EFFECT OF VARIOUS AGENTS ON THE BLOOD FLOW THROUGH THE CORONARY ARTERIES AND VEINS.[1]

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PLATES XLVII–LI.

Porter sums up the history of the early work on the coronary circulation as follows:

In 1689, J. Baptiste Scaramenci demonstrated that the vessels were squeezed during systole and filled in diastole. This view was supported by Stroem, in 1707, with the fact that the aortic valves close the coronary openings during systole. In 1855, Hyrtl stated that blood spurted from a cut coronary during systole, and his findings were confirmed by Perls, although they failed to mention which end of the vessel spurted. Klug, in 1876, ligated the vessels in diastole and systole and then coagulated the blood. He found a greater quantity present during systole.

This earlier work was followed by that of Chaveau and Rebatel who recorded the velocity of flow. They determined that there were two fillings, one in systole and one in diastole. Martin and Sedgwick, in 1895, showed that the pulse wave in the coronaries was synchronous with that in the carotid arteries, although they did not deny the possibility of a diastolic filling. In the same year, Martin observed the vagus control of vasodilation in the cardiac vessels.

With the introduction of perfusion by Martin, in 1890, there began a great deal of work concerning the effect of various factors on the coronary flow. Magrath and Kennedy, in 1897, demonstrated that the strength and not the frequency of the heart was dependent on the amount of coronary circulation. In the following year, Porter demonstrated that the flow is influenced by both the rate and strength of the heart beat. I. Hyde showed that distention of the ventricle diminished coronary flow. Pratt pointed

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out that the circulation was not entirely due to the coronary arteries, but was probably in part from the veins of Thebesius and retrograde flow in the coronary veins. Paul Maass established the nervous control of the coronary vasomotors, and showed that the dilators run in the sympathetic and the constrictors, in the vagus. Hedbom, in 1899, concluded that caffeine, atropin, and quinine act as dilators of the coronary vessels.

In 1903, Francois-Franck used the method of instantaneous photography of the superficial arteries of the heart. With amyl nitrite he found a marked vasodilatation.

O. Loeb in the same year worked out the effect of several drugs on the coronary arteries of the perfused heart as follows: strophanthus caused no change in coronaries or in flow; digotoxin gave a decrease in flow, and, therefore, must cause constriction of the coronaries; caffeine, theobromine, and diuretin caused no marked increase in flow; amyl nitrite in small doses had very little effect on the size of the coronary vessels.

Langendorff, in 1906, found that adrenalin gave only an uncertain effect on the coronaries in the perfused heart, while, in the following year, he demonstrated upon an excised strip of a large coronary artery that it produced, if anything, some dilatation of the vessel.

Wiggers, in a paper published in 1909, demonstrated by a special method of perfusion that adrenalin constricted the coronary vessels. By recording the outflow of blood from a wounded coronary vein of the living heart *in situ,* he also showed that stimulation of the vagus caused a diminished flow, and reasoned from this observation that diminished flow must be due to vasoconstriction.

It can be seen in this previous work that there is some confusion as to the results of various drugs. It is also probable that in the heart under normal condition, in contradistinction to the perfused heart, there are factors other than those affecting the heart which might be influenced by the drug. These in turn would affect the coronary flow. For this reason the results obtained with perfused hearts are not exactly comparable to those due to the action of the drug upon the blood supply of the heart *in situ.*

Francois-Franck's work was carried out under as nearly normal

conditions as possible, but his photographs show only the changes in the superficial vessels and do not deal with the blood supply of the heart muscle.

The experiments embodied in the present paper were begun at the suggestion and under the direction of Dr. A. D. Hirschfelder, in 1909, quite independently of the work of Wiggers and before his paper on coronary circulation was announced. The method employed was substantially the same as that which Wiggers had used for showing the circulation through the pulmonary artery. In this way any change in blood supply to the heart muscle could be demonstrated without regard to the various factors which might enter into its production. The experiments were performed on dogs, because their coronary veins are of sufficient size to be punctured readily and permit a slow dropping of blood from the wound.

The following procedure was adopted. The animal was anesthetized and kept alive by artificial respiration. Cutting away the chest wall as freely as possible exposed the heart in such a manner that there was no interference with the falling drops from the coronary vein. To record venous pressure a cannula was placed in the right auricle. The carotid pressure was noted by a Hürthle recording manometer. The animal was suspended face downward and the heart kept from dropping forward by fastening the apex to the base of the diaphragm with a long ligature. It was now necessary to make a small wound in one of the veins following the ramus descendens of the left branch of the coronary artery. The blood was allowed to drop from this opening upon a small mica plate fastened at an angle of 45° to a long lever of straw. The fulcrum of this lever rested on a tambour, so that each drop caused a movement of a recording lever.

Magrath and Kennedy have shown that the size of drops does not vary with differences in rapidity of flow or changes in strength or rate of the heart's contraction. Thus the number of drops furnishes a quantitative estimate of the flow.

There is no doubt that there is considerable shock entailed in the operation, but Wiggers has shown that the vasomotor action is still present in the coronaries after the same operation. We can assume, therefore, that it is still present in these experiments.

Pratt holds that some of the coronary circulation is a retrograde flow in the coronary veins. As we recorded the changes of pressure in the right auricle, we did not deem it necessary to ligate the vein above the point of injury.

At the beginning of these experiments, much trouble was caused by clotting in the punctured veins. To obviate this difficulty, the coagulability of the blood was previously reduced. Slowly withdrawing 250 to 300 cubic centimeters of blood, normal salt solution was simultaneously run in the femoral vein to an excess of 100 cubic centimeters. The latter compensated for the loss of blood during the operation. In some instances it was found necessary to reopen the vein occasionally. Periodical perfusions to replace the blood lost continuously at the coronary vein during experimentation soon eliminated entirely the factor of clotting. In practically no instance was any untoward result to the heart produced by the procedure, while in many instances the heart was greatly benefited, probably by the warmth and increase in quantity of circulating fluid.

All the drugs were given by hypodermic injection into the femoral vein. The order in which they were administered was constantly changed to rule out the factors of loss of vasomotor tone and the residue effect of other drugs. Normal tracings were taken before each drug for comparison. At the beginning of the work, those drugs were first chosen which were known to have the greatest effect on the vasomotor system. Adrenalin was used to represent the vasoconstrictor element, and for vasodilatation amyl nitrite and nitroglycerin were used.

Adrenalin.—The effects previously obtained with this drug have been somewhat contradictory. Schäfer could not produce any constriction, while Langendorff was even able to obtain a dilatation. Wiggers, on the contrary, demonstrated a marked vasoconstriction in an inactive heart.

In these experiments a fresh solution of 1 to 1,000 supradrenalin was used, doses varying from three to six drops being sufficient to produce a pronounced effect on the peripheral circulation. Twenty-five injections of this drug gave, on the whole, very uniform results. A typical chart is shown in Plate XLVII, Fig. 1 and Fig. 1 in text.

Following the introduction of the drug the marked effect on the peripheral circulation can be noted. A general increase in blood pressure with a primary decrease in cardiac output is followed shortly by increased strength of heart contraction and greater systolic output. The heart rate is, as a rule, only slightly affected. It

is slowed during the height of the effect of the drug, but may become more rapid as the blood pressure returns to its normal level. Simultaneous with the rise of arterial pressure, the flow through the coronary arteries, as judged by the number of drops, increases in volume. This increase follows the curve of arterial pressure, and

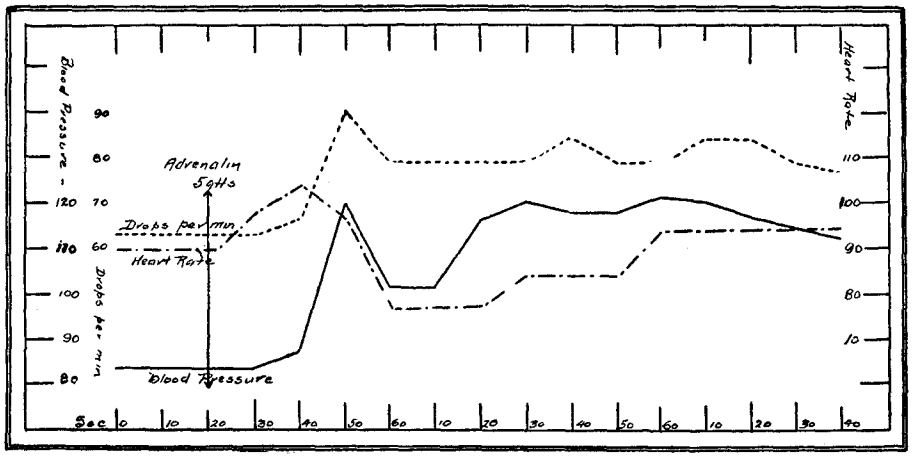


FIG. 1.

decreases gradually with its return to normal. In a few cases, simultaneously with the primary rise of blood pressure, there occurred a transitory slowing of the coronary flow, followed by a sudden increase. It might appear that in these instances the coronary arteries had entered into the general vasoconstriction. The number of such results was so few, as compared to those of opposite effect, that they hardly permit of any deduction.

The pressure as recorded in the right auricle usually showed a slight elevation, but this elevation did not begin until the blood pressure and flow had already reached their maximum. The increased outflow from the vein, therefore, cannot be attributed to a backflow from the veins, but must be considered as arterial in origin.

In the heart itself several things were noted which substantiate the graphic results. The organ changed to a much brighter hue and its contractions became stronger. The blood flowing from the wound, which had been dark, now changed to a bright crimson.

The flow increased in some cases to an almost constant stream, spurting with each ventricular systole.

From the results obtained, it can hardly be stated just what part vasomotor factor plays during the effect of adrenalin. It is evident, however, that either vasodilatation or constriction is of minor importance. The main element which here governs the blood supply to the heart is the condition of the peripheral blood pressure.

Adrenalin, from prolonged usage, has been shown to cause arterio-sclerosis and myocarditis. The deduction has been that the vasoconstriction of the coronaries caused an insufficient nutrition for the heart. These findings strongly oppose this view, because,

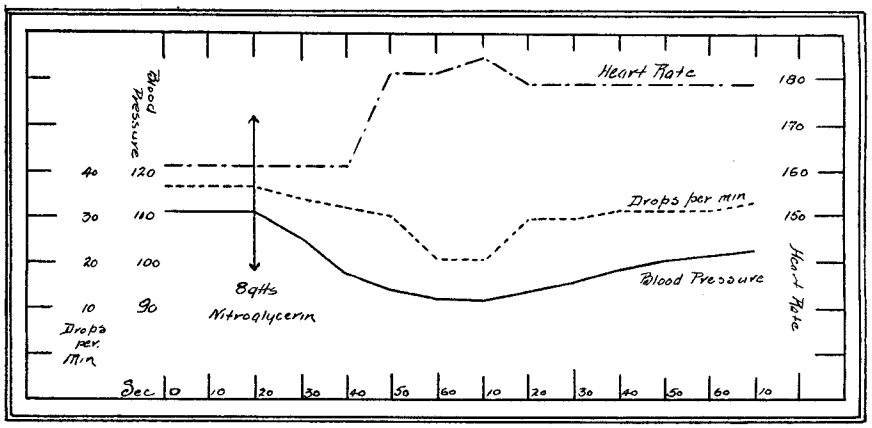


FIG. 2.

even with a certain amount of arterio-sclerosis, the increased blood pressure from the adrenalin should improve the nutrition of the heart muscle. The possibility suggests itself, however, that the resultant changes may be due to the increased circulation of the toxic product.

Nitroglycerin.—Fifteen experiments were performed with this drug. Injections were made slowly into the vein, and were continued in each case until after the administration of a sufficient dose there was a fall in peripheral blood pressure (Plate XLVIII, Fig. 2 and Fig. 2 in text). This decrease is greater in the minimal than in the maximal, so that the pulse pressure is increased through-

out. The frequency and strength of the heart's contractions remained practically the same during the experiment.

Coincident with this fall of blood pressure, the flow from the coronary vessels is diminished in amount and velocity. The latter follows a course quite parallel to the blood pressure curve, and both gradually return to their former height.

Although there was apparently some dilatation of the right side of the heart, there was little change in the pressure in the right auricle. Therefore, in this case a retrograde flow in the coronary veins need not be considered. In some instances where cessation of the heart beat took place, the venous pressure was markedly increased, but this increase never produced any effect on the coronary flow. The latter always diminished according to the decline of the curve of arterial pressure.

Amyl Nitrite.—The result of ten experiments with this drug show practically the same conditions present as with nitroglycerin. The effect, however, was somewhat more transient. We have decrease in the blood pressure with simultaneous slowing of the coronary circulation (Plate XLIX, Fig. 3 and Fig. 3 in text).

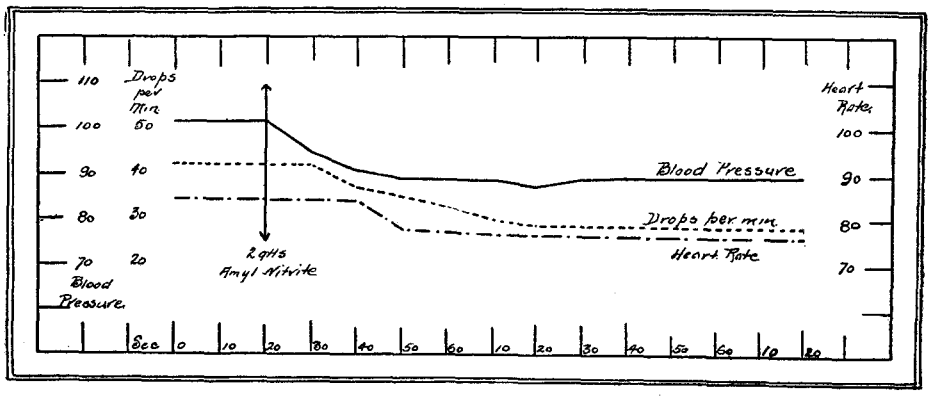


FIG. 3.

Where no other factors entered, in no instance was the retardation of the flow proportional to that obtained with nitroglycerin. This permits of two explanations. The toxicity of the drug was so great that only slight effects could be produced without injury

to the heart. Some effects, however, were comparable to those of nitroglycerin, and even here the change is not as marked. It is possible that with this drug there is present some vasodilation of the coronary vessels. This has been the common belief, though O. Loeb produced the opposite effect. The vasodilation, if present, was, however, not sufficient to overcome the results of the lowered peripheral pressure, and the blood supply to the heart was diminished.

The therapeutic value of amyl nitrite, in view of these findings, cannot be explained by the increased nutrition of the heart, as it has been generally supposed. It would be impossible to say without experimental evidence how great would be its effect on conditions of spasm of the coronary arteries. We can assume, however, from our results that considerable vasodilation would be necessary to counterbalance the effect of the lowered blood pressure.

Osler states that in anginal attacks there is usually a peripheral vasoconstriction and increased arterial tension. It would appear, therefore, that a large amount of the relief is probably obtained through the lowering of the general blood pressure and consequent lessened heart work.

Transfusion with Normal Salt Solution.—To obtain the effect of a simple increase in blood pressure, the flow was recorded during the slow injection of normal salt solution into the femoral vein. This produced a gradual rise in blood pressure, which, owing to the increased rate and strength of the heart, was manifested more in the arterial than in the venous system. As shown in the tracing (Plate L, Fig. 4 and Fig. 4 in text), there is a marked increase in coronary circulation. It begins at the initial rise of blood pressure and gradually increases as the pressure curve ascends.

The mechanical effect of the dilution of the circulating fluid might be given as a partial cause for the effect. It would operate in two ways: either causing an actual increase in the circulation, or an apparent one due to the change in size of the drops. It must be remembered, however, that the viscosity of the blood has already been lowered to about the consistency of salt solution to prevent clotting. The small change due to the added salt solution would, therefore, hardly show its effect.

Inhalation of Tobacco Smoke.—It has been the general belief

that nicotine as inhaled in tobacco smoke causes a constriction of the coronary arteries. This would decrease the blood supplied to the heart muscle. Lee devised a method by which tobacco smoke could be introduced by means of artificial respiration. With this method he demonstrated that its administration caused a rise in the peripheral blood pressure. This observation led us to believe that

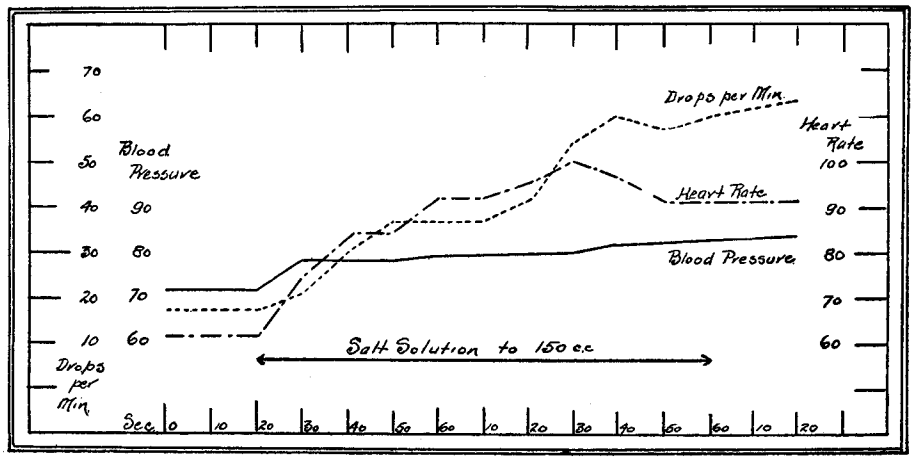


FIG. 4.

the blood supply is probably increased, and such proved to be the case in the few experiments we attempted (Plate LI, Fig. 5). Coupled with the rise of arterial pressure, the coronary flow showed a proportional increase. If there is any vasoconstriction, it is not sufficient to compensate for the results of the elevated arterial pressure. The blood supplied to the heart is, therefore, augmented by the inhalation of tobacco smoke rather than decreased.

Cardiac Stimulants.—Several other drugs that are supposed to have more or less of a selective action on the coronary vessels have been tried: digitalis, strophanthus, caffeine, strychnine, and theobromine in the form of agurin. After administration of all of these, however, we were unable to demonstrate any variations in the outflow from the coronary veins.

There are many factors which influence the coronary circulation. Magrath and Kennedy, as well as Porter, demonstrated that the

strength of the heart's contraction had its effect. Porter also showed that the flow was modified by the heart rate. In my experiments the strength rather than the rate seemed to produce the most marked results. Even this statement, however, has not an absolute foundation, because the increased strength produces a rise of blood pressure which may have been the cause of the variation in coronary flow.

It has been definitely shown that there is a vasomotor action in the coronary vessels. The influence of this action is probably present in all of the experiments, but appears most definitely in those with amyl nitrite.

These three factors are of importance, and under certain conditions probably exert a marked influence. But the main element which controls the coronary circulation is the arterial blood pressure. Its effects are sufficient to overbalance all the other influences. Thus the blood supply of the heart uniformly depends upon the pressure at the openings of the coronary vessels in the aorta.

Another phase is that shown by Langendorff, Paul Maass, and Magrath and Kennedy, namely, that both the rate and strength of the heart's contraction are dependent on the velocity of flow in the coronaries. This fact is very well shown in the results of both adrenalin and salt solution. After the increased flow is inaugurated, both the heart rate and strength are increased.

SUMMARY.

The results obtained show that adrenalin, transfusion with salt solution, and the inhalation of tobacco smoke caused an increased circulation in the coronary vessels. Amyl nitrite and nitroglycerin produce the opposite effect. Digitalis, strophanthus, caffeine, and theobromine give no change in the velocity of circulation.

We can conclude from the results that the blood pressure is the main element which influences coronary circulation, while the other factors play only a minor part in its variations.

In conclusion I wish to express my thanks to Dr. L. F. Barker for permission to work in his clinic, to Dr. A. D. Hirschfelder for his aid and suggestions, and to Dr. Elizabeth S. Hellweg for her valuable assistance in the experiments.

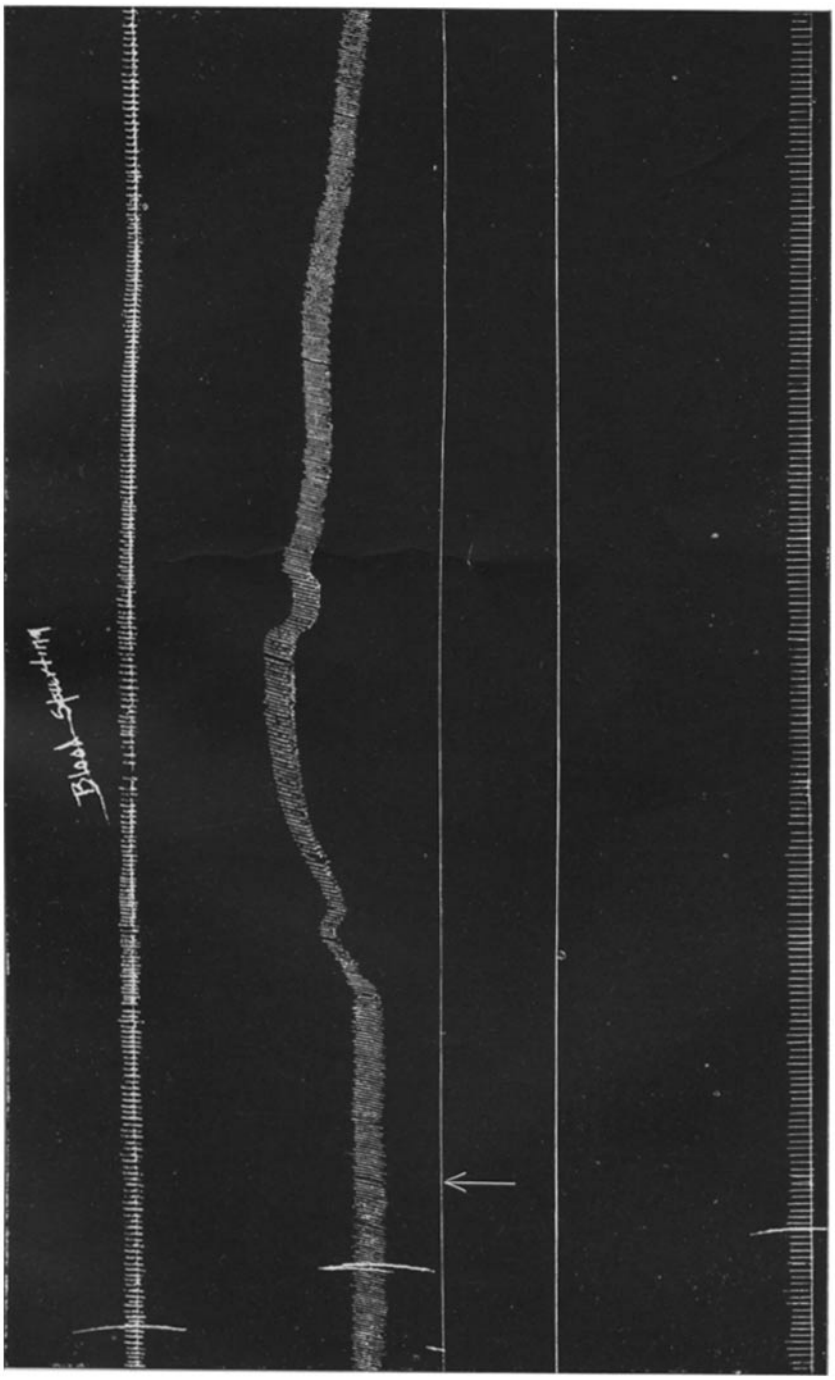


FIG. 1.

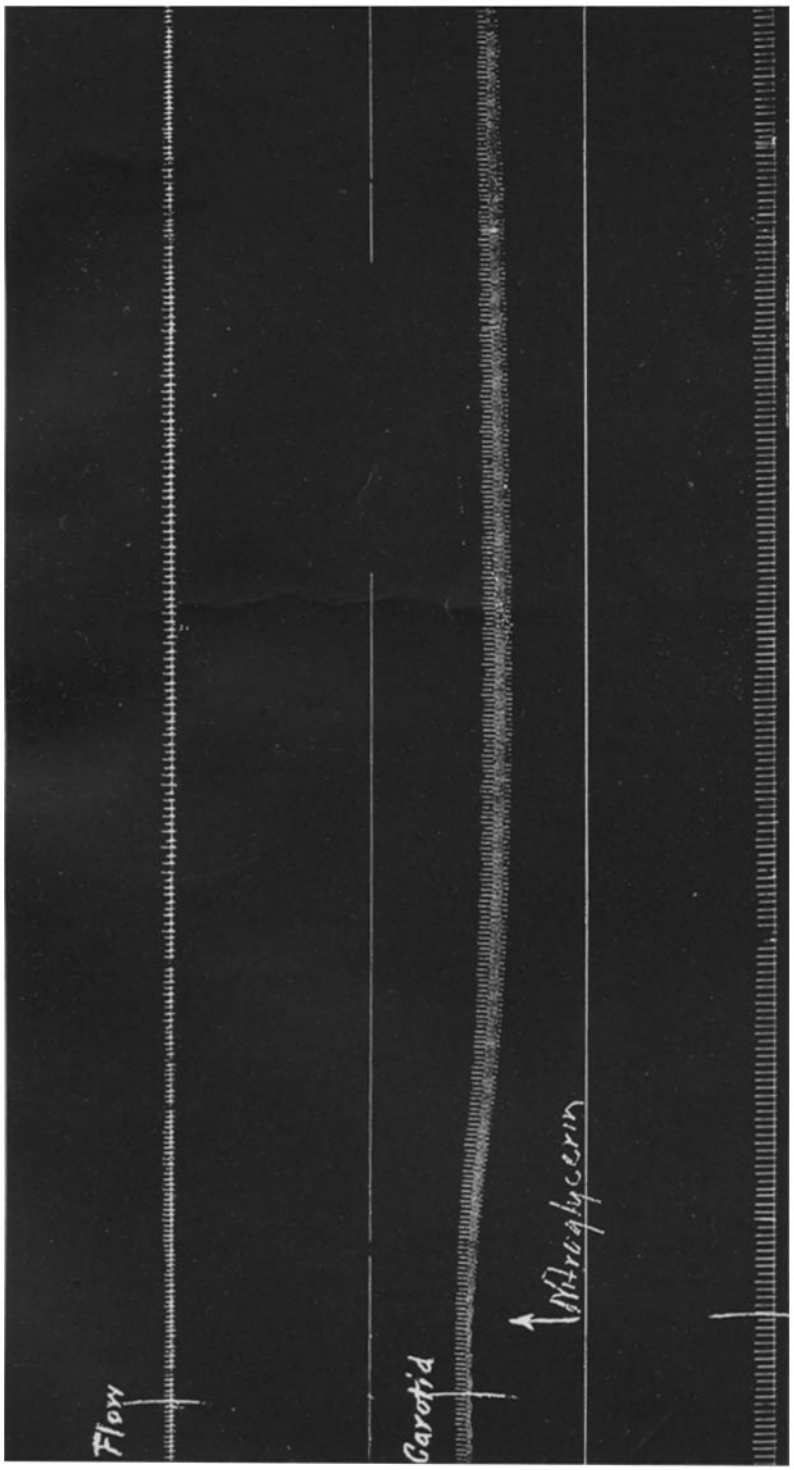


FIG. 2.

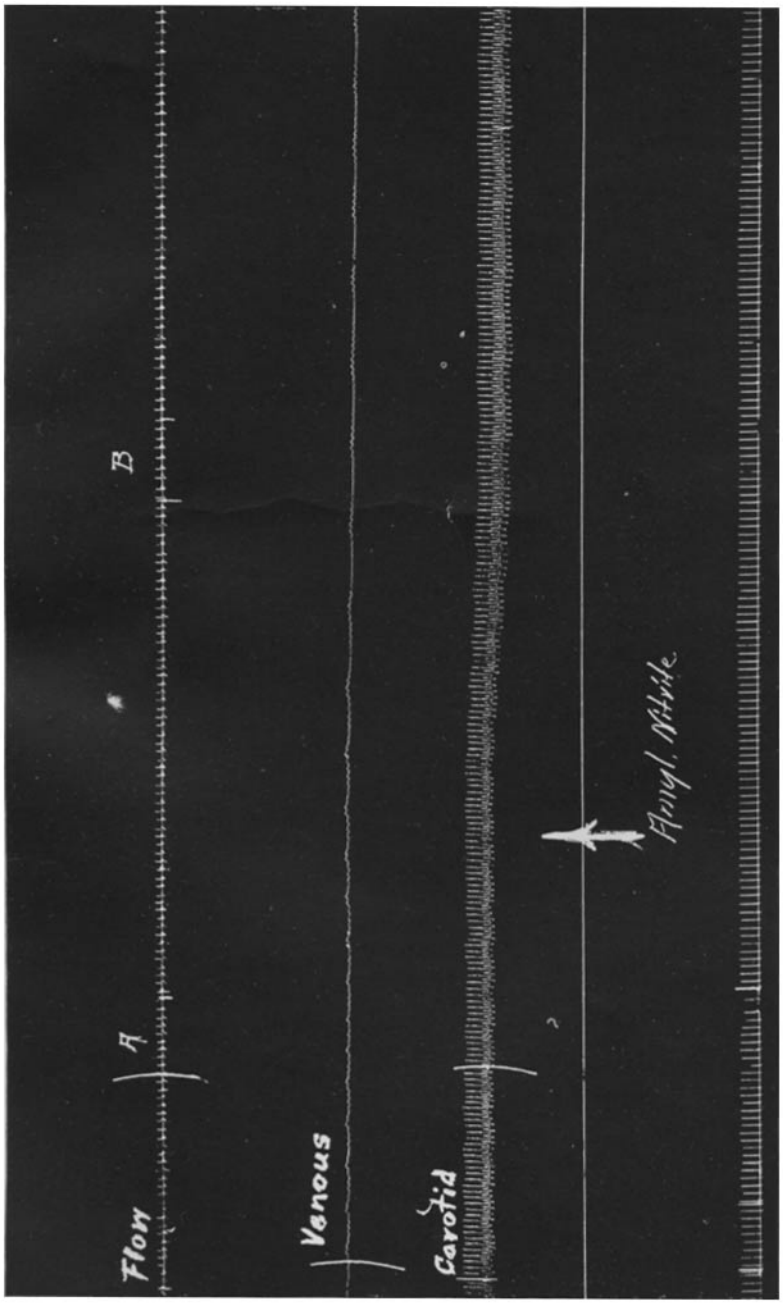


FIG. 3.

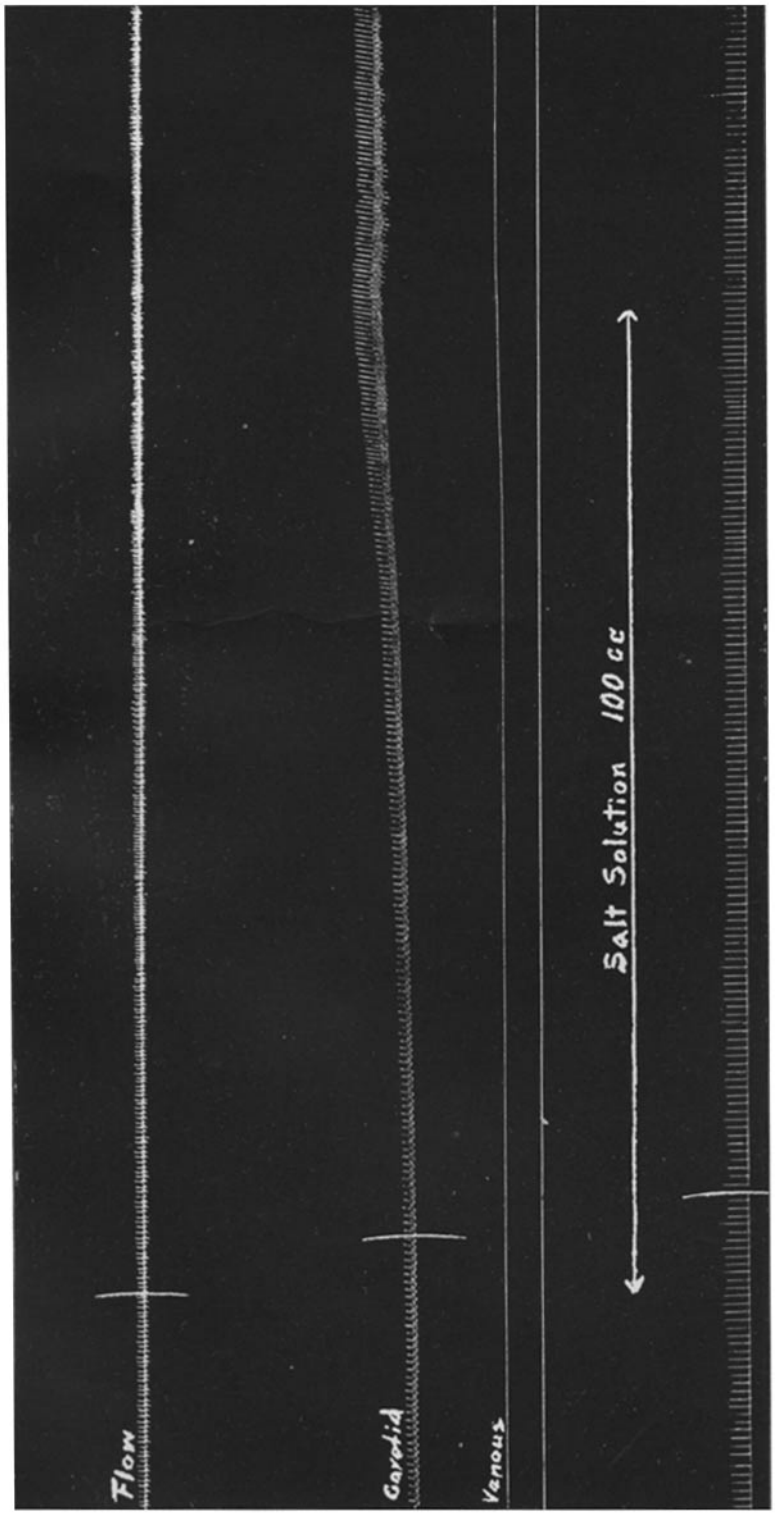
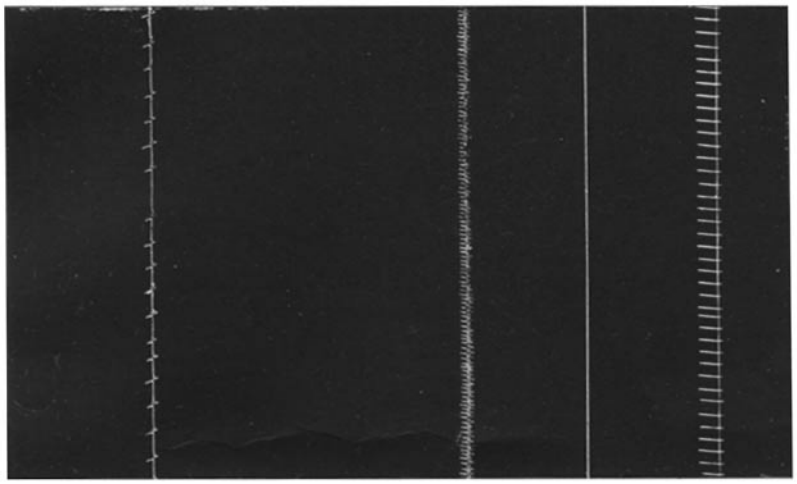
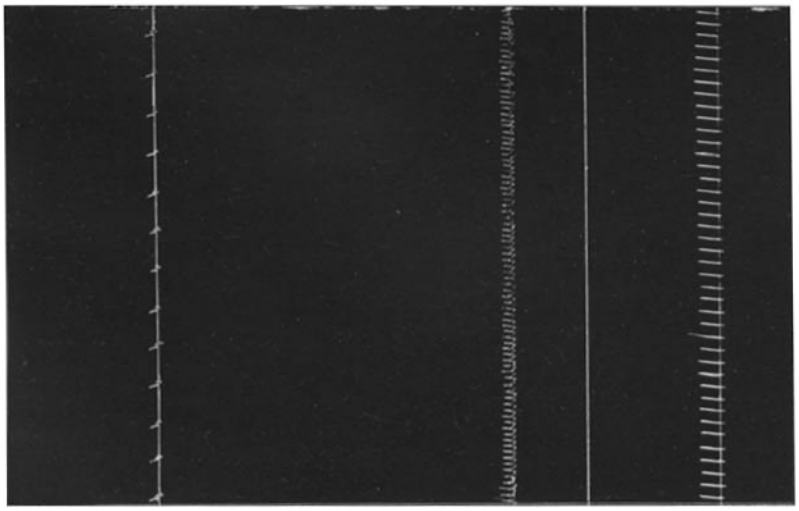


FIG. 4.



During inhalation.



Before inhalation.

FIG. 5.

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EXPLANATION OF PLATES

PLATE XLVII.

FIG. 1. The curves reading from above downward are: velocity of flow in drops, carotid blood pressure, pressure in right auricle. Base line represents time marked in seconds. Adrenalin injected at arrow.

PLATE XLVIII.

FIG. 2. The curves reading from above downward are: coronary flow in drops, pressure in right auricle, carotid pressure (Hürthle). Base line represents time marked in seconds. Nitroglycerin given at arrow.

PLATE XLIX.

FIG. 3. The curves reading from above downward are: coronary flow in drops, venous pressure, carotid pressure (Hürthle). Base line represents time marked in seconds. Amyl nitrite given at arrow. Flow at A, 59 drops per minute; at B, 48 drops per minute.

PLATE L.

FIG. 4. The curves reading from above downward are: coronary flow in drops, arterial pressure (Hürthle), venous pressure. Base line represents time marked in seconds. Arrow indicates the length of time consumed in the injection.

PLATE LI.

FIG. 5. Effect of inhaling tobacco smoke. The curves reading from above downward are: coronary flow in drops, arterial pressure (Hürthle). Base line represents time marked in seconds. The increase in arterial pressure is shown by the height above the base line. The coronary flow shows a marked increase.