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### A study of the relationship between blood flow and limb volume in the hind limb of the dog.

J. P. Holt

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UNIVERSITY OF LOUISVILLE .

A STUDY OF THE RELATIONSHIP BETWEEN BLOOD  
FLOW AND LIMB VOLUME IN THE  
HIND LIMB OF THE DOG

A Dissertation

Submitted to the Faculty

Of the Graduate School of the University of Louisville

In Partial Fulfillment of the

Requirements for the Degree

Of Master of Science

Department of Physiology

By

J. P. Holt

1938

Date June 4, 1938

Approved by

Committee: \_\_\_\_\_  
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English Department \_\_\_\_\_

A STUDY OF THE RELATIONSHIP BETWEEN  
BLOOD FLOW AND LIME VOLUME IN  
THE HIND LIMB OF THE DOG

### ACKNOWLEDGMENT

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J. P. Holt

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## INTRODUCTION



The view that the quantity of blood within the cranium is almost invariable was expressed as early as 1783 by Alexander Monro (1). He wrote, "for being enclosed in a case of bone the blood must be continually flowing out of the veins that room may be given to the blood which is entering the arteries. For as the substance of the brain, like that of the other solids of our body is nearly incompressible the quantity of blood within the head must be the same or nearly the same at all times, whether in health or disease, in life or after death, those cases only being excepted in which water or other matter is effused or secreted from the blood vessels; for in these a quantity of blood equal in bulk to the effused matter will be pressed out of the cranium." This doctrine was supported by Kellie (1) who found that animals killed by bleeding had as much blood in the brain as those killed in other ways. But if the skull was trephined and the animals bled to death, on post mortem examination the brain appeared empty of blood. He concluded that so long as the cranium was closed the volume of blood in the brain could not vary. The conception of the invariability of the volume of the intracranial contents came to be known as the Monro-Kellie doctrine.

Hill (1) studied the cerebral circulation and found that a foreign body of two or three cubic centimeters volume could

be added to the cranial contents of the dog without raising the intracranial pressure. The cerebral circulation was not changed with this added volume, presumably because cerebrospinal fluid was pushed from the ventricles into the spinal system, but if more than two or three cubic centimeters were added the venous sinuses were compressed, the cerebral capillaries were obliterated, the intracranial pressure rose, and the cerebral circulation was disordered. Bayliss, Hill, and Guiland (1) took simultaneous records of the general arterial, general venous, cerebral venous, and intracranial pressures and found no change in cerebral venous pressure on stimulation of the central end of the vago-sympathetic, the central end of the spinal cord cut at the level of the second to sixth dorsal nerves, and the cervical sympathetic nerve, that could not be accounted for by the change in general arterial pressure. They concluded that the cerebral circulation followed passively the changes in general arterial and general venous pressure, and in all physiological conditions a rise in arterial pressure accelerated the cerebral blood flow and a fall slowed it. No evidence for cerebral vasomotor nerves was found.

Wiggers (2) showed in perfusion of the brain that epinephrine caused a reduction in venous return. Finesinger and Putnam (3) measured the blood flow into the brain of cats and monkeys by pumping heparinized blood into the internal carotid

artery. The blood returned to the pump by way of the central end of the femoral or carotid artery. In this manner the perfusion pressure to the head was kept constant. They found that addition of epinephrine or pitressin to the perfusing fluid, or stimulation of the cervical sympathetic nerve caused a decreased flow into the head, while the addition of caffeine or histamine to the perfusing fluid, or stimulation of the central end of the vagus caused an increased flow. Gibbs and Lennox (4) measured the velocity of blood flow in the internal jugular vein in man using the Gibbs' thermo-electric blood flow recorder (5) and found an increased velocity of flow associated with increased carbon dioxide tension in arterial blood. They attributed this increase to an increase in the cerebral vascular bed.

While the volume of the cranial contents is relatively fixed, organs such as the spleen, kidney, limb, etc. are relatively free to change their volume. Oliver and Schafer (6) showed that an intravenously administered extract of the adrenal gland decreased spleen, kidney, and limb volume in the dog, and that it caused almost complete cessation of flow of the circulating fluid in the arterioles of the frog. Hoskins and Gunning (7) showed that intravenous epinephrine caused diminution of the volume of the limb of the intact dog and decreased venous outflow from the skin area. When the skin was removed,

epinephrine caused an increase in the volume of the limb and an increase in the blood flow from the muscles of the limb. The same investigators (8) working on the spleen showed a decreased volume and decreased venous outflow from the spleen following the administration of epinephrine intravenously. Richards and Plant (9) perfused the limb of the dog with hirudinized blood at a constant volume of flow from a perfusion pump and found that the perfusion pressure rose and the limb volume decreased when epinephrine was added to the perfusing fluid.

It is generally agreed that in organs whose volume is free to change, vasoconstriction, with reduction in the flow of blood, is associated with a reduction in the volume of the organ; and conversely, that an increase in volume flow is associated with an increase in the volume of the organ. Indeed, oncometry, or the measurement of organ volume, is a classical method for studying vasomotor changes (10). There is no agreement, however, on the essential relationship between the volume change in the organ and the vasomotor change. Since volume changes accompany vasomotor changes in most vascular beds, it may be argued that the two are inseparable. Most workers on the cerebral circulation, in their application of the Monro-Kellie doctrine, have implied that since the instantaneous volume of blood within the cranium is relatively fixed, the volume flow is governed only by the head of pressure, i.e., carotid blood pressure. The rich nerve supply to the cerebral vessels has been supposed merely to shunt

blood from one brain area to another, not to govern the total flow.

Since the work of Hill shows that considerable volume change can occur within the cranium without affecting total flow, the cerebral vascular bed cannot be considered a bed of constant volume. It was decided, therefore, to attempt complete fixation of the total volume in a peripheral vascular bed, for study of flow changes in the absence of volume change.

## METHODS

Dogs anesthetized with ether or sodium barbital were used. Blood flow was measured in one hind limb. Carotid blood pressure was taken with a mercury manometer. In the development of methods numerous unsuccessful experiments were done which are not reported here. Early attempts were made at fixing the volume of the limb by placing it in a plaster of Paris cast, and later by placing the limb and cast in a plethysmograph and applying negative pressures in the plethysmograph. It was thought that the negative pressure would draw the limb out against the cast and thereby immobilize it. The cast was found to be relatively nonporous so gauze was substituted for the plaster. Blood flow was measured by the direct method of venous outflow, the thermo-stromuhr method as modified by Herrick and Baldes (11), and by the use of a differential manometer as explained below.

The thermo-stromuhr was found to be unsuited to this problem as it showed a paradoxical increase in flow when the limb was constricted below the stromuhr. No satisfactory explanation for this paradoxical effect has been found.

The principle of the Venturi-meter has previously been applied to the study of the velocity of flow in blood vessels (12, 13). A glass Venturi-meter of the conventional type may be inserted into a divided artery, which, of course, requires the use of an anticoagulant; or an oblique ligature may be

thrown about the stem artery at the origin of a side artery. In the latter case the side artery originating in the constricted portion of the stem vessel, and another side artery originating above the constriction are cannulated and led to the differential manometer. Under these conditions the difference in pressure is a function of velocity in the constricted portion of the stem vessel.

As it is quite difficult to place an oblique ligature about an artery, and to keep it from slipping, it was decided to make use of the fall in lateral pressure which occurs across the constricted portion of a vessel as a measure of velocity. As an empirical comparison of the two methods a model was set up with water flowing through a system of rubber tubes past a constant constriction in the tubes. A side arm above the constriction was led to one limb of a differential manometer. In applying the Venturi principle, the other limb of the manometer was connected with a side arm leading off at the constriction. It was found that the pressure difference was actually slightly greater for a given flow, if the lower limb of the manometer was connected below the constriction.

The differential membrane manometer is a modified Pachon capsule (Fig. 1). It consisted of two tambours having their rubber membranes in apposition, with a light lever attached between the membranes. Each tambour was filled with five per cent sodium citrate solution and connected through citrate-filled



tubes to an arterial cannula; the upper tambour was connected with the carotid artery and the lower with the femoral artery. All side branches of the common iliac, external iliac, and femoral arteries were ligated down past the femoral trigone. With one femoral artery cannulated and led to the differential manometer, all the blood flowing past the bifurcation of the aorta thus passes into the opposite limb.

Although under certain conditions there may be considerable difference between lateral pressure in the carotid and the femoral artery (14), in the heavily barbitalized dog no difference was measured with our differential manometer. Furthermore, any slight difference in pressure was unrelated to the velocity of flow in the femoral artery, since no change in the differential pressure occurred on occluding the artery below the lower limb of the manometer. Such changes in carotid pressure as occurred spontaneously under our experimental conditions were evidently closely paralleled by femoral pressure, since the differential remained unchanged for periods of observation lasting fifteen to thirty minutes.

The difference in pressure between the carotid and the femoral artery may be expressed as:

$$H = \frac{flv^2}{d \cdot 2g}$$

where H is the loss of head, l is the length of the vessel, v is the velocity, d is the diameter of the vessel, f is a

Fig. 1

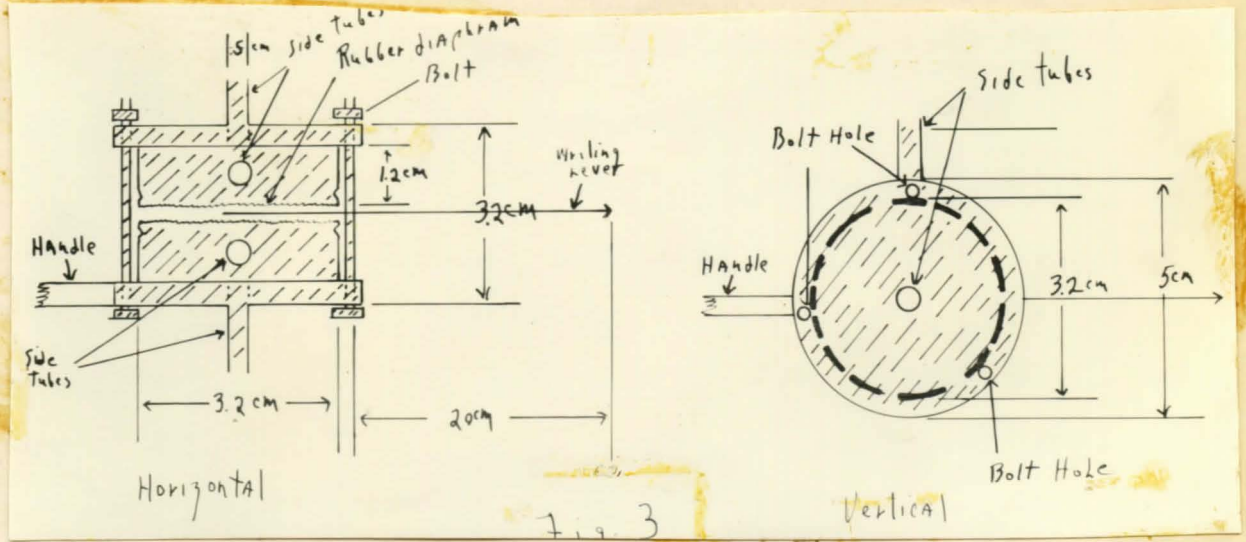


Fig. 3

The Double Membrane Differential Manometer

constant depending on the roughness of the walls, and  $g$  is the coefficient of acceleration due to gravity. The application of this formulation to the carotid-femoral differential pressure, however, is somewhat difficult, since neither velocity nor diameter are uniform throughout the intervening length of aorta. Without attempting a rigid formulation, it may be said that the loss of head between these two points is a function of the velocity of flow between the carotid and femoral. Our observations suggest that under our experimental conditions the loss of head due to such changes in velocity remains practically constant.

A constriction was placed on the aorta just above the bifurcation by tying a string around the aorta or applying a screw clamp. The ligature or clamp was tightened until pressure fell in the femoral artery between five and ten millimeters of mercury. This differential was immediately abolished by clamping the femoral artery below the constriction. If the femoral artery was opened and flow controlled with a screw clamp, the differential was found to be proportional to the flow. The flow meter was empirically calibrated in this way at the end of each experiment.

It is justifiable to assume that a constant differential exists between the carotid and the aorta just above the constriction, under the conditions of these experiments, and that

changes in the differential are due only to changes in velocity of flow through the constriction. Since all branches of the aorta and the iliac below the constriction are tied off except those supplying the leg, the differential thus reads velocity of flow into the leg.

The loss of head due to a constriction in a tube is given as:

$$H = \left( \frac{a}{a^1} - 1 \right)^2 \frac{v^2}{2g} \quad (15)$$

where  $a$  is the cross-section of the vessel,  $a^1$  is the diminished cross-section at the constriction, and  $v$  is the velocity of the unstricted portion. Since the cross-sections of the aorta just above and just below the constriction are practically equal, velocity above and below may be taken to be equal. Hence the loss of head caused by the constriction is accurately measured as the difference in lateral pressure above and below. It is clear, therefore, that the difference in lateral pressure on the two sides of the constriction is a function of the velocity of flow in the femoral artery.

## RESULTS

Two etherized dogs were given 300 mg. per kg. of body weight of the anticoagulant dye Chicago blue B 2. One hind limb was placed in a plaster of Paris cast which reached to about the proximal third of the femur. All branches of the common and external iliac arteries were tied, and all branches of the femoral artery as low as the lower third of the femur. The femoral vein was cannulated and the outflow measured. Section of the sciatic nerve increased venous return in each case. See Table 1.

A comparison of blood flow on the two sides (opposite leg not in a cast) showed that although the flow through the limb in the cast was greatly reduced (as much as one-twentieth) the percentage increase on section of the sciatic nerve was at least as great as in the limb which was not in a cast. The actual increase in flow, in c.c. per minute, however, was many times greater in the limb without a cast.

With the flow meter described above, the injection of nitroglycerine into the femoral artery, 2 c.c. of a 1/20 dilution of the U.S.P. spirits, caused an increased blood flow in the limb in the cast. The blood pressure was constant during most of the period of increased flow, but began to fall slightly as the flow returned to normal.

Since the volume of limb plus cast may have been changing, a plethysmograph connected to a volume recorder was placed over

the cast and sealed to the skin. Intra-arterial spirits of nitroglycerine caused an increase in flow without a recorded change in limb volume (Fig. 2). Since, if the cast were only difficultly permeable to air, small changes in volume of the limb within the cast might not have been transmitted to the volume recorder, negative pressures, of 145 to 170 millimeters of mercury were developed in the plethysmograph in the hope that the negative pressure would draw the limb out tight against the cast and thus fix the limb volume. Intra-arterial nitroglycerine, 2 c.c. of a 1/20 dilution of the U.S.P. spirits, caused an increased flow, and epinephrine hydrochloride, 1 c.c. of 1/50,000 solution, caused a decreased flow (Fig. 3). These drugs caused approximately the same change in flow whether negative or atmospheric pressure was in the plethysmograph. The plethysmograph was made air-tight at its junction with the skin by tightly wrapping a wire around the rubber end of the plethysmograph. The femoral artery and vein were protected from the pressure of the wire by a brass tube which was placed around them (Fig. 4).

The plaster of Paris was tested for porosity and found to be relatively non-porous. The limb may, therefore, have changed in volume in the above experiment if air pockets existed between the skin and the cast. It was thought that the limb volume might be fixed by wrapping the limb with porous but inelastic bandage, and exposing the wrapped limb to large negative pressures in the

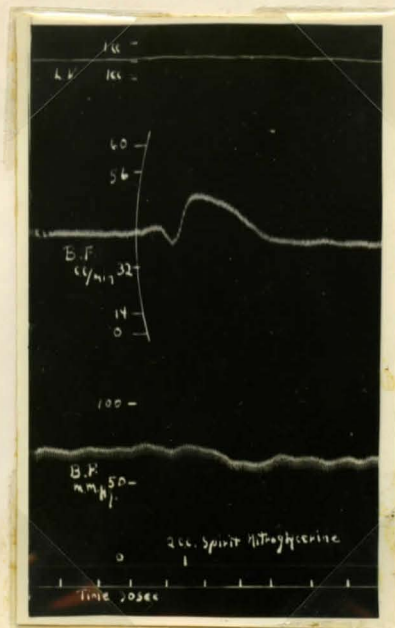
Table 1

	Flow in c.c.per minute before sciatic section c.c./ min.	Flow in c.c.per minute after sciatic section c.c./ min.	Percentage increase after sciatic section %
1 Limb in cast	9.8	12.7	29.5
2 Limb in cast	2.2	4.1	86.4
Control limb not in cast	44.4	70.7	59.2

The change in outflow from the femoral vein on section of the sciatic nerve in limbs with and without plaster casts.



Fig. 2

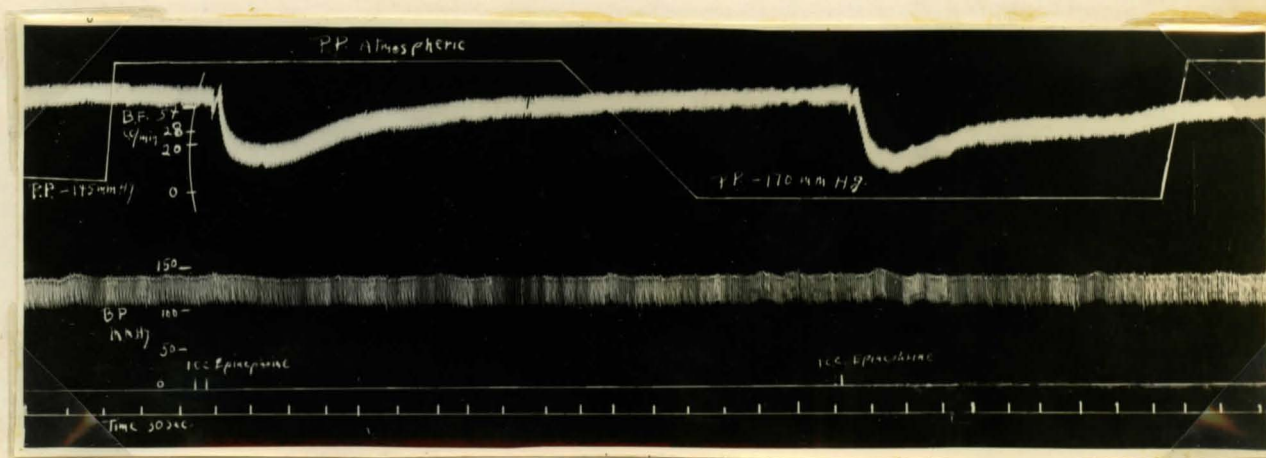


Limb in plaster of Paris cast with plethysmograph over the cast measuring volume change. L.V., limb volume. B.F., blood flow. B.P., blood pressure. Time in thirty-second intervals.

plethysmograph. If it could be assumed that the drop in plethysmograph pressure under these conditions produced no swelling of the leg, the force with which the surface of the leg was held to the bandage would be equal at least to the difference between atmospheric and plethysmograph pressure. If swelling occurred, and elastic tissues in the leg were stretched by the drop in plethysmograph pressure, the force with which limb volume was fixed would be the above less the elastic recoil of the stretched tissues. It was found in preliminary experiments that a reduction in pressure on the limb (without bandages) caused a definite, though at times temporary, increase in blood flow. With the leg bandaged, low pressure was applied at increments of minus 50 to minus 100 mm. of mercury, until no further change in flow occurred. It was assumed that this marked cessation of swelling. Pressure was then dropped approximately 100 mm. of mercury further (Fig. 5). At this time, the force holding the surface of the leg against the bandage should have been equal to an excess pressure of 100 to 150 mm. of mercury. This was equal to or greater than arterial pressure. Therefore, it was assumed that no change in leg volume would occur as a result of even maximal changes in intravascular pressure.

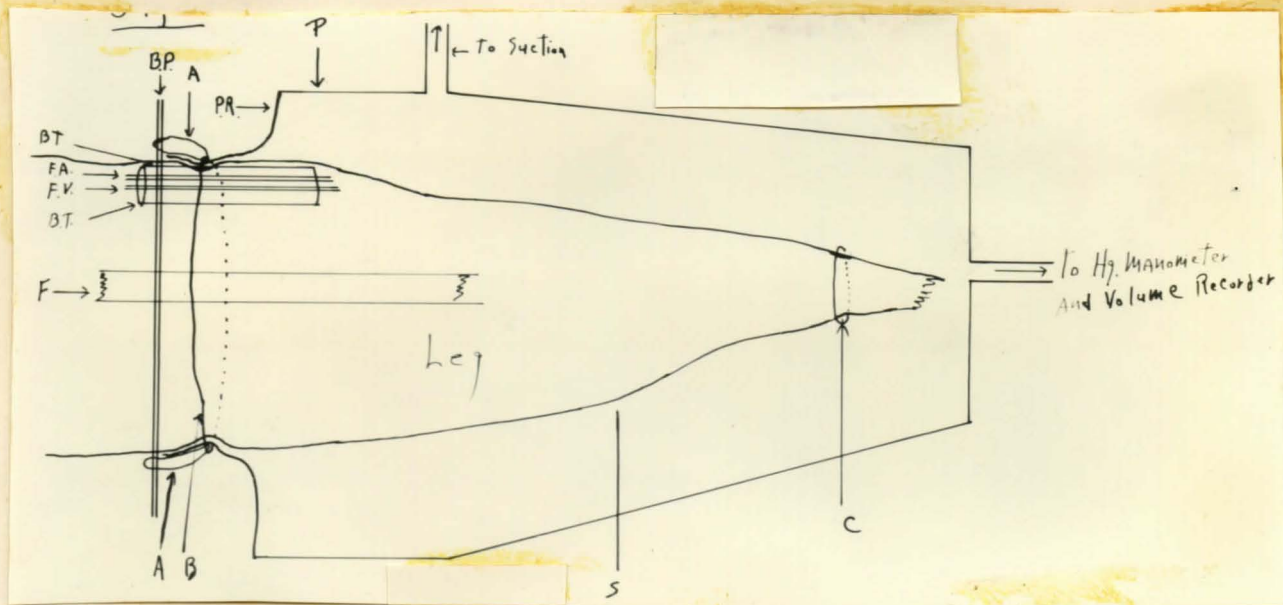
The changes in flow from intra-arterial epinephrine (Fig. 6) and spirits of nitroglycerine (Fig. 7) were essentially the same whether the bandaged limb was at atmospheric or at negative

Fig. 3



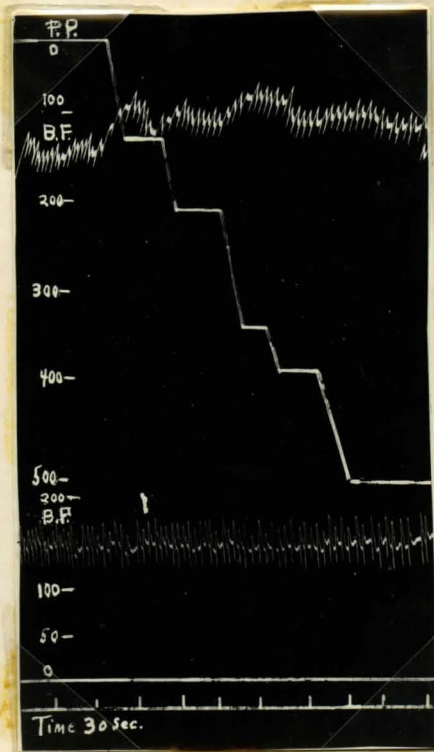
Limb in plaster of Paris cast with plethysmograph over the cast and negative pressure in the plethysmograph. P.P., plethysmograph pressure. B.F., blood flow. B.P., blood pressure. Time in thirty second intervals.

Fig. 4



Limb in a plethysmograph with a wire around the rubber end of the plethysmograph to make an air-tight seal. Brass tube, with a longitudinal slit in it, around the femoral artery and vein to protect them from the pressure of the wire around the limb. Bone pin through the femur anchoring the brass tube and wires which anchor the wire that is around the limb. P., plethysmograph. P.R., rubber end of plethysmograph. A., wire anchoring the wire that is around the limb to the bone pin. B.P., bone pin. B.T., brass tube. F.A., femoral artery. F.V., femoral vein. F., femur. B., wire around limb. S., skin. C., wire around foot.

Fig. 5



Limb wrapped with gauze and placed in a plethysmograph. The pressure in the plethysmograph is lowered in steps to minus 500 mm. mercury. B.F., blood flow. P.P., plethysmograph pressure. B.P., blood pressure. Time is in thirty second intervals.

pressure such as would be expected to fix limb volume. The negative pressure varied in different experiments between minus 300 and 500 mm. of mercury.

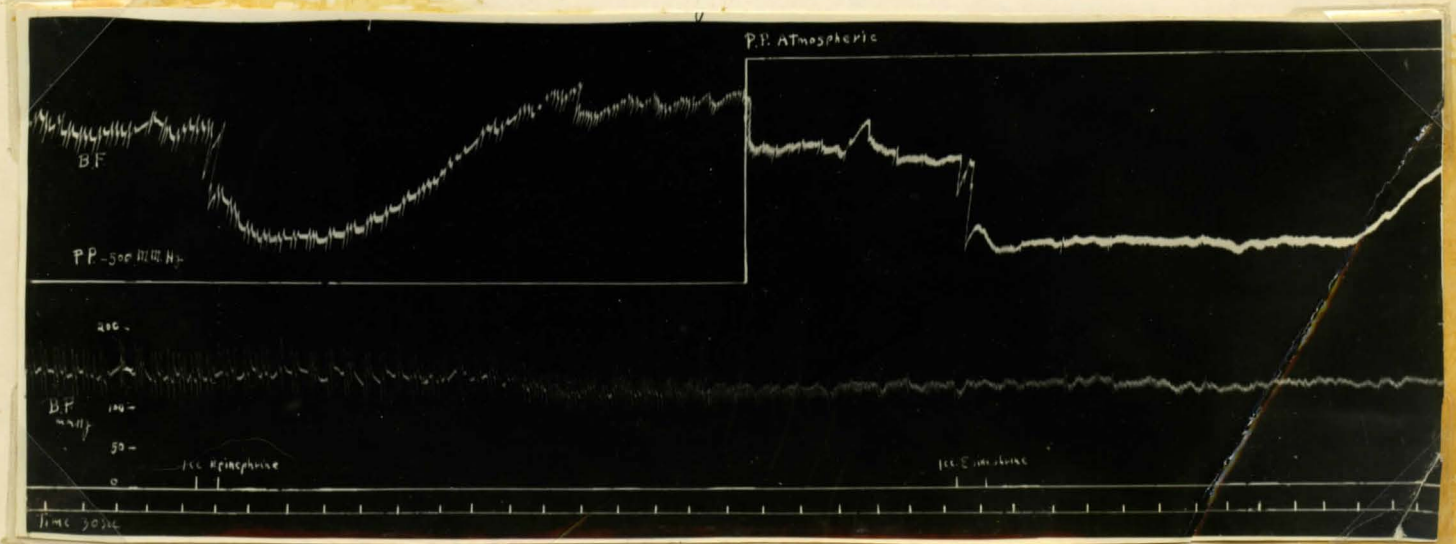
This demonstration is valid only if it can be assumed that there is actually an excess force fixing the leg against the bandage equal to or greater than blood pressure. Since there was no direct assurance that the leg plus bandage was ever fixed in volume, i.e., since the forces acting at the surface of the bandaged leg might still have been at equilibrium, the experiment was not considered crucial.

Attempts were made to measure the change in limb volume when epinephrine was given by weighing the leg. The leg, wrapped in gauze bandage and in a negative pressure plethysmograph, was amputated leaving only the femoral artery and vein intact. It was then suspended by a long spring balance which measured the weight accurately to 500 mg. Out of ten injections of epinephrine, nine gave no change or a slight increase in weight and one gave a decrease in weight. Since a simultaneous satisfactory record of blood flow was not obtained in a single case, these data, although suggestive, are not conclusive.

An attempt was made to measure the volume with the limb subjected to negative pressure. The limb was wrapped with gauze and placed in a water-filled plethysmograph connected by water-filled tubing to a mercury manometer. The open arm of the manometer was connected to a magnifying volume-recording tambour. Negative pressures were applied in the plethysmograph

and the plethysmograph calibrated by adding or removing 1 c.c. of water. The volume-recording system was found accurate to 1 c.c. or less. With the limb under a negative pressure of 260 mm. of mercury, intra-arterial epinephrine, 1 c.c. of 1/50,000 solution, decreased flow from 100 c.c. to 2 c.c. per minute (Fig. 8) with no change in limb volume. When the pressure was brought to atmospheric and the epinephrine repeated the blood flow fell from 135 c.c. to 2 c.c. per minute and the limb volume decreased 4 c.c. (Fig. 9). When the mercury trap was removed from the volume recording system, in order to prevent any pressure change in the plethysmograph due to a volume change of the limb, and the epinephrine repeated, flow decreased from 65 c.c. to 15 c.c. per minute and the limb volume decreased 8 c.c. (Fig. 10). Intra-arterial nitroglycerine, 2 c.c. of a 1/20 dilution of the U.S.P. spirits, with the limb under a negative pressure of 280 mm. of mercury, increased flow from 125 c.c. to 180 c.c. per minute with no change in limb volume (Fig. 11). When the pressure was brought to atmospheric and the nitroglycerine repeated, the blood flow increased from 110 c.c. to 160 c.c. per minute and the limb volume increased 1 c.c. (Fig. 12). When the mercury trap was removed from the volume recording system, nitroglycerine increased flow from 70 c.c. to 130 c.c. per minute and the limb volume increased 1 c.c. (Fig. 13).

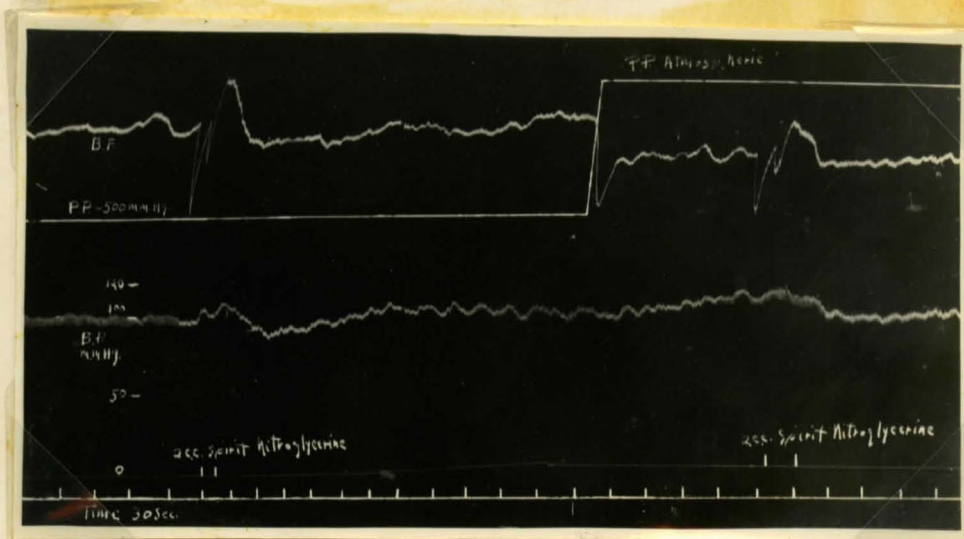
Fig. 6



Limb wrapped in gauze and placed in plethysmograph having negative pressures in it. P.P., plethysmograph pressure. B.F., blood flow. B.P., blood pressure. Time in thirty second intervals.

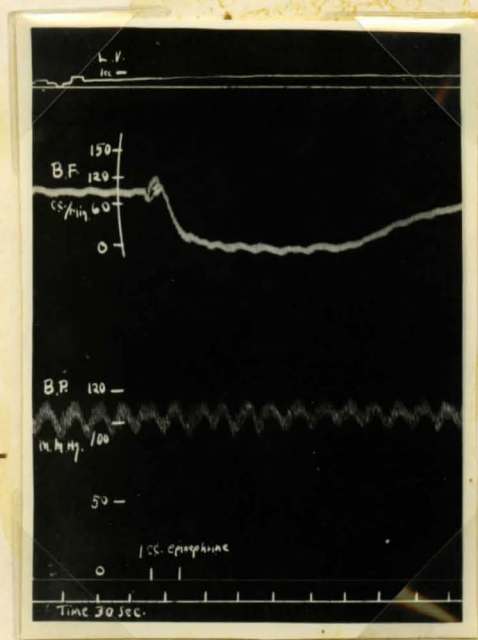


Fig. 7



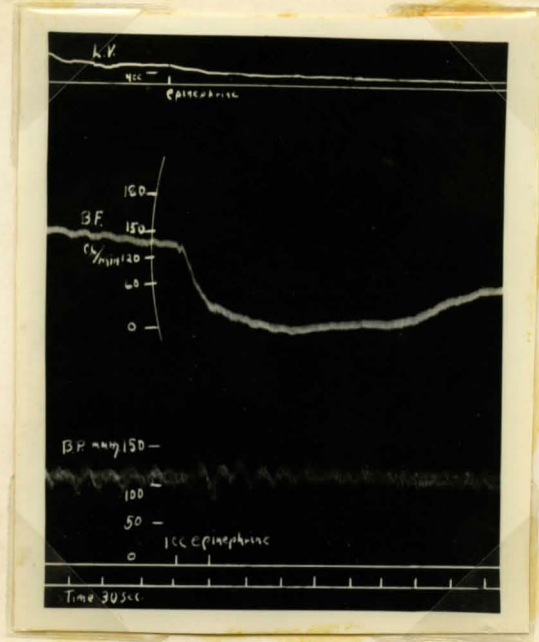
Limb wrapped in gauze and placed in a plethysmograph having atmospheric and negative pressure in it. P.P., plethysmograph pressure. B.F., blood flow. B.P., blood pressure. Time in thirty second intervals.

Fig. 8



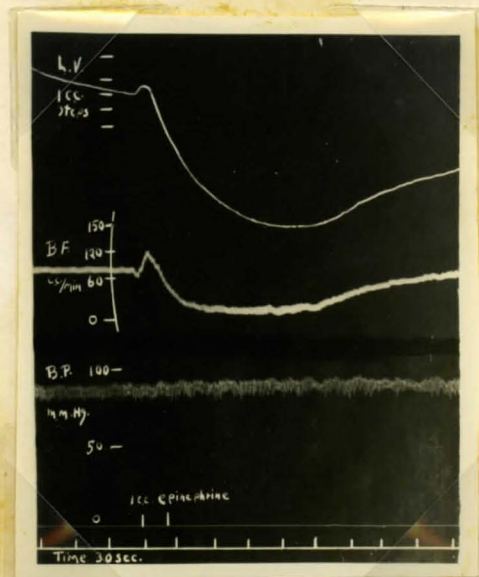
Limb wrapped with gauze and placed in a water-filled plethysmograph at a pressure of minus 260 mm. of mercury. For limb volume measurement see text. L.V., limb volume. B.F., blood flow. B.P., blood pressure. Time in thirty second intervals.

Fig. 9



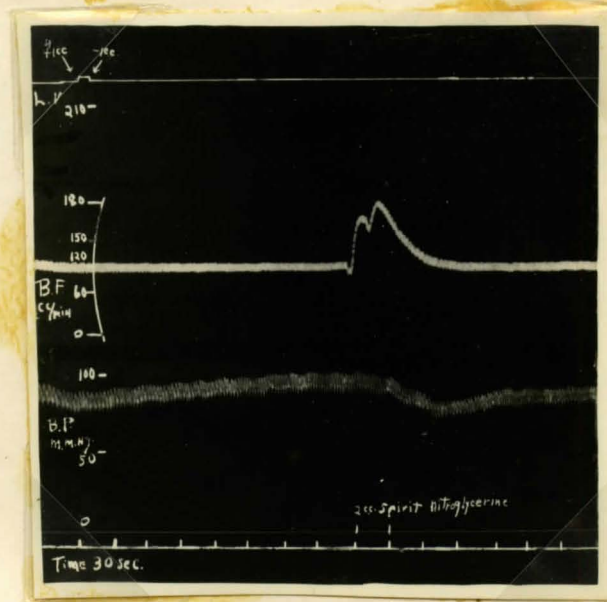
Same as Fig. 8 except that there is atmospheric pressure in the plethysmograph instead of negative pressure.

Fig. 10



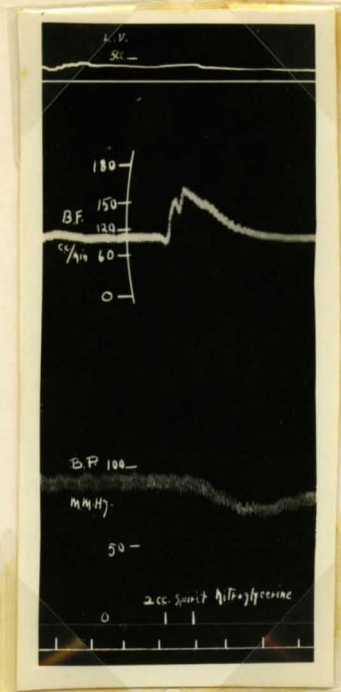
Same as Fig. 9 except that the mercury manometer has been removed from the volume recording system.

Fig. 11



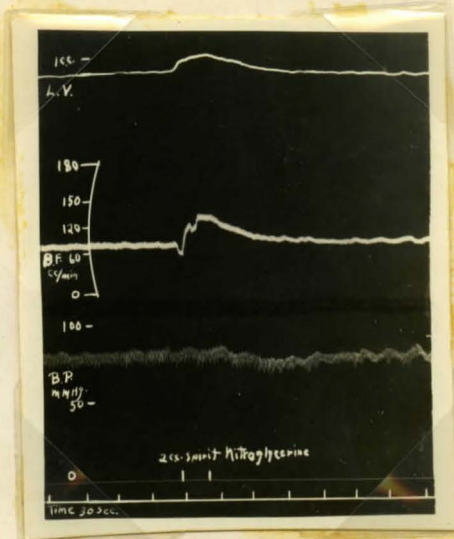
Limb wrapped with gauze and placed in a water-filled plethysmograph with a negative pressure of 280 mm. of mercury. B.F., blood flow. B.P., blood pressure. L.V., limb volume. Time in thirty second intervals.

Fig. 12



Same as Fig. 11 except that there is atmospheric instead of negative pressure in the plethysmograph.

Fig. 13



Same as Fig. 12 except that the mercury manometer has been removed from the volume recording system.

## DISCUSSION

The implications of the Monro-Kellie doctrine as applied to the cerebral circulation are that within the rigid-walled cranium the total volume of flow is determined almost, if not entirely, by the head of pressure. It is conceded by most workers on the cerebral circulation that velocity of total flow may be locally regulated by constriction of very short segments of vessels, probably arterioles, compensated by dilatation of others, probably veins. Data proving such mechanisms, however, are scattered and inconclusive. It was expected, in the limb with fixed volume, that such mechanisms for local control of velocity of flow would be active; the finding that such mechanisms are totally independent of the volume-changing mechanisms, however, was not expected.

It is generally believed that the local regulation of blood flow is primarily a function of the arterioles. Except in a few studies (9) no serious consideration has been given to the site of volume changes which normally accompany changes in blood flow. The data given here throw additional light on the latter question by suggesting that the segments in which the volume change occurs do not contribute significantly to the total peripheral resistance. If these data are accepted as showing that blood flow through the limb may change independently of limb volume and the head of pressure, it would seem that the fact that the cranial contents are relatively constant, as stated by the Monro-Kellie doctrine, is of little importance in

the regulation of the cerebral circulation.

A criticism of the data which cannot be definitely answered is that the negative pressure may have held the skin rigid against the gauze bandage and that gas may have been released in the tissues because of the negative pressure, or that air may have been drawn into the limb through the brass tube which was placed around the artery and vein. Under these conditions the contents of the limb may have changed in volume inside the skin by compressing or decompressing the gas, without change in the recorded limb volume.

The data on limb weights were expected to rule out this possibility. In nine cases intra-arterial epinephrine caused a slight increase or no change in limb weight, when the volume was fixed by this method. This was interpreted to mean dilatation of the arterial segment because of the injection, since control injections of saline gave the same effect. In no experiment, however, were satisfactory simultaneous records of blood flow and leg weight obtained. This possibility, therefore, will have to be investigated further.

This study has been confined to only two vascular drugs, epinephrine for vasoconstriction, and nitroglycerine for vasodilatation. In view of Gibb's data on the cerebral circulation, showing that epinephrine does not change the flow, whereas carbon dioxide does, it is important that a large series of constrictor and dilator effects be studied. It is possible



that, while with the two agents studied the effect on peripheral resistance and the effect on limb volume are independent, with other agents the two may be interdependent.

## SUMMARY AND CONCLUSIONS

(1) The blood flow through the hind limb of dogs anesthetized with ether or sodium barbital was measured by a differential manometer method.

(2) Intra-arterial epinephrine decreased, and intra-arterial spirits of nitro-glycerine increased the flow.

(3) The change in flow with these drugs was approximately the same with the limb free to change its volume and with the limb volume fixed.

(4) These data are presented as evidence that the blood flow through the limb can change with the limb volume remaining constant.

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