STUDIES ON INTRACRANIAL PRESSURE.[1]

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Plates XVI–XVIII.

The effects of a gradual increase of pressure within the skull cavity have been the subject of may physiological and clinical investigations. In the former, the effects upon the circulation, respiration, the motor phenomena of convulsions, reflex evacuations of the bladder and rectum and other attending phenomena, have been minutely analyzed by a number of observers. The more important of these investigations are reviewed in the works of Hill (1) and Cushing (2).

Cushing was the first to show clearly the exact effects of an increase of the intracranial pressure on the arterial blood pressure. This observer produced both local pressure on various portions of the brain and also general compression of the whole brain and cord by the inflow of fluid under pressure between the brain and brain membranes. He differentiated sharply between the effects produced by these two methods. Local compression of the brain produced symptoms which varied with the area upon which the pressure was directed, or with the portion or portions of the brain which suffer compression indirectly from displacement of the brain. In general compression, on the other hand, quite definite and constant effects upon the blood pressure and pulse rate were observed. These observations led to the formulation of a physiological law, namely that "an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted upon the medulla."

One of the present writers in 1905 undertook a study of intracranial pressure with especial reference to its effects upon respiration and the development of a periodic rhythm, or as it is commonly known, Cheyne-Stokes respiration (3), a condition that had been observed by Cushing and other observers in conditions of increased

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intracranial pressure. The present communication embodies some observations made in these experiments as well as in numerous later experiments.

The main object in the present work has been to gain a clearer insight into the conditions accompanying the blood flow through the brain in states of increased intracranial pressure. With this object in view, several series of experiments were performed as follows: (1) Measurement of the lateral pressure in the circle of Willis under various degrees of intracranial pressure, by connecting the central end of the internal carotid artery with a manometer [method of Hürthle (4)]. (2) Measurement of the cerebral venous outflow under intracranial pressure (*a*) from the torcula and (*b*) from the emissary veins, a constant inflow of Ringer's fluid or of defibrinated blood being maintained through the peripheral (cerebral) ends of the internal carotids. (3) Injections of the brain vessels under different relations between the intracranial pressure and blood pressure.

Intracranial pressure was increased by the method previously employed by Cushing. "General compression" was used in all experiments. A trephine opening was made over some portion of the skull and into this was screwed an accurately fitting brass canula. The dura under the opening was excised and the cortex laid bare. The canula was connected with a reservoir of the fluid used for compression (defibrinated blood, undiluted or diluted with Ringer's fluid, Ringer's fluid, physiological saline solution), and the amount of pressure exerted measured by a mercury manometer connected with a side branch. The remaining details of the procedure differed in the different series of experiments and will be described separately.

THE EFFECTS UPON BLOOD PRESSURE AND PULSE RATE OF A GRADUAL INCREASE OF INTRACRANIAL PRESSURE.

It will be well to consider here somewhat briefly the main effects upon blood pressure and pulse rate that result from a gradual increase of intracranial pressure. It was observed by Cushing that experimentally degrees of intracranial compression less than the mean blood pressure have little or no effect upon blood pressure,

pulse rate or respiration. In several experiments we have maintained such low degrees of compression for considerable periods. In one experiment an intracranial pressure of 120 millimeters (40 millimeters lower than the blood pressure) was maintained for over five minutes with no change in the carotid blood pressure, pulse rate or respiration. If the animal is lightly anæsthetized, lower grades of intracranial pressure may cause changes in the respiration and pulse rate, probably due to stimulation of sensory nerves of the dura.

When the intracranial pressure is increased to a point approximately equal to mean arterial pressure as measured in the cardiac end of the carotid or femoral, the first effect is usually a slight rise of blood pressure. This is succeeded in six to ten seconds by a fall of longer or shorter duration, which in turn is followed by a rise of the blood pressure above the line of intracranial pressure. Following the first rise of blood pressure, two effects upon the circulation are usually seen, acting in opposite directions as regards blood pressure, namely, vaso-constriction and decrease in pulse rate. The latter at first usually exceeds the former and following the preliminary rise there is usually a fall of blood pressure, though even at this time the effect of the vaso-constriction may be seen on the blood pressure curve, the pressure not falling to so low a point as would ordinarily occur with the slow pulse rate, or even rising in the interval between the slow heart beats. The blood pressure may now rise to above the intracranial pressure and to a point higher than that before the intracranial pressure was increased, even though the pulse is still much slower than normal. With the rise of the blood pressure above the intracranial pressure the vagus inhibition passes off to a considerable extent, though the pulse usually remains permanently somewhat slower. If the intracranial pressure is still further raised, the changes in blood pressure and pulse rate may be duplicated in every detail, and within a short interval the blood pressure may assume a new and higher level somewhat above the intracranial pressure. In this way enormous systemic pressures may be attained—mean arterial pressures of 230 millimeters of mercury, or even more. If the intracranial pressure is lowered at any time, a rapid fall of blood pressure follows, and if the former reaches zero, conditions as regards blood pressure and

pulse rate return usually to that present before the intracranial pressure was increased.

The decrease in pulse rate, as was shown by Cushing, is due to a stimulation of the cardio-inhibitory center in the medulla, since it is not present after section of both vagi. It seems to be due to an anæmia of the center, since it occurs also from ligation of the cerebral arteries (Eyster) (3). Stimulation of the cardio-inhibitory center in intracranial pressure may apparently result from at least two causes—anæmia, and a considerable and fairly sudden increase of blood pressure. The former is probably the one acting when the intracranial pressure is raised, and is especially interesting when seen under the condition, which is not infrequent, of blood pressure rising and falling in the form of vaso-motor waves above and below the line of intracranial pressure. With each rise above the line of intracranial pressure the inhibition may partially or completely disappear, to return as the blood pressure falls below the intracranial pressure. The first of these relations between the intracranial and the blood pressure results in an anæmia of the medullary centers, the latter in a fairly normal blood supply. The second cause of vagus inhibition in intracranial pressure, a sudden increase of blood pressure, is seen not infrequently when the blood pressure is suddenly lowered. The result of the sudden lowering of the intracranial pressure from a point above blood pressure to a point considerably below is a sudden flow of blood to the brain and a rapid increase of pressure. This may produce marked inhibition (Plate XVI, Fig. 1). If the arterial pressure in the circle of Willis is recorded simultaneously, a sudden sharp rise in this pressure is seen to occur, and this rise is coincident with the inhibition.

The vaso-constriction, as was shown by Cushing from the fact that it was absent after section of the cord or paralysis of the medulla with cocaine, is also central in origin. Cushing exposed a loop of the small intestines and observed paling of the vessels with the rise of blood pressure produced by intracranial pressure. He therefore referred the rise to splanchnic constriction. We have repeated this observation a number of times and the paling is frequently perfectly definite. We have furthermore recorded the volume of an intestinal loop, of a kidney and of a limb, and have

found that all undergo constriction. This constriction is preceded however in all three of these parts by dilatation, as may be seen in the records (Plate XVI, Fig. 2, Plate XVII, Fig. 3). As has been stated above, the first effect of increasing the intracranial pressure is usually a small rise of blood pressure. This has been spoken of as the preliminary rise in order to distinguish it from the marked rise that occurs later and which is due to vaso-constriction. This preliminary rise of pressure is not due to vaso-constriction, since at this time the limb, intestine and kidney all show an increase in volume. The effect of increasing the intracranial pressure to above blood pressure is to render the whole brain anæmic with the exception of the basal arteries, as injections under such circumstances clearly show, and the systemic pressure is probably increased as a passive result of this reduction in size of the circulation and the forcing of blood from the cerebral circulation into the systemic circulation. The preliminary increase of volume of limb, kidney or intestine may occur in some cases when the preliminary rise of systemic pressure is practically absent (Fig. 2), and usually the degree of dilatation is much greater than that produced by similar rises of systemic pressure at other times. This suggests the possibility of an active process concerned in the dilatation. Figs. 2 and 3 are records of the intestinal and renal volume, respectively, in increased intracranial pressure.

The condition of blood pressure waves rising and falling above and below the line of intracranial pressure is seen in Fig. 3, and this record shows that the renal volume in this case shows corresponding variations, constricting as the blood pressure rises and dilating as it falls. Similar changes of volume associated with the waves of blood pressure occur also in the intestines and limb. The changes in blood pressure are therefore due to variations in the degree of vaso-constriction. It was suggested in a previous paper (3) that these waves probably arose from rhythmic stimulation of the constrictor center due to the periods of anæmia of the center that result when the blood pressure is below the intracranial pressure. The center thus stimulated responds with a rise in blood pressure. As the blood pressure rises above the intracranial pressure, the stimulus is much reduced, owing to the fact that the center is again supplied

with blood. The activity of the center is thus lessened and a fall of blood pressure follows. The following period of anæmia as the blood pressure falls below the intracranial pressure causes another period of stimulation and the same process is repeated.

In certain cases there is no reaction of the vasomotor center to the stimulus produced by the anæmia when the intracranial pressure exceeds the blood pressure. No rise of blood pressure follows, or there may be a slight rise too small to cause the blood pressure to rise above the intracranial pressure. In other cases the center may respond when the intracranial pressure is first raised, while an attempt to obtain a higher level by the still further increase of the intracranial pressure may be unsuccessful. If the reaction is not obtained and the intracranial pressure is maintained above the blood pressure for several minutes, death of the animal results from the medullary anæmia. The pressure falls quite rapidly and reaches a very low point, followed after some time by the stoppage of the heart. If the intracranial pressure is lowered shortly after this fall begins, and especially if artificial respiration is begun, recovery frequently follows. That this fall of pressure is actually due to a relaxation of the vaso-constrictor center is shown by recording simultaneously the intestinal volume. In such an experiment the intestine is seen to undergo rapid dilatation accompanying the fall of blood pressure.

THE LATERAL PRESSURE IN THE CIRCLE OF WILLIS UNDER INTRACRANIAL PRESSURE.

The method of measuring the lateral pressure in the circle of Willis was that used by Hürthle (4) and others. All the branches of the common carotid artery in the dog were tied on one side with the exception of the internal carotid. A canula was now placed in the common carotid facing toward the head and connected with a manometer. Arterial pressure from the central end of the same carotid was also recorded as well as the pressure exerted by the intracranial fluid. All these manometers recorded on the same surface and all were referable to the same base line.[2]

[2] It was found to be necessary, in order to record the pressure from such a small artery as the internal carotid in the dog, to use some fluid in the manometer

If the intracranial pressure is gradually raised from zero to a point equal to mean carotid pressure, there is a gradual rise of circle of Willis pressure, which may be great enough to cause the two pressures to become approximately equal. When the intracranial pressure is gradually raised to a point slightly below mean carotid pressure and then lowered, the pressure in the circle of Willis may be increased to a level approximately equal to that of carotid pressure with little or no effect on the latter. An example of this is seen in Chart 1. If on the other hand the intracranial pressure is

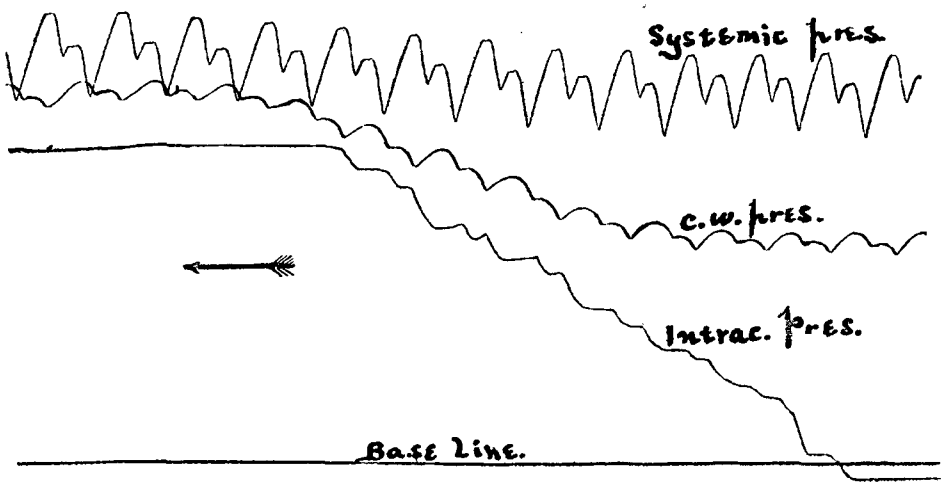

CHART 1. Increase of the lateral pressure in the circle of Willis with little change in the systemic (femoral) pressure from a gradual increase of intracranial pressure. The lowest line is the line of zero pressure for the intracranial, systemic and circle of Willis pressures. The kymographion was revolving at the rate of about 4.5 millimeters per second.

raised rapidly from zero to a point equal to carotid pressure, there is a rapid but small rise of pressure in the circle of Willis (Fig. 1). When the intracranial pressure rises above the carotid pressure, there begins a fall of circle of Willis pressure which, however, never reaches zero. The pulsations of the manometer in the circle of Willis are usually much reduced in size but do not disappear. If

and connections which does not have the marked vaso-constricting action of a saturated solution of sodium carbonate. Several of our first experiments were unsuccessful, due entirely to this factor. Sodium citrate (from 6 per cent. to 10 per cent.) proved entirely satisfactory.

the carotid pressure now rises, as is the usual result, the pressure in the circle of Willis rises very slowly until the carotid pressure becomes equal to the intracranial pressure and then rises much more rapidly as the carotid pressure becomes still greater. The pressure in the circle of Willis usually now becomes equal to carotid pressure. If the carotid pressure again falls below the intracranial pressure, or if the latter is raised above the carotid pressure, there is another fall of pressure in the circle of Willis, which again rises when the arterial pressure exceeds the intracranial pressure. If the intracranial pressure is lowered at any time, there is a sharp but short rise of pressure in the circle of Willis and then a fall accompanying the fall of carotid pressure. These various changes may be seen in Table I and in Plate XVI, Fig. 1, Chart 2 and Plate XVII, Fig. 4. Chart 2 shows the changes of pressure in the circle of Willis,

TABLE I.

No.	Intracranial pressure.	Femoral pressure.	Pressure in circle of Willis.	Pulse rate per min.	Remarks.
1	3	130	50	70	Intracranial pressure raised from
2	46	130	58	68	zero to above femoral pressure in
3	74	132	74	75	course of 54 seconds.
4	96	132	82		
5	120	146	81	73	"Preliminary increase" of femoral
6	146	145	60		pressure.
7	173	150	52	62	
8	173	91	22	20	Pulsations in C. W. small.
9	173	148	29	33	
10	173	160	32		9, 10 and 11 within 11 seconds.
11	173	173	34		Pulsations in circle of Willis in-
12	173	200	50	36	crease.
13	173	210	72		6 secs. after 12.
14	173	208	92		5 " " 13.
15	173	206	102		6 " " 14.
16	173	202	116	37	13 " " 15.
17	173	200	118		3 " " 16.
18	154	200	120		2 " " 17.
19	140	194	132		Rise of pressure in circle of Willis fol-
20	22	186	115	38	lowing fall of intracranial pressure.
21	15	170	90		19 to 21 within 15 secs.

carotid pressure and pulse rate that occurred in an experiment as the result of an increase of intracranial pressure.

These changes in the circle of Willis pressure under the influence of cerebral compression make it quite evident that an increase of intracranial pressure in the dog to a point above systemic pressure,

a condition which seems unquestionably to cause a complete absence of all circulation through the smaller vessels of the brain, does

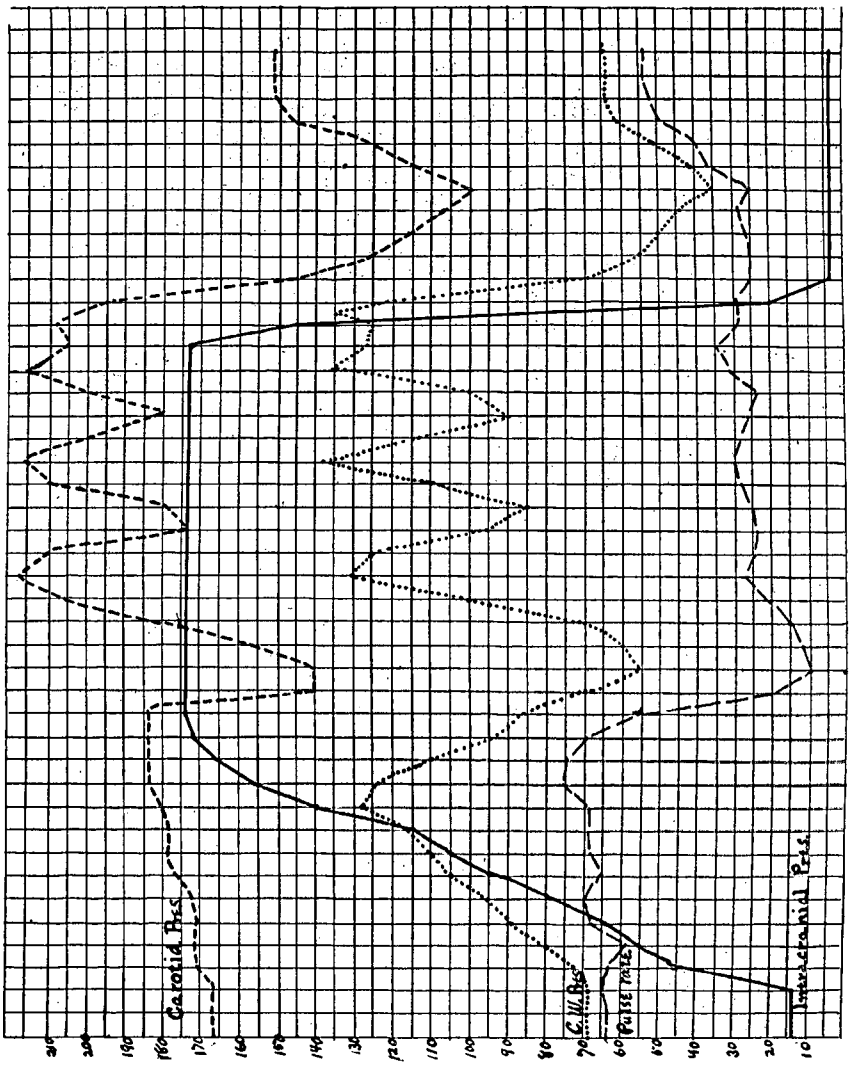

CHART 2. Chart from an experiment showing the changes of pressure in circle of Willis and in carotid after an increase of intracranial pressure. The abscissas represent time intervals of ten seconds, the ordinates pressure in millimeters of mercury and pulse rate per minute.

not cause a collapsed and bloodless condition of the circle of Willis nor a complete shutting off of this portion from the rest of the circulation. Direct observation of the cortical blood vessels through

a glass window fitted in the skull, at a time when the intracranial pressure is higher than the blood pressure, shows the presence of a complete anæmia of the capillaries and smaller vessels of the cortex. This observation was first made by Cushing and has been repeatedly confirmed by the present writers. Injections of the brain under these circumstances show also a complete anæmia. The circulation in the circle of Willis is however considerably affected under these conditions; the amount of blood that is received, as shown by the decrease in the size of the pulsations of the manometer connected with it, as well as by the pressure of this blood, are reduced. An interesting condition develops when the intracranial pressure is suddenly raised to a point far above carotid pressure. Under these circumstances there is a sudden sharp rise of pressure in the circle of Willis, which however is of small degree; there is little or no fall following, the pulsations cease entirely, and the whole picture shows that the circle is suddenly and completely clamped off from the rest of the circulation. It neither receives blood nor is there any flow of blood away from it either through arteries or veins.

The gradual increase of pressure in the circle of Willis when the intracranial pressure is slowly raised is probably due to a certain compression of the arteries as well as to a hindrance to the outflow through the veins. The fall when the intracranial pressure reaches carotid pressure may be explained by supposing that certain of the vessels entering the circle are clamped off, while the fact that the fall is not to zero and the pulsations do not entirely cease, is met by supposing that all of the arteries entering the circle are not thus occluded. With very high degrees of intracranial pressure, the results are such as would indicate a complete clamping off of the circle of Willis from the systemic circulation. The pressure does not fall but remains constant and there is an entire cessation of all pulsations of the circle of Willis. Injections of the brain under various degrees of intracranial pressure tend to support these suppositions in both cases, as will be shown later.

It is of some interest to compare the changes of pressure in the circle of Willis resulting from an increase of intracranial pressure with those caused by the actual ligation of the cerebral arteries. The results from one experiment of this kind are given in Table II.

TABLE II.[3]

Procedure.	Carotid Pressure.	Pressure in the Circle of Willis.	Amount of Fall of Pressure in Circle of Willis
Normal[4]	132	82	
Ligation of right carotid	140	64	18
Ligation of right vertebral	144	54	10
Ligation of left vertebral	154	22	32
Release of left vertebral	150	52	
Release of right vertebral	152	66	
Release of right carotid	140	82	

MEASUREMENT OF VENOUS OUTFLOW UNDER INTRACRANIAL PRESSURE.

The outflow from the cerebral vessels under artificial perfusion was measured in some experiments directly from the torcular, in others, from the emissary veins. The procedure may be best described by the following proctocol from an experiment:

Experiment of April 23, 1907.—Dog; morphia-ether anæsthesia; tracheotomy. Common carotids were dissected free to their bifurcation and the external carotid and all branches except the internal carotid ligated. Canulas were placed in the common carotids facing toward the brain. The two emissary veins were dissected down to their entrance into the skull, and canulas placed in them after ligating all branches between the point of entrance of the canulas and the emergence of the veins from the skull. The skull was trephined over the left temporal region and a brass canula screwed in and connected with the intracranial pressure apparatus. Ligatures were placed around the ascending aorta just above the heart and around the descending aorta near the diaphragm. All blood was washed out of the brain by running Ringer's fluid into the carotid canulas until the clear fluid emerged from the emissary veins. Death of the animal occurred at this point. The pressure of the entering perfusing fluid and of the exerted intracranial pressure were measured on the record by two mercury manometers. The outflow from the emissary veins was measured by a piston recorder which recorded on

[3] The pressure in the circle of Willis in this experiment falls from 82 to 22 millimeters of mercury following the ligation of the carotids, two vertebrals and subclavian arteries. As low a pressure as this is obtained in the circle of Willis in intracranial pressure only when there is very marked vagus inhibition with a considerable fall of systemic pressure, such as occurs in the experiment given in Table I. If pronounced slowing of the heart does not result, the fall of pressure in the circle of Willis from an increase of intracranial pressure above the systemic pressure is far less than that which occurs from ligation of the cerebral arteries. Thus, in Fig. 1, the fall was only from 40 to 30 millimeters in one case and from 40 to 36 in the other.

[4] The left carotid and the two subclavians had been previously ligated.

the same record. Measurement of the outflow was made under various relations between the intracranial and perfusion ("blood pressure") pressures.

The results from part of this experiment are given in Table III.

TABLE III.

The Perfusion Pressure Throughout the Experiment was Maintained at 96 Millimeters of Mercury. The Intracranial Pressure was Varied, as Shown in the Table.

No.	Intracranial pressure.	Outflow in c.c. per min.
1	30–166	3
2	172	2.2
3	172– 60	2.2
4	60– 40	2.7
5	40	2.7
6	30	3.0
7	30	3.3
8	18	5.3
9	130	5.0
10	190	2.1
11	190	0.3
12	18	1.5
13	18	2.7

In this experiment it is evident, with an intracranial pressure considerably above the perfusion pressure, that the outflow from the emissary veins is only slightly reduced below that present with an intracranial pressure considerably less than the perfusion pressure. Observation of the cerebral cortex as well as injections of the brain, show that under the former conditions the capillaries are completely occluded and free from blood or injection mass, not only on the surface of the brain but throughout the whole mass of the cerebrum, medulla and at least the greater part of the cord. It is therefore apparent, that with an artificial perfusion of the dog's brain through the internal carotid arteries, the whole capillary system may be entirely collapsed without decreasing to any considerable degree the outflow from the intracranial vessels as measured in the usual way from the emissary veins. With very high degrees of intracranial pressure relative to the blood pressure (190 millimeters in the preceding table) there is usually however a marked decrease in the amount of perfusing fluid flowing through the brain.

A number of experiments similar to the one described above have been performed with like results in all. In fact, the changes in

outflow as given in the table are greater than those usually obtained. The experiments in which the outflow was measured from the torcula gave similar results. In all experiments an increase of intracranial above the perfusion pressure produced none or an inconsiderable change in the outflow until the former pressure was approximately double the perfusion pressure.

A certain amount of the fluid used to increase the intracranial pressure escapes by way of the cerebral veins, and it is probable that in certain experiments this escape is sufficient to mask in some degree the decrease in flow through the brain that results from an increase of the intracranial pressure to above blood pressure. This loss of intracranial fluid is greater in some cases than in others, and its effects in extreme cases has been shown by the fact that a greater outflow from the emissary veins or the torcula occured when the intracranial pressure was above the perfusion pressure than when it was below it. The fact however that in many experiments there is no marked leakage of the intracranial fluid has been shown by a measurement of the outflow under intracranial pressure alone, in other cases by a direct measurement of the intracranial fluid lost during the course of an experiment, and in one experiment by measuring the inflow of the perfusing fluid into the carotids as well as the outflow from the veins. In several experiments the fluid for increasing the intracranial pressure was contained in a burette. The burette was connected on one side with the canula in the skull and on the other with the mercury pressure apparatus. In these experiments the leakage of intracranial fluid was too small to suppose that it masked to any considerable degree the reduction of outflow when the intracranial pressure was above the perfusion pressure. The results from one of these experiments are given in Table IV, and it is seen that if allowance is made for the loss of intracranial fluid the reduction in perfusion that results from an increase of the intracranial pressure above the perfusion pressure is inconsiderable. In this experiment defibrinated pig's blood was used for the intracranial compression, defibrinated dog's blood for the perfusion. The outflow was measured by a piston recorder.

TABLE IV.

Intracranial pressure.	Perfusion pressure.	Reading of intracranial burette.	Loss of intracranial fluid in c.c.	Period in secs.	Outflow in c.c.	Outflow in c.c. per min.	Corrected outflow in c.c. per min.[5]	Percentage of reduction of corrected outflow.
0	125	33.4		79	2.6	1.97		
140	125	33.4		176	5.2	1.71	1.61	18 per cent.
0	125	33.6	0.2	87	2.8	1.92		
0	165	34		115	2.5	1.30		
190	165	34		163	5.0	1.80	1.25	3 per cent.
0	165	35.6	1.6	107	3.8	2.10		
180	165	35.6		132	4.7	2.13	1.80	14 per cent.
0	165	36.3	0.7	102	4.0	2.35		
0	165	36.3		120	4.7	2.37		
160	0	36.3		50	0.165	0.20		
160	125	36.6	0.3	125	4.25	2.05		
0	125			92	4.1	2.67		

In one experiment the inflow of the perfusion fluid into the internal carotids was measured as well as the outflow. The results are given in Table V.

TABLE V.

Intracranial pressure.	Perfusion pressure.	Inflow into internal carotids in c c. per min.	Outflow from emissary veins in c.c. per min.
0	120	3.6	1.363
160	120	2.6	1.363
0	120	3.1	1.090
0	120	3.2	1.090
160	120	2.2	1.070
0	120		
0	120	2.8	0.818
150	120	2.0	0.818
0	120	2.7	0.800

An increase of the intracranial pressure to a point 40 millimeters above the perfusion pressure, a condition which, as shown by direct observation of the cortex and by injection, causes a complete occlusion and bloodless condition of all the capillaries of the brain,

[5] The loss of intracranial fluid during the period is subtracted from the total outflow and the result reduced to outflow in cubic centimeters per minute. Thus, when the intracranial pressure was increased to 190 millimeters, there was a loss of 1.6 c.c. of intracranial fluid in 163 seconds. The total outflow during this period was 5.0 c.c.; 1.6 subtracted from 5 gives a corrected outflow of 3.4 c.c. in 163 seconds or 1.25 c.c. per minute.

results in only a moderate decrease of the flow into the internal carotid arteries and of the outflow from the emissary veins. The outflow shows even less changes, a part being masked probably by a small leakage of the intracranial fluid.

Discussion of Results.—It seems quite evident from the results of the experiments described in the preceding pages that the method of perfusion of the dog's brain that has been used frequently in investigations on the cerebral circulation is open to grave criticism, since the whole capillary area of the brain may be completely collapsed with only a relatively small decrease in either the outflow or inflow of the perfusing fluid. This method as ordinarily employed consists in measuring the outflow from the emissary veins; the inflow, if the perfusion is an artificial one, is directed into the peripheral end of one or both of the common carotid arteries. Even if care is taken, as in all our experiments, to ligate all branches of the common carotids other than the internal carotids, the outflow from the emissary veins gives little or no indication of the condition of the cerebral vessels. This method has been used especially in the investigation of cerebral vaso-motor nerves, and as would be expected from the considerations presented above, has given rise to various and conflicting results. When the cerebral arterioles and capillaries are completely collapsed under a higher intracranial pressure than perfusion pressure, the change in outflow from the emissary veins is very small, and the dimunition in caliber which they would suffer as a result of vaso-constriction would probably not affect the outflow to any appreciable degree, certainly not sufficiently to warrant a positive conclusion.

So far as we are aware, only one investigator of cerebral vasomotors, namely, Wiggers, has realized the fact that the ordinary method of perfusion of the dog's brain is open to severe criticism because of the possibility of collateral branches and anastomotic connections. This observer therefore severed the head, removed the lower jaw and laid bare the basilar artery and circle of Willis by removing carefully the basal portion of the skull, and then ligated all branches except those passing to the brain. He was able to show quite marked changes in outflow caused by the action of drugs in the perfusing fluid. Adrenalin caused a decrease in the

outflow under these circumstances, and other drugs caused changes which indicate with considerable certainty the presence of vaso-motor nerves (5). Due to the rather extensive injury to structures lying near the base of the brain it has been difficult to employ this method for the study of cerebral vaso-motors by means other than the action of drugs. Wiggers has attempted, however, to show changes in the outflow occurring as an effect of stimulation of the sympathetic plexus on the carotid artery (6). His results, while suggestive of the action of vaso-motor nerves on the caliber of the blood vessels, are not entirely conclusive.

The same criticism applies to those experiments performed in the investigation of cerebral vaso-motor nerves in which the lateral pressure has been measured in the circle of Willis. The method as employed consists in the simultáneous measurement of the pressure in the circle of Willis by connecting a manometer with the peripheral end of the internal carotid artery and of the pressure in the systemic circulation. A rise of the former without corresponding change in the latter is regarded as evidence of constriction. It is quite evident that if there are several paths open to the flow, constriction in one of these will cause an increase of presssure proportionately to the degree of constriction and the importance of this path relative to the other paths. Now if that path, the changes in which it is desired to investigate, namely, the vascular system of the brain itself, may undergo total collapse, and yet the other paths be sufficient so that the total outflow is affected only in very small degree, it is hardly to be supposed that the ordinary degree of vaso-motor constriction or dilatation in this path would cause any appreciable change in the blood pressure in the afferent vessel which is common to this and other paths.

Our experimental results indicate therefore quite clearly that in perfusion of the dog's brain, the inflow being directed into the internal carotid arteries and the outflow measured from the emissary veins, the perfusing fluid passes in part through some other path or paths than that of the vascular system of the brain itself, and that this collateral path is sufficient to prevent marked changes in the blood vessels of the brain affecting the total outflow to any considerable degree. Our attention was now directed to a determination,

if possible, of these collateral paths and an attempt to obtain a complete or practically complete isolation of the brain circulation in the dog without the removal of the brain from its nervous connections or opening of the skull cavity. With this object in view we made injections and dissections of the head, both under normal conditions and under different relations between the intracranial and injection pressures. When the injection was made into the internal carotids with a mass, such as Berlin blue, that passes through the capillaries, at a time when the intracranial pressure exceeded the injection pressure, then, as under normal conditions, the mass emerged from the emissary veins and the lateral sinuses were found fully injected, although the capillaries of the brain were entirely uninjected. When a mass was used which does not pass through the capillaries, such as ultra-marine blue, under similar relations of intracranial and injection pressure to that above, it was observed that those branches of the common carotid artery besides the internal carotid, namely, the internal maxillary, posterior auricular and occipital, vessels which have no direct communication with the circle of Willis, were partially filled with injection mass. These vessels were ligated at their origin from the common carotid; their injection therefore must have occurred from a peripheral direction, and this is only explicable on the assumption that there is some collateral arterial connection, independent of capillaries and veins, between the internal carotid artery, on the one hand, and the internal maxillary, posterior auricular and other branches of the common carotid, on the other. This connection may be along the course of the internal carotid before it enters into the circle, or these arteries may form anastomotic connections with some one or other of the branches of the circle of Willis. In suitably injected preparations we traced the internal carotid artery carefully from its origin to its entrance into the circle, and found in all animals that we examined, five in number, a surprisingly large communication of this artery with the ophthalmic branch of the internal maxillary.[6] This branch

[6] In man the ophthalmic artery arises from the internal carotid artery within the skull. In the dog, it arises from the internal maxillary artery after its exit from the pterygoid canal. It breaks up into branches to the muscles, lachrymal gland and eye, and gives rise to a branch which anastomoses with the artery of the corpus callosum.

is described by Ellenberger and Baum (7) as follows: "The internal carotid artery . . . having passed through the dura mater gives rise to two small rami which anastomose in the cranial cavity with the middle meningeal artery. One of these (the internal ophthalmic artery of Bellarminow) leaves the cranial cavity by the orbital fissure and anastomoses with the ophthalmic artery."[7]

In the animals that we have examined, this connection in three was single; in two it consisted of several small arteries running together. The vessel when single is usually larger than the internal carotid artery outside of the skull, and from its size, and from the fact that the internal carotid is approximately twice the size above the point from which this artery connects with it, it is rather to be regarded in the animals that we examined as a branch from the ophthalmic artery joining the internal carotid artery immediately before it enters the circle of Willis. The internal maxillary artery in the dog is therefore probably to be regarded as a cerebral artery equal or almost equal in importance to the internal carotid itself.

This arterial branch connecting the internal carotid and the ophthalmic division of the internal maxillary, although lying in the greater part of its length within the skull, occupies such a position that it is in great part protected from any but excessive degrees of intracranial pressure. It passes along the base of the skull on the floor of the middle cranial fossa. This fossa is unusually deep in the dog and across its upper border there is stretched a thick and tense plate of dura mater. In all but very high degrees of intracranial pressure it probably suffers no compression, as is shown by the fact that the artery is always found well filled in injections made with an intracranial pressure moderately increased above the injection pressure. The injection mass passes up the carotid to the point where this artery pierces the dura immediately below its entrance into the circle, but beyond the point where the connection is made with the anastomotic branch. If the intracranial pressure is only slightly higher than the injection pressure, the mass may pass into the circle of Willis, which will show a more or less complete injection. With an intracranial pressure much higher than

[7] A similar anastomosis between the internal carotid and middle meningeal arteries has been described by de Vries (*Archiv de Biol.*, 1904, xx, 375).

the injection pressure—two or three times as great—the pressure is such as to stretch the roof of membranes covering the middle cranial fossa, the anastomotic connection is compressed and is found free from injection. It is suggestive to note that it is only by such high degrees of intracranial pressure that any considerable change in the outflow in the perfusion experiments occurs, and that the point at which this occurs is quite sharply marked. The relations and connections of this artery are shown in Plate XVIII, Fig. 6.

The ophthalmic branch from the internal maxillary artery with which this anastomotic branch or branches connect, is quite a large artery and offers a path for the flow of blood or perfusing fluid which may be regarded as only slightly less than the path through the circle of Willis. Returning from the capillaries of the contents of the orbital cavity, the eye and the surrounding muscles and tissues, are the large ophthalmic veins, frequently forming a well-marked sinus at the base of the orbital cavity, and emptying into the cavernous sinus. It is to be further noted that in all of our injections with the exception of those in which the intracranial pressure was excessively high, the contents of the orbital cavity showed a complete injection.

The venous sinuses of the skull receive blood not only from the cerebral veins, but also from the veins of the pia mater, the dura mater, from the bone (diploic veins) and from the eye (ophthalmic veins) (8). The system of diploic veins and sinuses in the dog are of considerable importance in draining the cerebral hemispheres. The superior cerebral veins, the principal venous trunks formed from the veins of the cerebrum, according to the work of Cushing (2), after their entrance into the dura, divide into two main branches, one of which enters into the parietal foramen and opens into the lateral diploic sinus, the other passes within the dura and opens into the sagittal sinus. Cushing further states that because of their large size and connections the diploic sinuses must be regarded as important outflow paths, and that indeed a greater portion of the venous outflow must occur by this path than by way of the sagittal sinus. These offer furthermore a communication between the veins of the head outside of the cranial cavity and the cerebral sinuses. Another possible path besides that through the

optic circulation is therefore through the internal carotid to the internal maxillary, to the extra-cranial regions supplied by the branches of this artery, through the capillaries into the veins, to the diploic sinuses and thence by the connections above described to the lateral sinuses and emissary veins.

ATTEMPT TO OBTAIN AN ISOLATED CIRCULATION IN THE BRAIN.

We attempted in five animals to eliminate the accessory paths described above. Theoretically this should be obtained by ligation of the anastomotic branch connecting the ophthalmic and internal carotid arteries. The operation necessary is a very extensive one and attended with great technical difficulty, and in only one of these animals did we obtain results which would indicate that we had succeeded and in which it was evident at the autopsy that we had ligated this connection on both sides. The great difficulty was due to the fact that the nature of our experiments precluded opening any portion of the skull cavity. If this could be done, the operation would be much simplified. The artery to be ligated emerges from the skull at the base of the orbit through a small foramen and within a space of several millimeters joins the ophthalmic artery. In the one successful experiment we isolated these arteries on each side from any connection except the internal carotid. A description of this experiment follows.

Experiment of June 2, 1908.—Large dog; morphia-ether anæsthesia. The common carotid arteries were dissected up to the origin of the internal carotid arteries and all branches with the exception of the internal ligated. The emissary veins were exposed on each side. The lower jaw was completely removed and the zygomatic processes were resected on each side. The temporal muscles were peeled back from their origin, the outer portion of each orbital rim was removed and the base of the orbit was carefully dissected. Ligations were then made of the internal maxillary artery immediately before its entrance into the pterygoid canal, and of the ophthalmic vessels at the base of the orbit. This isolated not only the anastomosis between the ophthalmic and internal carotid, but also the middle meningeal, which arises from the internal maxillary immediately before this artery passes into the canal. Canulas were placed in the common carotid arteries facing toward the head and in the emissary veins. A trephine opening was made over the temporal region and a brass canula screwed in for the production of intracranial pressure. The dog was bled to death through the central end of one carotid; the blood was defibrinated, mixed with an equal volume of Ringer's fluid and used for perfusion. Undiluted defibrinated

dog's blood was used for the intracranial pressure. The inflow into the carotids, the loss of intracranial fluid and the outflow from the emissary veins were measured, the last by means of a piston recorder, the two former by means of burettes according to the method previously described.

The results from this experiment are given in Table VI, and in Plate XVII, Fig. 5.

TABLE VI.

No.	Perfusion pressure.	Intracranial pressure.	Inflow into carotids in c.c. per min.	Outflow from emissary veins in c.c. per min.	Loss of intracranial fluid.
2-3	130	0	1.6	1.0	
3-4	130	180	0.25	0.59	0
4-5	130	0	2.6	1.363	
5-6	130	170	0.3	0.545	0
6-7	130	0	1.35	0.954	
15-16	120	0	2.2	1.000	
16-17	120	180	0.5	0.681	0
17-18	0	180	0.0	0.454	0
18-19	120	0	2.3	0.612	

The amount of outflow in this experiment was reduced about fifty per cent. when the intracranial pressure was higher than the blood pressure. The reduction in the inflow through the carotids was much more marked, amounting to from one-fourth to one-eighth of the original flow in the examples given in the table. This would indicate that while the cerebral circulation was not completely isolated in this experiment, it was much more nearly so than in any of our previous experiments, and that the inflow, at least under these conditions, should show changes with any considerable change in the caliber of the cerebral arterioles. Of the other probable open paths, we have no indication from our experiments.

The outflow, as given in the table for the periods of compression, gives the average from the instant of increase of intracranial pressure until it was lowered. Reference to the figure will show that this does not give the whole state of affairs. The outflow at first is only slightly decreased; later a considerable decrease occurs and if the pressure is kept up for several minutes the outflow almost entirely ceases. Why the inflow should suffer a sudden and great reduction and a similar change in the outflow develop only gradually is not at present clear.

INJECTIONS OF THE BRAIN UNDER DIFFERENT RELATIONS BETWEEN THE INJECTION PRESSURE AND THE INTRACRANIAL PRESSURE.

Similar experiments to the ones we have performed have previoulsy been made by Cushing (2), and his results may be first summarized as follows:

Effect of Local Compression.—This study may be carried out in two ways: either the injection mass may be allowed to enter and then local pressure exerted greater than the blood pressure, both being maintained until hardening occurs, or the mass may be injected under a pressure lower than that of an already existing local compression. Both methods show absence of capillary injection in the region of compression, and if this compression is exerted over one hemisphere there is also absence of injection in the corresponding region of the opposite hemisphere. In the region of "injection anæmia," when the injection is made before the intracranial pressure is raised, the veins are filled with the injection mass, if the intracranial pressure is raised before injection, the veins are filled with blood. If the brain is hardened *in situ,* the point of stoppage of the injection in the latter case is seen where the veins leave the sulci and pass over the gyrus longitudinalis superior to the longitudinal sinus.

Effect of General Compression.—If the intracranial pressure is higher than the injection pressure a complete capillary "injection anæmia" occurs. The veins are filled either with blood or injection mass as in local compression according to the method of injection.

Our experiments were undertaken in this connection to determine, in the first place, the condition of the vessels when the general compression was less than the injection pressure, and the state of the vessels, especially in the medullary regions and interior of the brain mass when the intracranial pressure was higher than the injection pressure and was caused by the entrance of fluid over the cerebral cortex. Doubt has been expressed by several writers as to whether such procedure results in general compression of the whole brain, and though the experiments performed by Cushing and the present writers leave little question that "general compression" actually ensues, an anatomical proof has been desirable.

The *method of procedure* in these experiments was as follows: in all cases the intracranial pressure was produced by fluid and was exerted before injection was begun. The injection mass used was gelatin and Berlin blue. The carotids were exposed in the living anæsthetized animal and all branches but the internal carotids were ligated. The emissary veins were exposed and opened. The skull was trephined and connected with the intracranial pressure apparatus. The animal was bled to death from the central end of one carotid artery. The fluid employed to increase the intracranial pressure was warmed to body temperature to prevent setting of the gelatin before complete injection occurred. A ligature was drawn tightly around the lower part of the neck, the cerebral vessels washed out with warm Ringer's solution, the intracranial pressure raised to the desired point and injection begun. When the clear injection mass emerged from the emissary veins, the head of the animal was plunged into ice water, both the intracranial and injection pressures being maintained at their former constant level. After complete setting of the gelatin mass had occurred, the head was severed from the body and the brain removed or hardened *in situ*.

The results from these experiments may best be given by the description of certain typical specimens.

Specimen No. 3.—Injection pressure 160; intracranial pressure 100 millimeters of mercury. The circle of Willis and its connecting arteries and the veins around the base of the brain are normally injected. The whole lower and lateral surfaces of the brain show a normal capillary injection. The upper surface of the two hemispheres shows a good injection of the large arteries; the smaller arteries on exposed surfaces are only partially injected and in the more exposed surfaces there is an absence of capillary injection. Over the dorsal surface of the brain the veins in general are well injected; in certain of the more exposed situations, as in passing over convolutions, they are only partially injected or the injection shows breaks. The medulla shows a rich capillary injection. The interior of the brain mass shows a normal injection with the exception that for a distance of a few millimeters below the surfaces the injection as described above is not complete.

Specimen No. 4.—Injection pressure 100; intracranial pressure 150 millimeters of mercury. The circle of Willis and some of the larger arteries coming off from it are quite well injected. This is true especially of the anterior branches of the circle. The injection in these arteries ceases quite abruptly eight to ten millimeters after their origin from the circle. The smaller arteries and arterioles in this region are completely uninjected and the whole base of the brain with the exception of those vessels mentioned is completely colorless. The arteries, capillaries and veins throughout the rest of the specimen are completely uninjected. The medulla is entirely uninjected. The meninges show only faint traces of injection mass. The transverse sinus is incompletely injected; the lateral sinuses are full of injection mass. The eye is well injected.

Specimen No. 6.—Intracranial pressure 160; injection pressure 120 millimeters of mercury. The circle of Willis is fairly well injected. The rest of the brain, on the surface and in sections, shows an entire absence of injection mass. The medulla shows no trace of injection. About 12 cm. of the cervical cord shows entire absence of injection.

Specimen No. 13.—Injection pressure 100; intracranial pressure 200 millimeters of mercury. Entire absence of injection from any portion of the brain, superficial or deep. The circle of Willis is entirely free from injection.

The above experiments show that a condition of intracranial pressure produced by the general method and higher than the injection pressure, causes an "injection anæmia" of the capillary areas of the whole brain, including the medulla, the cervical cord and the interior of the brain mass. The larger arteries at the base of the brain are more or less protected from the compression when the intracranial pressure is not much higher than the injection pressure. The pressure is therefore transmitted not only throughout the cranial cavity but also through the brain substance. In these preparations the cerebral veins were uninjected, the sagittal sinus was partially injected and the lateral sinus and torcular were invariably full of the injection mass. In all cases the fluid used to increase the intracranial pressure entered over the temporal region of the cerebral cortex. In degrees of cerebral compression less than the injection pressure, the injection of the greater part of the brain was equal to that normally present. The regions directly beneath the entrance of the compressing fluid show a decrease in the capillary injection in certain areas and a collapse of certain veins in exposed situations. The local pressure seems to be therefore somewhat greater than the general pressure, but the fact seems to be well established that a considerable increase in the pressure of the intracranial fluid causes an increase of pressure upon the whole surface of the brain, the medulla, and at least the cervical portion of the spinal cord, and that this pressure is transmitted to the interior of the brain mass. If the intracranial pressure is greater than the blood pressure, complete anæmia of the brain occurs, both superficial and deep.

CONCLUSIONS.

1. The results of this work form a confirmation of the earlier work of Cushing in all details investigated.

2. The increase of blood pressure that results from an increase of the intracranial pressure above the blood pressure is due in the dog to a vaso-constriction of the vessels of the intestine, the kidney and the limbs. Preceding this constriction there is dilatation.

3. The anastomotic connection between the internal carotid artery within the skull and the ophthalmic branch of the internal maxillary is of a size in the dog approximately equal to the internal carotid outside of the skull. The anatomical relations are such as to indicate that the internal maxillary artery in this animal is a cerebral artery equal in importance to the internal carotid. The anastomotic connection because of its position within the cranial cavity is unaffected except by extreme grades of intracranial compression.

4. The ordinary method of artificial perfusion of the dog's brain as used in physiological investigation appears from this work to be of no value, since there is at least one important path open besides that through the vessels of the brain.

5. The increase of the intracranial pressure above the blood pressure leads to a complete anæmia, superficial and deep, of the blood vessels of the brain. If the intracranial pressure is not greatly increased above the blood pressure, the circle of Willis and some of the larger arterial connections at the base of the brain are more or less well injected. An intracranial pressure somewhat below blood pressure leads apparently to a certain degree of anæmia directly beneath the point of entrance of the intracranial fluid; the condition of the rest of the brain as regards blood supply is normal.

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EXPLANATION OF PLATES XVI, XVII AND XVIII.

FIG. 1. Vagus inhibition from sudden lowering of the intracranial pressure. The lowest line is the line of zero pressure for the intracranial pressure, the lateral pressure in the circle of Willis and the pressure in the central end of the common carotid artery. The time is in intervals of one sceond.

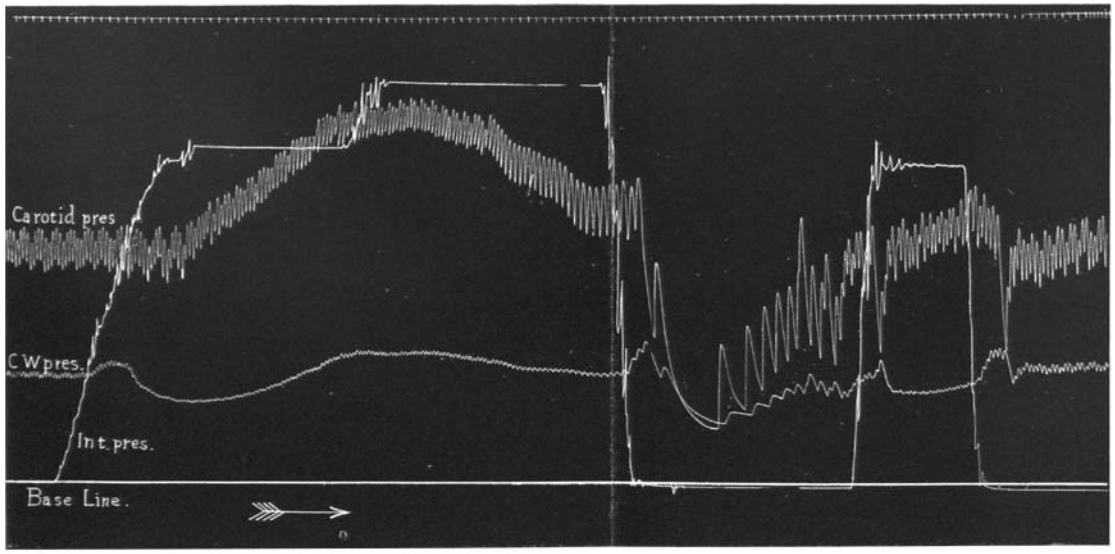
FIG. 2. Record of the volume of an intestinal loop during an increase of intracranial pressure. The lowest line is the line of zero pressure for the carotid and intracranial pressures, and also records the time in intervals of one second. The numbers refer to corresponding points on the different curves.

FIG. 3. Record of volume of kidney during an increase of intracranial pressure. The record shows variations in volume of the kidney accompanying the vaso-motor waves of blood pressure. The numbers refer to corresponding points. Time in intervals of one second.

FIG. 4. The circle of Willis and carotid pressures during an increase of intracranial pressure. The record is to be interpreted as in Fig. 7.

FIG. 5. Measurement of the venous outflow from the emissary veins in the dog under intracranial pressure after ligation of the arterial connection between the internal carotid and ophthalmic arteries. The upper line represents the outflow as measured by a piston recorder; the lower line, the time in intervals of one second.

FIG. 6. From a dissection of the arteries in the region of the middle cranial fossa in the dog. The internal carotid artery is seen entering the skull and joined by the artery connecting it with the ophthalmic artery. This connecting artery and the internal carotid lie in the greater part of their course deep in the fossa and are protected by a covering of the brain membranes, on top of which is the circle of Willis. The internal carotid is seen piercing these membranes just before it enters the circle of Willis.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C.W.pres.
Int. pres.
Base Line.

FIG. 1.

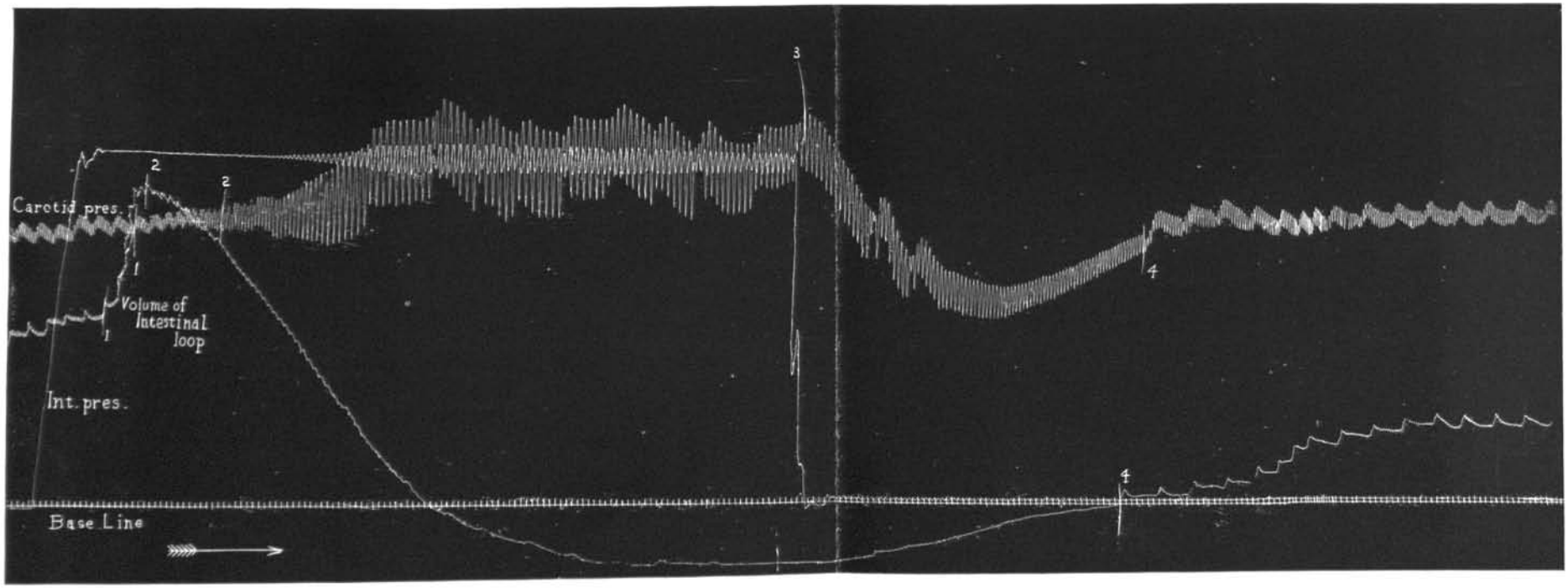
3
2
2
Carotid pres.
1
Volume of Intestinal loop
1
4
Int. pres.
4
Base Line

FIG. 2.

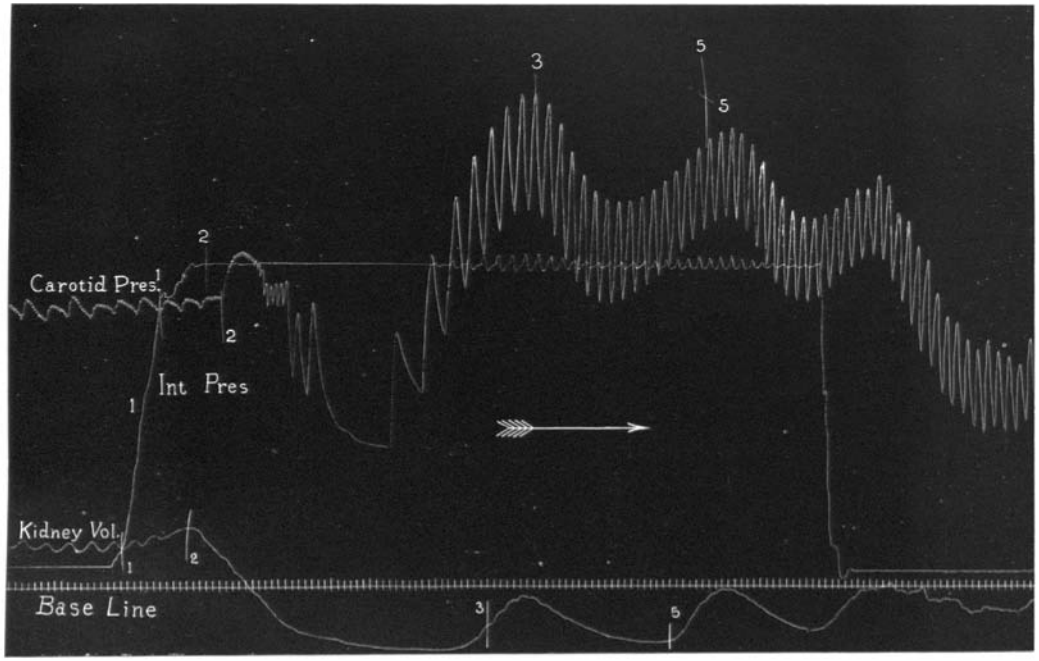

FIG. 3.

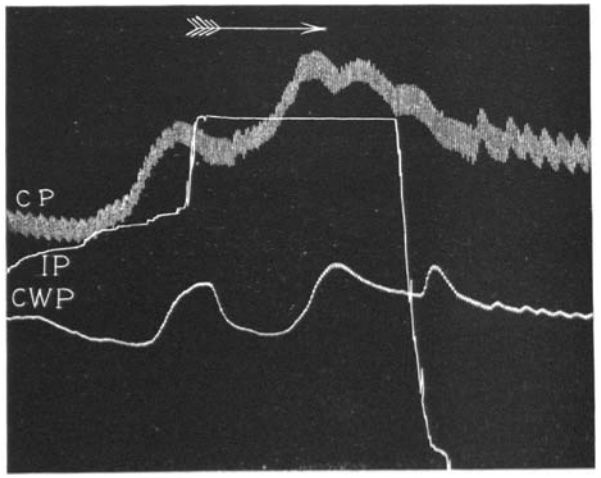

FIG. 4

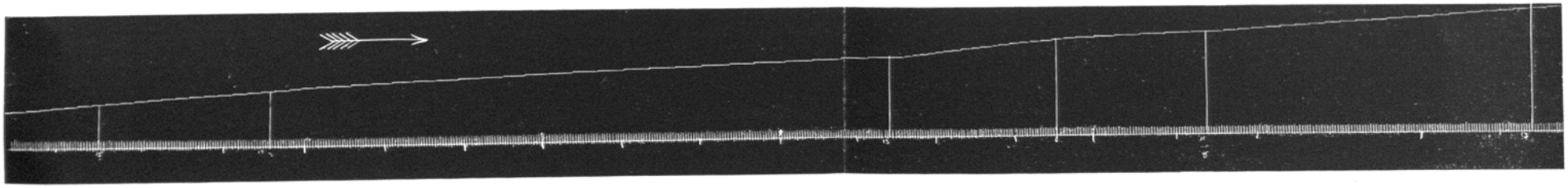

FIG. 5.

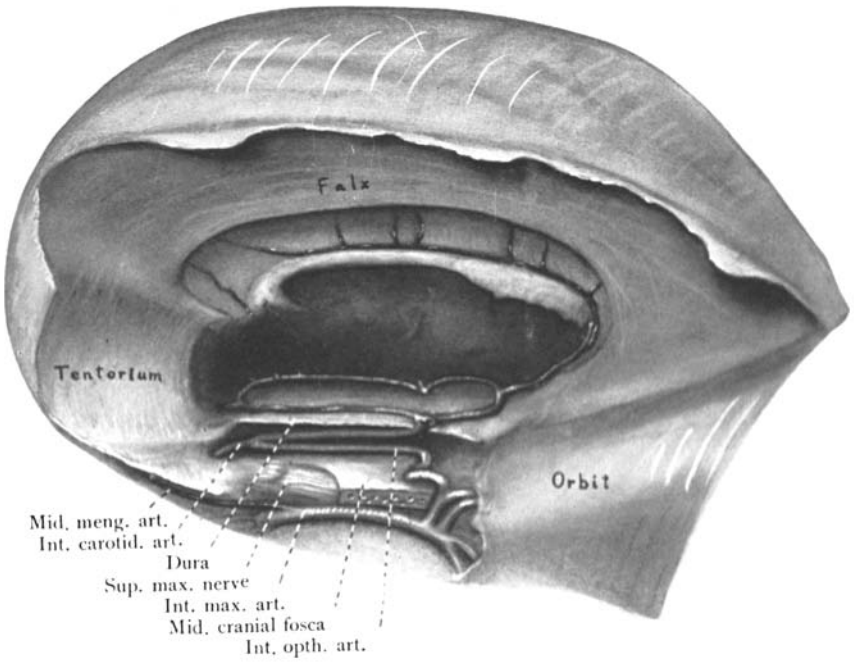
Falx
Tentorium
Orbit
Mid. meng. art.
Int. carotid. art.
Dura
Sup. max. nerve
Int. max. art.
Mid. cranial fosca
Int. opth. art.

FIG. 6.