. O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:58:30</td>
<td>3</td>
<td>108:71:59</td>
<td>49</td>
<td>0</td>
<td>3.9</td>
<td>108</td>
</tr>
<tr>
<td>3:59:30</td>
<td>3</td>
<td>108:71:59</td>
<td>49</td>
<td>0</td>
<td>3.9</td>
<td>108</td>
</tr>
<tr>
<td>4:1:30</td>
<td>4</td>
<td>108:68:59</td>
<td>49</td>
<td>0.25</td>
<td>4.25</td>
<td>108</td>
</tr>
<tr>
<td>4:5:30</td>
<td>5</td>
<td>108:68:62</td>
<td>46</td>
<td>0.25</td>
<td>4.4</td>
<td>104</td>
</tr>
<tr>
<td>4:7:45</td>
<td>S3</td>
<td>108:68:62</td>
<td>46</td>
<td>0.25</td>
<td>4.25</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 19. - Experiment XX. Atropin Sulphate Previously Administered; \( \frac{1}{90} \) Grain Strychnin Sulphate \((1/585\text{ gr. per pound})\) Injected into the External Jugular.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:26:30</td>
<td>8</td>
<td>102:68:50</td>
<td>52</td>
<td>-0.7</td>
<td>4.4</td>
<td>84</td>
</tr>
<tr>
<td>4:29</td>
<td>D</td>
<td>102:66:50</td>
<td>-0.7</td>
<td>4.3</td>
<td>88</td>
<td>Strych. 1/90 gr.</td>
</tr>
<tr>
<td>4:33</td>
<td>9</td>
<td>102:60:49</td>
<td>53</td>
<td>-0.7</td>
<td>4.4</td>
<td>82</td>
</tr>
<tr>
<td>4:34</td>
<td></td>
<td></td>
<td>-0.7</td>
<td>4.4</td>
<td>82</td>
<td>5</td>
</tr>
</tbody>
</table>

\(5\) 2 6 1 2 2 5
Table 20. - Experiment 21, Vagus Paralyzed with Atropin. Strychin Sulphate 1/45 grain (1/427 gr. per pound) Injected into the External Jugular.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:33</td>
<td>9</td>
<td>102:60:48</td>
<td>54</td>
<td>-0.75</td>
<td>4.4</td>
<td>82</td>
</tr>
<tr>
<td>4:34</td>
<td>E</td>
<td></td>
<td>-0.75</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:39</td>
<td>x</td>
<td></td>
<td>-0.75</td>
<td>4.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:42:30</td>
<td></td>
<td>100:59:47</td>
<td>53</td>
<td></td>
<td></td>
<td>80 Very little change if any</td>
</tr>
</tbody>
</table>

Strych. 1/45
Table 21. - Experiment XXII, Shown in Figure 32. Strychnin Sulphate 1/15 grain (1/202 gr. per pound) into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:45</td>
<td>9</td>
<td>47:47:31</td>
<td>-6</td>
<td>13</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>6:45:55</td>
<td>F</td>
<td>Strych. Sulph. 1/15</td>
<td>-6</td>
<td>13.5</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>6:50</td>
<td>10</td>
<td>47:47:31</td>
<td>-5.5</td>
<td>13.5</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>6:50:20</td>
<td>S6</td>
<td></td>
<td>-5.5</td>
<td>13.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The heart being now well under the influence of strychnin, the aorta was clamped at G.

Fig. 32:

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6:57</td>
<td>G</td>
<td>Aorta clamped</td>
<td>-5.2</td>
<td>13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>6:57:15</td>
<td>b</td>
<td></td>
<td>-8</td>
<td>13.5</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>6:58:14</td>
<td>c</td>
<td></td>
<td>-6</td>
<td>16.5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>7:0:0</td>
<td>d</td>
<td></td>
<td>-6.5</td>
<td>14</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>7:0:15</td>
<td>H</td>
<td>unclamped</td>
<td>-1.4</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>7:0:26</td>
<td>e</td>
<td></td>
<td>-4</td>
<td>9</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7:2:45</td>
<td>S7</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 22. - Experiment XXIII, Shown in Figure 33. Strychnin
previously Administered. Two injections each 1 c.c. Potassium chlorid
into Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Torus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:4:15</td>
<td>19</td>
<td>84:41:34</td>
<td>+ 3.5</td>
<td>2.4</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>2:5</td>
<td>M</td>
<td>1 c.c. KCl sol.</td>
<td>+ 3.5</td>
<td>1.75</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>2:8:30</td>
<td>N</td>
<td>1 c.c. KCl</td>
<td>+ 3.75</td>
<td>1.75</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>2:18</td>
<td>S6</td>
<td>+ 4.2</td>
<td>1.4</td>
<td></td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

25 2 1/2 6 2 1/2 2 1/2 1
Table 23. - Experiment XXIV, Shown in Figure 34. Fluidextract Digitalis, 1 in 40 water, 5 minims injected into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:14</td>
<td></td>
<td>102:96:81</td>
<td>-2.75</td>
<td></td>
<td></td>
<td></td>
<td>124</td>
</tr>
<tr>
<td>5:29</td>
<td>A</td>
<td>fluid extr. digitalis m.v</td>
<td>-2.75</td>
<td>915</td>
<td>5.6</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>5:32:30</td>
<td>S₂</td>
<td>105:93:84</td>
<td>-3.5</td>
<td></td>
<td>910</td>
<td>5.5</td>
<td>124</td>
</tr>
<tr>
<td>5:33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:36:10</td>
<td>S₃</td>
<td></td>
<td>+3.75</td>
<td></td>
<td>905</td>
<td>5.5</td>
<td>124</td>
</tr>
</tbody>
</table>
Table 24. - Experiment 24, Shown in Figure 35. Second Injection of Fluidextract Digitalis, 5 minims, 1 in 407, into External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Plath.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:33</td>
<td></td>
<td>105:93:84</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:40</td>
<td>B</td>
<td>Digitalis minims v</td>
<td>+ 4</td>
<td>906</td>
<td>5</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>5:43:10</td>
<td>1</td>
<td>108:91:84</td>
<td>+ 5.25</td>
<td>910</td>
<td>4.5</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>5:45</td>
<td>S4</td>
<td>108:87:84</td>
<td>24</td>
<td>+ 5.25</td>
<td>880</td>
<td>5.1</td>
<td>120</td>
</tr>
<tr>
<td>5:51:45</td>
<td>2</td>
<td>108:95:84</td>
<td>24</td>
<td>+ 5.9</td>
<td>890</td>
<td>5.1</td>
<td>120</td>
</tr>
<tr>
<td>5:53</td>
<td></td>
<td></td>
<td></td>
<td>+ 5.9</td>
<td>894</td>
<td>5.3</td>
<td>124</td>
</tr>
</tbody>
</table>
Table 25. - Experiment XXV. Digitalis Solution 10 minims injected into the External Jugular.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:14:30</td>
<td>E</td>
<td>87:56:50</td>
<td>37</td>
<td>+2.2</td>
<td>4.2</td>
<td>136</td>
</tr>
<tr>
<td>1:16:30</td>
<td>E</td>
<td>87:56:50</td>
<td>37</td>
<td>+2.2</td>
<td>4.5</td>
<td>132</td>
</tr>
<tr>
<td>1:20</td>
<td>9</td>
<td></td>
<td></td>
<td>+2.4</td>
<td>4.4</td>
<td>132</td>
</tr>
<tr>
<td>1:22:30</td>
<td>S4</td>
<td>87:62:54</td>
<td>33</td>
<td>+2.5</td>
<td>4.2</td>
<td>132</td>
</tr>
<tr>
<td>1:27:30</td>
<td>10</td>
<td>87:62:54</td>
<td>33</td>
<td>+2.7</td>
<td>4.2</td>
<td>132</td>
</tr>
<tr>
<td>1:29:45</td>
<td>11</td>
<td>87:62:54</td>
<td>33</td>
<td>+2.7</td>
<td>3.7</td>
<td>132</td>
</tr>
<tr>
<td>1:31:30</td>
<td></td>
<td></td>
<td></td>
<td>+2.7</td>
<td>3.5</td>
<td>128</td>
</tr>
</tbody>
</table>

S.O. = Systolic, O.C. = Diastolic.
Table 26. - Experiment XXVI, Shown in Figures 36, 37, and 38. Atropin Sulphate. Vagus paralyzed. Digitalis 5 minims, 1 in 40, injected into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fig. 36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:10</td>
<td>2</td>
<td>106:81:68</td>
<td>38</td>
<td>+18</td>
<td>118</td>
<td>8.25</td>
<td>108</td>
</tr>
<tr>
<td>5:11:30</td>
<td>B</td>
<td>Digitalis 5 m</td>
<td>+18</td>
<td>118</td>
<td>7.75</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>5:17</td>
<td>S7</td>
<td></td>
<td></td>
<td>+17</td>
<td>116</td>
<td>7.75</td>
<td>120</td>
</tr>
<tr>
<td>Fig. 37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:24:30</td>
<td>S8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:29:45</td>
<td>C</td>
<td>Digitalis 10 m</td>
<td>+17</td>
<td>116</td>
<td>7.75</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>5:30:30</td>
<td>3</td>
<td>105:84:81</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fig. 38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:33:30</td>
<td>S9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:41:20</td>
<td>S10 all increased</td>
<td></td>
<td>+18 1/2</td>
<td>116</td>
<td>8.5</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>5:52</td>
<td>4</td>
<td>102:100:84</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures 36, 37, and 38 show the changes in blood pressure, pulse pressure, tonus, pleth, and S.O. rate over time.
Table 27. - Experiment XXVII, Shown in Figure 39. Tincture Strophanthus 1/2 minim Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1:8</td>
<td></td>
<td>75:68:59</td>
<td>16</td>
<td>-11.4</td>
<td>119</td>
<td>4</td>
<td>117</td>
</tr>
<tr>
<td>1:9:21</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:10:20</td>
<td>E</td>
<td>Tr. Strophanthus</td>
<td>-11.2</td>
<td>119</td>
<td>4</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>1:15</td>
<td>S_4</td>
<td>64:78:62</td>
<td>22</td>
<td></td>
<td>120</td>
<td>3.8</td>
<td>126</td>
</tr>
<tr>
<td>1:17</td>
<td></td>
<td></td>
<td></td>
<td>-11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:18:45</td>
<td>S_5</td>
<td>64:78:68</td>
<td>16</td>
<td>-10.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Limb plethysmograph shows no material variation.
Table 28. - Experiment XXVIII, Shown in Figure 40. Tincture Strophanthus 2 1/2 minims Injected into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:11</td>
<td>11</td>
<td>91:68:62</td>
<td>+1</td>
<td></td>
<td>3.2</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>4:12:30</td>
<td>D</td>
<td>Tr. Strophanthus m.11 ss</td>
<td>+0.5</td>
<td>6</td>
<td>3.2</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>4:14</td>
<td>12</td>
<td>98:71:67</td>
<td>+1.2</td>
<td>6.4</td>
<td>3.5</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>4:15:20</td>
<td>S13</td>
<td></td>
<td>-2.5</td>
<td>5.2</td>
<td>3.5</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>4:15:54</td>
<td>S14</td>
<td></td>
<td>0</td>
<td>4.9</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:16:20</td>
<td>S15</td>
<td></td>
<td>-5.7</td>
<td>2</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:22</td>
<td>S16</td>
<td></td>
<td>-5</td>
<td>3.3</td>
<td>6</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>
Table 29. - Experiment XXIX, Shown in Figure 41. Nitroglycerin 1/100 grain (1/1200 gr. per pound) Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press</th>
<th>Pulse Press</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:40</td>
<td>3</td>
<td>84:81:78</td>
<td>6</td>
<td>-11.3</td>
<td>4</td>
<td>111</td>
</tr>
<tr>
<td>Fig. 49</td>
<td>G</td>
<td>Nitroglycerin gr. 1/100</td>
<td>13</td>
<td>-11.3</td>
<td>4</td>
<td>111</td>
</tr>
<tr>
<td>1:43</td>
<td>4</td>
<td>53:43:40</td>
<td></td>
<td>-10.2</td>
<td>3</td>
<td>102</td>
</tr>
<tr>
<td>Fig. 50</td>
<td>1:48:30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84</td>
</tr>
</tbody>
</table>

\[\text{\textfrac{1}{12}}\] \[\text{\textfrac{1}{2}}\] \[\text{\textfrac{2}{3}}\]
Table 30. - Experiment XXX, Shown in Figures 42, 43 and 44. Nitroglycerin 1/300 grain (1/2700 gr. per pound) injected into the External Jugular. Strychnin and Digitalis previously administered.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4:20:30</td>
<td>8</td>
<td>65:76:68</td>
<td>17</td>
<td>+14</td>
<td>99</td>
<td>6.7</td>
<td>100</td>
<td>670</td>
</tr>
<tr>
<td>4:21</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td>6.7</td>
<td>100</td>
<td>670</td>
</tr>
<tr>
<td>4:24</td>
<td>9</td>
<td>65:70:62</td>
<td>23</td>
<td>+15.1</td>
<td>99</td>
<td>6.7</td>
<td>100</td>
<td>670</td>
</tr>
<tr>
<td>4:25:30</td>
<td>10</td>
<td>64:53:44</td>
<td>20</td>
<td>+14</td>
<td>99</td>
<td>7.1</td>
<td>104</td>
<td>738</td>
</tr>
<tr>
<td>4:28</td>
<td>11</td>
<td>65:59:50</td>
<td>15</td>
<td>+12.5</td>
<td>102</td>
<td>5.5</td>
<td>100</td>
<td>550</td>
</tr>
<tr>
<td>4:32</td>
<td>517</td>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td>5.2</td>
<td>88</td>
<td>457</td>
</tr>
<tr>
<td>4:36</td>
<td>518</td>
<td>65:60:51</td>
<td>17</td>
<td>+10</td>
<td>99</td>
<td>6.5</td>
<td>76</td>
<td>494</td>
</tr>
<tr>
<td>4:42</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td>6.7</td>
<td>100</td>
<td>670</td>
</tr>
</tbody>
</table>

Time Marked by: 1/2 1/2 1/2 1/2 1/2 1/2 1/2
Table 31. - Experiment XXXI, Shown in Figures 45 and 46. Nitroglycerin 1/100 Grain (1/1000 gr. per pound) Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press</th>
<th>Pulse Press</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:23:30</td>
<td>1</td>
<td>90:68:51</td>
<td>39</td>
<td>+3</td>
<td>14.25</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>2:26</td>
<td></td>
<td>Nitroglycerin gr. 1/100</td>
<td></td>
<td>39</td>
<td>14.25</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>2:28:30</td>
<td>31</td>
<td>87:67:50</td>
<td>37</td>
<td>+3</td>
<td>14.25</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>2:30</td>
<td>32</td>
<td>87:64:50</td>
<td>37</td>
<td>+3.25</td>
<td>14.25</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>2:36:15</td>
<td>34</td>
<td>90:62:51</td>
<td>39</td>
<td>+3.75</td>
<td>15</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2:40</td>
<td>35</td>
<td>87:62:53</td>
<td>34</td>
<td>+3.75</td>
<td>13</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2:44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 32. - Experiment XXXII, Shown in Figure 47. Calcium Chlorid 1 c.c. (sol. 2.316 per cent) Injected into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
<th>Veloc. of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inj.</td>
<td></td>
<td>Max. Mean. Min.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:3</td>
<td>13</td>
<td>50:31:28</td>
<td>22</td>
<td>+11</td>
<td>3.7</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>2:10</td>
<td>D</td>
<td>1 c.c. 2.3 CaCl₂ sol.</td>
<td></td>
<td>+11</td>
<td>3.5</td>
<td>72</td>
<td>252</td>
</tr>
<tr>
<td>2:12:15</td>
<td>14</td>
<td>53:37:31</td>
<td>22</td>
<td>+11</td>
<td>4.2</td>
<td>68</td>
<td>285</td>
</tr>
<tr>
<td>2:14:30</td>
<td>15</td>
<td>54:37:31</td>
<td>23</td>
<td>+12</td>
<td>4.2</td>
<td>64</td>
<td>268</td>
</tr>
<tr>
<td>2:16</td>
<td>16</td>
<td>54:34:26</td>
<td>28</td>
<td>+10.5</td>
<td>3.2</td>
<td>56</td>
<td>179</td>
</tr>
<tr>
<td>2:20</td>
<td>17</td>
<td></td>
<td></td>
<td>+8.2</td>
<td>2.7</td>
<td>54</td>
<td></td>
</tr>
</tbody>
</table>
Table 33. - Experiment XXXIII, Shown in Figure 48. Calcium Chlorid 5 c.c. (2.316 per cent sol.) Injected into Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse</th>
<th>Toned</th>
<th>Plath.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:29:15</td>
<td>11</td>
<td>87:62:54</td>
<td>33</td>
<td>+2.7</td>
<td>119</td>
<td>3.7</td>
<td>132</td>
</tr>
<tr>
<td>1:31:30</td>
<td>F</td>
<td>5 c.c. CaCl₂</td>
<td></td>
<td>+2.7</td>
<td>119</td>
<td>3.5</td>
<td>123</td>
</tr>
<tr>
<td>1:35</td>
<td>12</td>
<td>87:59:50</td>
<td>37</td>
<td>+2.7</td>
<td>115</td>
<td>4</td>
<td>132</td>
</tr>
<tr>
<td>1:39:30</td>
<td>13</td>
<td>85:57:50</td>
<td>35</td>
<td>+3.2</td>
<td></td>
<td>3.9</td>
<td>123</td>
</tr>
<tr>
<td>1:44</td>
<td>G</td>
<td></td>
<td></td>
<td>+3</td>
<td></td>
<td>3.6</td>
<td>124</td>
</tr>
</tbody>
</table>
Table 34. - Experiment XXXIV, Shown in Figure 49. Potassium Chloride (6.31 per cent) 1 c.c. into the Superior Vena Cava following thirteen and one-fourth minutes after 5 c.c. Calcium Chloride.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:43:30</td>
<td>14</td>
<td>85:56:48</td>
<td>37</td>
<td>+3.1</td>
<td>129</td>
<td>3.75</td>
<td>124</td>
</tr>
<tr>
<td>1:44:45</td>
<td>0</td>
<td>85:54:48</td>
<td>37</td>
<td>+0.4</td>
<td>129</td>
<td>1.9</td>
<td>144</td>
</tr>
<tr>
<td>1:46:15</td>
<td>15</td>
<td>85:54:48</td>
<td>37</td>
<td>+3</td>
<td>125</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>1:47:5 (2'20&quot;)</td>
<td>15</td>
<td>84:53:47</td>
<td>37</td>
<td>+3.4</td>
<td>126</td>
<td>2.9</td>
<td>124</td>
</tr>
</tbody>
</table>

---

1:51
Table 35. - Experiment XXVI, Shown in Figure 51. Calcium Chloride Injected into the Superior Vena Cava, Following Sodium Citrate.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Tenus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:54:10</td>
<td>X</td>
<td>-14.6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3:55</td>
<td>A</td>
<td>-9.5</td>
<td>4.7</td>
<td>180</td>
</tr>
<tr>
<td>3:55:20</td>
<td></td>
<td>-9.5</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>3:55:26</td>
<td></td>
<td>-6</td>
<td>5</td>
<td>168</td>
</tr>
</tbody>
</table>

5 2 3 3 3 8

Before injected sodium citrate solution.

After injected 5 mg calcium chloride (3.6 mg).

After injected 5 mg calcium chloride (3.6 mg).
Table 36. - Experiment XXXVII, Shown in Figures 52, 53 and 54. Vagus paralyzed with Atropin. Calcium chloride 1 c.c. Injected into the External Jugular Vein, and Same Amount Later Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:42:15</td>
<td>F</td>
<td>100:59:47</td>
<td>53</td>
<td>-0.75</td>
<td>4.75</td>
<td>80</td>
</tr>
<tr>
<td>4:44</td>
<td>F</td>
<td>1 c.c. CaCl₂ ext. Jug.</td>
<td>-0.75</td>
<td>4.75</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>4:47:30</td>
<td>G</td>
<td>1 c.c. CaCl₂ sup. V.C.</td>
<td>-0.75</td>
<td>5</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>4:48:30</td>
<td>L</td>
<td>98:59:47</td>
<td>51</td>
<td>-0.75</td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>4:53</td>
<td>S₅</td>
<td>96:57:50</td>
<td>46</td>
<td>-0.75</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>4:58</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 37 - Experiment XXXVIII, Shown in Figures 55 and 56. Vagus Nerve Previously Paralyzed with Atropin Sulphate. Potassium Chlorid 1 c.c. Injected into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:58</td>
<td>12</td>
<td>96:57:50</td>
<td>46</td>
<td>- 0.75</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>5:3:15</td>
<td>13</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.6</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>5:4:15</td>
<td>5</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.5</td>
<td>4.6</td>
<td>76</td>
</tr>
<tr>
<td>5:7:15</td>
<td>5</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.3</td>
<td>4.4</td>
<td>76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>96:57:50</td>
<td>46</td>
<td>- 0.75</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.6</td>
<td>5</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.5</td>
<td>4.6</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>96:59:50</td>
<td>48</td>
<td>- 0.3</td>
<td>4.4</td>
<td>76</td>
</tr>
</tbody>
</table>

No. 2
Table 38. - Experiment XLII, Shown in Figure 60. Effect of Asphyxia.

<table>
<thead>
<tr>
<th>Time (min. sec.)</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Pulse Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:56:15</td>
<td>1</td>
<td>103:102:62</td>
<td>41</td>
<td>-11.9</td>
<td>118.5</td>
<td>4.3</td>
<td>138</td>
</tr>
<tr>
<td>12:59</td>
<td>D</td>
<td>110:102:62</td>
<td>-11.9</td>
<td>118.5</td>
<td>4.5</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>1:2:14</td>
<td>R</td>
<td>Increase Respiration before 12.8</td>
<td>119</td>
<td>5.2</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:2:14</td>
<td>S</td>
<td>75:68:59</td>
<td>16</td>
<td>-11.5</td>
<td>118.5</td>
<td>4</td>
<td>120</td>
</tr>
</tbody>
</table>
Table 39. - Experiment XLIII, Shown in Figure 62. Dilatation Produced by the Injection of 1 minim of Air along with 1/250 Grain (1/2562 gr. per pound) Strychnin Sulphate into the External Jugular Vein.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Tonus</th>
<th>Pleth.</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:20:15</td>
<td></td>
<td>79:41:31</td>
<td>+6</td>
<td>106</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>4:25</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>44</td>
</tr>
<tr>
<td>4:27:45</td>
<td>1</td>
<td>79:39:31</td>
<td>0</td>
<td>105</td>
<td>11.2</td>
<td>66</td>
</tr>
<tr>
<td>4:29</td>
<td>S2</td>
<td></td>
<td>+4.2</td>
<td>105.5</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td>4:36</td>
<td>S3</td>
<td></td>
<td>+9.5</td>
<td>104.5</td>
<td>8.5</td>
<td>80</td>
</tr>
<tr>
<td>4:38:15</td>
<td></td>
<td>78:60:53</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 2 6 3½ 3½ 2 2
Table 40. - Experiment XLIv, Shown in Figure 63. Formic Acid (4 minims 10 per cent, 1 1/2 minims 50 per cent, 5 minims 50 per cent) Injected, Followed by 1 minim Aconite.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Blood Press.</th>
<th>Mark</th>
<th>Drug dose</th>
<th>Injected</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:26</td>
<td>124:96:93</td>
<td>A</td>
<td>Formic Ac.+ 1/2 S.V.C.</td>
<td>-4.5</td>
<td>7</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>5:29</td>
<td>122:99:93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:32</td>
<td>122:96:93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:34</td>
<td>122:96:93</td>
<td>B</td>
<td>Formic Ac.+ 5/8 S.V.C.</td>
<td>-4.5</td>
<td>7.2</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>5:40</td>
<td>122:96:93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:41:50</td>
<td>134:115:100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:50</td>
<td>134:115:100</td>
<td>C</td>
<td>Formic Ac.+ 5/8 S.V.C.</td>
<td>-2.7</td>
<td>7.5</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>5:58</td>
<td>134:115:100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:0:20</td>
<td>140:124:108</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:58</td>
<td>140:124:108</td>
<td>D</td>
<td>Tinot. Aconite \1/2 S.V.C.</td>
<td>0</td>
<td>4</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>5:59:50</td>
<td>140:129:124</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:0:45</td>
<td>145:137:124</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:10:45</td>
<td>145:137:124</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:13:50</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:16</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:22</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:24</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:26</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:27:5</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:28:50</td>
<td>145:141:131</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S.V.C = Superior Vena Cava.
Table 41. - Experiment XLV, Shown in Figure 64. Two Injections of Tincture Aconite (1 minim and 5 minims) into the Superior Vena Cava.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mark</th>
<th>Blood Press.</th>
<th>Tonus</th>
<th>S.O.</th>
<th>Rate</th>
<th>Rate Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>4:39:10</td>
<td>8(1)</td>
<td>102:93:87</td>
<td>0</td>
<td>4</td>
<td>204</td>
<td>clamped carotid</td>
</tr>
<tr>
<td>4:44:30</td>
<td>E</td>
<td>Tr. aconite minim</td>
<td>+0.5</td>
<td>3.7</td>
<td>204</td>
<td></td>
</tr>
<tr>
<td>4:49:15</td>
<td>F</td>
<td>Tr. aconite minims</td>
<td>+0.7</td>
<td>3.7</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>4:51:30</td>
<td>↑</td>
<td></td>
<td>-1.7</td>
<td>5</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>4:54:15</td>
<td>8(2)</td>
<td>100:96:91</td>
<td>-1</td>
<td>4.5</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>4:55:15</td>
<td>S1</td>
<td></td>
<td>0</td>
<td>4.5</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>4:57:15</td>
<td>S2</td>
<td></td>
<td>+0.2</td>
<td>4.2</td>
<td>186</td>
<td></td>
</tr>
</tbody>
</table>
References.


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