ON INTRA-CRANIAL PRESSURE AND THE CEREBRAL CIRCULATION. Part I. Physiological.

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Part I. By W. M. Bayliss, and Leonard Hill.

The methods hitherto employed in researches on the cerebral circulation have, in one way or another, proved incomplete or defective. Important questions remain still undecided.

Such problems as these suggest themselves:—Is the brain supplied with vaso-motor nerves which regulate its blood supply, or does it, in the varying conditions of life, passively endure every to-and-fro swing of the blood-pressure? Does the volume of the blood within the brain vary in amount, or does it remain constant, "cabin'd, cribb'd, confin'd" by the wall of the skull? Is the brain matter exposed to the full tension of the varying blood-pressure, or is there existent some compensatory mechanism by means of which the intra-cranial pressure is kept constant? Lastly we ask, Does a rise of arterial pressure increase the supply of blood to the brain, or does it, as some investigators have supposed, cause an anæmia? For it is conceivable, that, in the closed box of the skull, the cerebral capillaries might be obliterated by the pressure of the expanding arteries, since the tension of the vessels at the base of the brain may be directly transmitted through the brain substance.

In order to settle these vexed questions, upon the subject of which so much of the pathology of morbid cerebral conditions depends, it is obviously required that the arterial pressure at the cerebral inlet, the venous pressure at the cerebral outlet, and the intra-cranial pressure in the closed skull cavity should all simultaneously be made the subject of observation and record. This has not yet been fully achieved by any of the older methods.

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History. On passing to the examination of former methods we find, as early as 1783, Alexander Monro the younger, putting forward the view that the quantity of blood within the cranium is almost invariable, "for being enclosed in a case of bone," he writes, "the blood must be continually flowing out of the veins that room may be given to the blood which is entering by 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 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 clear-sighted and undoubtedly true doctrine was supported by Abercrombie and Kellie, but was denied by Burrows and Donders.

After he had killed animals by bleeding and had found that the brain after death still contained as much blood as in the normal condition, Kellie went on in further experiments, to trephine the cranium and then bleed the animals to death. On post-mortem examination the brain appeared to be empty of blood. He therefore concluded that, so long as the cranium was closed, the volume of blood in the brain could not vary.

On the other hand, Donders, who observed the capillaries of the pia-mater through a glass window which he screwed into a trephine hole, found that, with the skull closed, the amount of injection of the capillaries varied. This, however, seems to us to be no proof of the variation in the total volume of blood within the cranium. It may only indicate a variation in the relative distribution of the *same* quantity of blood. Thus, if the capillaries are expanded the veins may be proportionately compressed. Donders' experiment gives no proof in either direction. In this matter, therefore, his method of observation is incomplete. In support of Kellie's experiments, one of us (Hill) has lately shown in a research on the Influence of Gravity on the Circulation, that so long as the skull is a closed cavity the brain cannot collapse or empty itself of blood, but that it will empty itself if the skull be opened and the cerebral capillary pressure fall below the height of a column of blood reaching from the heart to the brain.

The method employed by Salathé is also incomplete. He registered changes in intra-cranial pressure by screwing a tube into the skull and this tube he connected with a manometer. One of us (Hill) has found that with any increase of intra-cranial pressure the brain

floats up against the trephine hole, and acts towards it as a valve, so that no more fluid can escape into the manometer. Thus it is impossible, by injecting fluid into the sub-dural space of the vertebral canal, to drive it out of a hole in the cranium.

Another method, which was first employed by Falkenheim and Naunyn, and later, in a modified form, by Dean, cannot be regarded as complete. These investigators connected the spinal sub-dural space with a manometer by means of a catheter. Falkenheim and Naunyn passed this catheter up the lower end of the dural sac in the region of the cauda equina, and by Dean it was passed up the sheath of a spinal nerve.

Now it has been found (by one of us, Hill) that when the intra-cranial pressure rises the small quantity of cerebro-spinal fluid within the skull cavity passes into the spinal canal. The base of the brain then descends and blocks up the foramen magnum and no further rise of cerebral pressure can be communicated to the manometer which is in connection with the spinal sub-dural space.

Knoll's method meets with the same objection. He measured the pressure in the spinal sub-dural sac by passing a cannula through the occipito-atlantal membrane and this he connected with a manometer.

By no one of these methods can the changes in intra-cranial pressure be completely measured. The smaller variations only can be shown. The brain, on its increased expansion, closes up, not only a trephine hole in the roof of the cranium, but the foramen magnum in the base. The intra-cranial pressure therefore may vary exceedingly, but the manometers of not one of these investigators can fully record the variations.

The results of the last four authors can be regarded as true records of variations of pressure in the contents of the vertebral canal, but not in the contents of the cranial cavity.

Of considerable value is Gaertner and Wagner's method of recording the outflow of blood from the lateral sinuses, but their results, although of great interest, are not conclusive because they did not *simultaneously* record the arterial and venous pressures with the cerebral venous outflow.

None of the investigators whom we have mentioned have made records in their researches of the general venous pressure as well as of the arterial pressure. The method employed by Roy and Sherrington is more complete. These authors, by a most ingenious plethysmographic method, recorded the variations of the vertical diameter of the brain with the cranium open. At the same time they registered the arterial

pressure, and in some cases, they investigated the general venous pressure in similar conditions of experiment. Their method seems to us incomplete in so far as that the normal condition is not maintained, since throughout the experiments the cranium is open. In the closed cranium large alterations of blood volume are impossible. In the open cranium with the atmospheric pressure brought to bear upon the cerebral capillaries, the physical conditions of the cerebral circulation are altered. These authors, moreover, do not seem to us to have recorded, simultaneously with the general venous pressure, the variations of the brain volume and the arterial pressure. In their search for vaso-motor nerves, they did not, after division of the spine in the dorsal region, stimulate either the vaso-motor centre or the spinal nerve roots. Nevertheless their work has yielded valuable results on many points which we shall be able to confirm in this paper. Some other of their results we have been entirely unable to obtain.

Our object has been to make the method of research complete by simultaneously recording the arterial pressure, the general venous pressure, the intra-cranial pressure, and the cerebral venous pressure, the cranium as in the normal condition being a closed cavity.

Method of Research. The animals employed for this research were in all cases dogs. Throughout the experiments morphia was the anæsthetic used. The method of procedure of the experiments was as follows:—A cannula was placed in the central end of the carotid artery. A second long cannula was passed down the external jugular vein, and on the same side, into the right auricle. The torcula Herophili was trephined and a third cannula, this time of brass, was screwed into the hole thus made. The cannula in the carotid artery was placed in connection with a mercurial manometer, and the other cannulas with manometers filled with a saturated solution of magnesium sulphate. These venous manometers were, in their turn, connected with very delicate tambours or piston recorders. (The method of obtaining the cerebral venous pressure and the pressure in the sub-dural space was communicated by one of us, Hill, to the Royal Society in 1894.)

Thus, records were obtained of the general arterial pressure, of the general venous pressure, and of the cerebral venous pressure.

In some experiments, the intra-cranial pressure, that is the pressure in the sub-dural space, was also recorded. This was only necessary so far as to prove the fact, which always holds true, that the intra-cranial pressure and the cerebral venous pressure are, in all physiological con-

ditions of the circulation, the same. The first suggestion of such a method of research was given by Prof. Burdon-Sanderson. The skull is trephined in the parietal region, the dura mater freely divided and the trephine hole 'wormed' with an ordinary mechanic's tap. A piece of brass tube, over the end of which a membrane of very thin india-rubber has been tied, is then screwed in. Attached to the end of the brass tube is a piece of glass tubing of a fine-bore. This is connected with a T piece, one branch of which leads to a pressure bottle and the other to a mercury manometer. The whole apparatus is completely filled with water and then a bubble of air is introduced within the fine-bored glass tubing so as to act as an index. After the apparatus has been screwed into the trephine hole, the position of the air index is marked on this glass tube. When by increase of intra-cranial pressure the air index is displaced outwards it can be brought again to its initial position by raising the pressure bottle to the required amount. When by decrease of intra-cranial pressure the index is sucked inwards it can in like manner be brought back to the mark by lowering the pressure bottle. In either case the pressure required is indicated by the mercurial manometer and is the intra-cranial pressure at the time. Such is our method of record, and this we used to investigate the existence of cerebral vaso-motor nerves. We carried on the research in the following ways :—

(i) We divided the vago-sympathetic nerves and stimulated the central end in both the curarised and the uncurarised animal.

(ii) We divided the spinal cord in the upper dorsal region at a level of the 2nd to the 6th dorsal nerves, and we stimulated, either the central end of the cord, or the vaso-motor centre in the bulb.

(iii) We planned a new method of stimulating the cervical sympathetic nerve so as to include any of its possible branches to the vertebral arteries together with the supply to the carotid arteries.

In the experiments carrying out this last method the animals were placed under morphia and then lightly curarised, and artificial respiration supplied. The thorax was then opened in the middle line, and weighted hooks were used to keep the walls of the cavity well apart. The heart was protected from exposure by a pad of cotton wool. The sympathetic nerve was then caught up—with an aneurism needle—where it lies high in the thorax and as it passes over the 1st rib just below the stellate ganglion, and a ligature was passed under it and tied. The nerve was then divided below the seat of the ligature, and a pair of long shielded electrodes were placed on the nerve between the

ligature and the stellate ganglion. Finally the ligature was tied on to the electrodes in such a way that the nerve could not be displaced, and the thorax was then closed. By this means was insured the stimulation of the whole of the sympathetic fibres which supply one side of the head and neck. The accelerating fibres to the heart were also included.

By all these methods of research we found that the cerebral venous pressure (and the intra-cranial pressure) passively followed the changes in the general arterial and general venous pressure. We could obtain no evidence whatever of any independent change pointing to the existence of any vaso-motor nerves supplying the brain.

Experimental Results.

i. Excitation of the central end of the vagus produces either a rise or a fall in cerebral venous pressure, according as there is in the

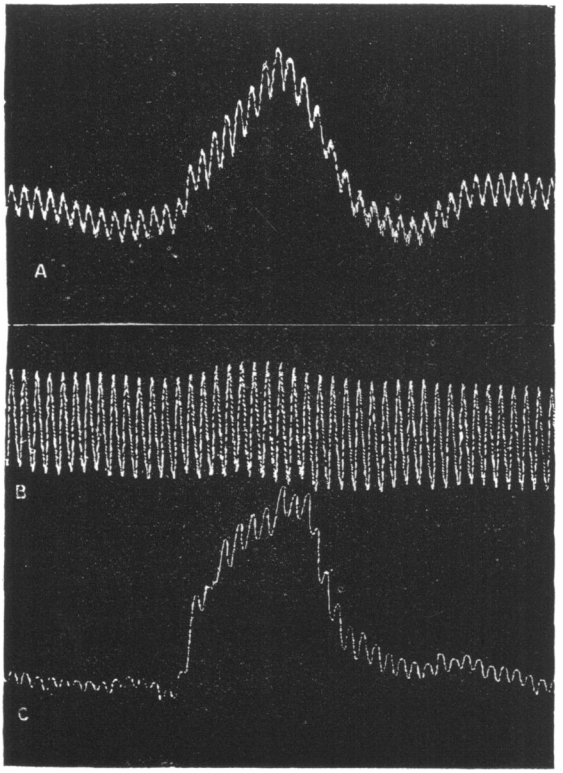

Fig. 1. A. Carotid Artery. B. Right Auricle. C. Torcula Herophili.

ascendancy the sensory constrictor influence or the depressor action of the nerve on the vaso-motor centre.

ii. After division of the dorsal cord, and upon stimulating the central end of the divided cord, or the vaso-motor centre, there is a slight rise of general arterial pressure, and the cerebral venous pressure passively follows this rise. The general venous pressure may remain unaltered or may suffer an insignificant rise or fall.

In Fig. 1 is shown the effect of stimulating the central end of the cord after it has been divided at the level of the 3rd or 4th dorsal vertebra.

On dividing the cord still higher at the level of the 2nd dorsal vertebra the effect, although very much slighter, was still the same in character.

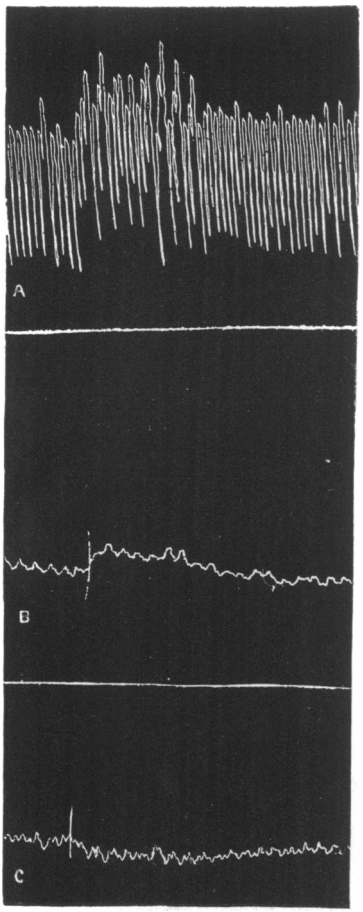

Fig. 2. A. Carotid Artery. B. Torcula Herophili. C. Right Auricle.

iii. On stimulating the stellate ganglion in the thorax acceleration of the heart and a slight rise of arterial pressure occurs, the general venous pressure may fall slightly or remain unaffected while the cerebral venous pressure follows the arterial rise (Fig. 2).

Thus we have been entirely unable to find any evidence of a vaso-motor supply to the brain. Each of these experiments has been many times repeated, and the injury to vaso-motor excitability by shock or the use of curare has been carefully prevented by slight curarisation, by keeping the animals on warm baths, and by rapid experimentation. We have stimulated the whole of the sympathetic supply, and the whole of the cranial nerve supply, and we have, by dividing the spinal cord, diminished the overpowering passive effect of the general circulation to a vanishing point. Yet we have obtained no positive

results. The cerebal venous pressure has never varied in a contrary sense to the general circulatory pressures.

We have further investigated the result on the circulation of the brain of a number of other effects, as given below.

1. *Interference with the circulation of the blood in the brain* was caused by a ligature being placed round the neck. If a cannula be placed in the trachea and a ligature be then drawn round the neck so as to exert gentle pressure on the veins, there is an immediate, marked, and sustained rise of cerebral venous pressure (Fig. 3).

Directly the ligature is withdrawn, the pressure again falls to normal.

In our general experimental method we occluded one carotid artery and one jugular vein. This makes little difference to the cerebral circulation. Roy and Sherrington found this also.

Occlusion of both carotids causes a marked fall in cerebral venous pressure.

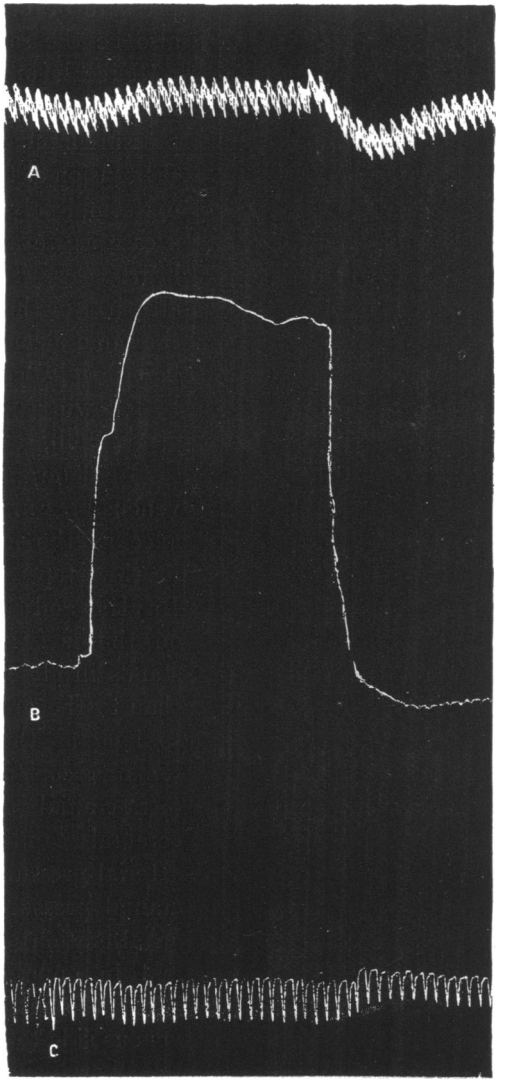

Fig. 3. A. Carotid. B. Torcula Herophili. C. Right Auricle.

2. *Stimulation of the peripheral end of the vagus.* These experiments have led to very interesting results which help to explain the physical conditions of the cerebral circulation. If one vagus

nerve be divided and the peripheral end stimulated the arterial pressure rapidly falls while the general venous pressure as rapidly rises to the mean pressure of the whole circulatory system (Fig. 4).

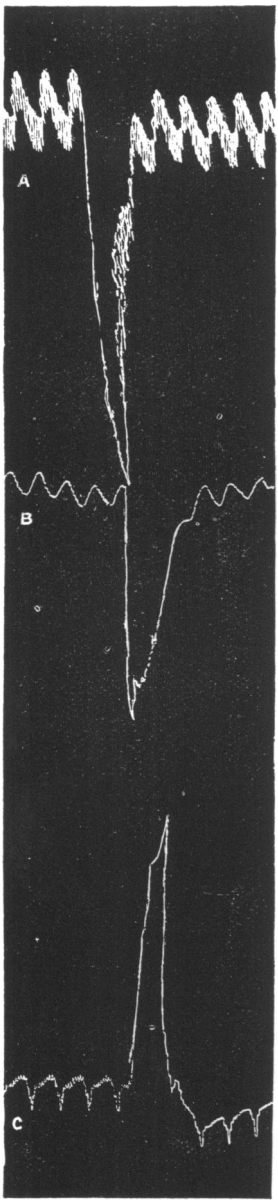

Fig. 4. A. Carotid. B. Torcula Herophili. C. Right Auricle.

If the animal be horizontal and the effect of gravity absent the intra-cranial pressure or cerebral venous pressure will also be the same as the mean pressure.

Fick has postulated "that the pressure in a closed cavity is equal to the arterial pressure minus the resistance which opposes the tension of the vascular wall." This does not completely state the truth, for, in such a case as we are now discussing, when the heart ceases to beat and the pressure in all parts of the circulatory system reaches the same mean point (the effect of gravity being neglected) the intra-cranial pressure, by following the venous rise as well as the arterial fall, reaches the same mean point.

In determining capillary pressure the venous pressure is of equally great importance as the arterial pressure. Following in the steps of the school of Ludwig, Bayliss and Starling have lately insisted on the fact that the capillary pressure stands in closer relationship to the venous than to the arterial pressure. In general, so long as the systemic venous pressure remains constant, but only so long, the intra-cranial pressure—and that is the cerebral capillary pressure—follows the arterial pressure. If both alter, the intra-cranial pressure is affected by both, and an alteration of pressure of equal amount and in opposite directions in both, will affect the intra-cranial pressure from the venous side to a greater degree than from the arterial side, because it is on the arterial side that the resistance lies.

There is another point in the mechanism of the cerebral circulation. The cerebral vessels enclosed in the unyielding box of the cranium are more of the nature of rigid tubes. Any alteration of pressure, in a circulatory scheme produced by a pump, reaches its maximum more rapidly in a rigid tube than in an elastic tube. If great resistance lies in the outlet of a rigid tube, on varying the force of the pump, pressure will rise still much more rapidly and fall much more slowly there. Such an effect is shown on many of our tracings in cases where the venous outlet has been accidentally impeded either by clotting or kinking of the veins arising from the position of the head; or where it

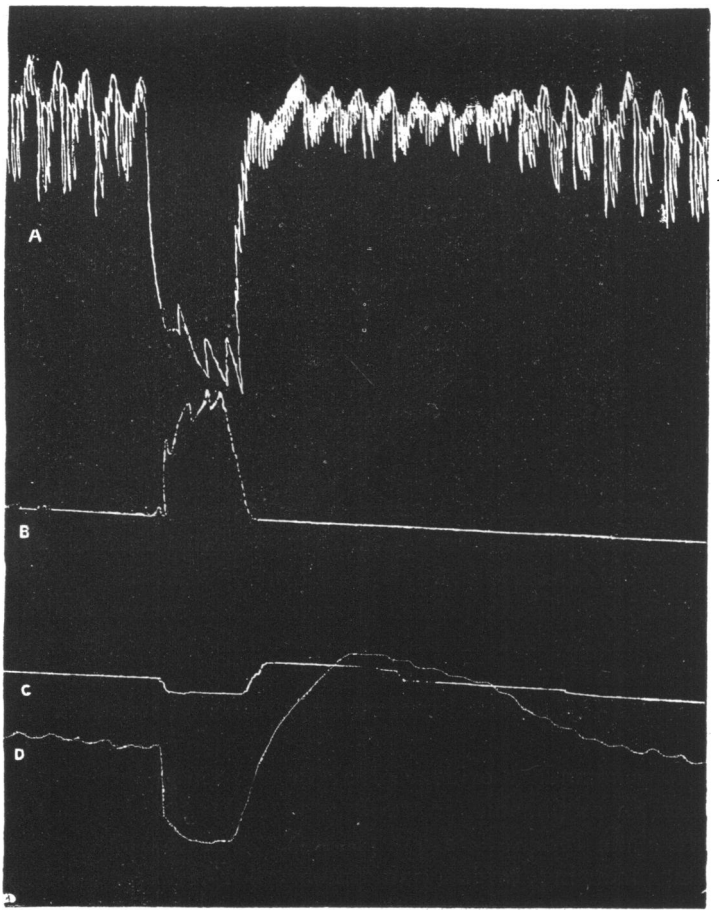

Fig. 5. A. Carotid. B. Right Auricle. C. Intra-cranial Pressure. D. Torcula Herophili.

has been experimentally produced by gently tightening a ligature round the neck or by plugging the lateral sinuses (Fig. 5).

Thus in this tracing cerebral venous pressure and the intra-cranial pressure are seen to fall somewhat when the heart ceases to beat, to rise much above the normal when the heart begins again to beat, and finally to fall slowly back to the normal.

On stimulation of the peripheral end of the vagus, therefore, we normally obtain a fall of intra-cranial or cerebral venous pressure if the resultant effect of the fall of arterial pressure be greater than the effect of the rise of general venous pressure.

On the other hand, if the outlet of the cerebral veins be impeded, a large rise of intra-cranial pressure always occurs when the heart again begins to beat.

Roy and Sherrington observed, after vagus stimulation, a marked expansion of the brain, and their tracings show exactly the same result as has been obtained by us where the cerebral venous outlet was blocked. These authors curiously ascribe this phenomenon to some constricting influence of the peripheral end of the vagus on the general venous system.

They write "that according to our observations there are in the vago-sympathetic nerves, descending fibres, section or stimulation of which can produce either a rise or a fall of the general venous pressure, and these fibres can be called into action, either by direct stimulation or reflexly, by excitation of ascending fibres, the corresponding nerve of the other side being intact."

Dean, by his ingenious method of recording cerebro-spinal pressure never obtained this marked expansion observed by Roy and Sherrington. It is probably owing to his method that Dean never found any indication of this effect. It was unlikely that the veins of the neck would be kinked or pressed as his records were obtained from the vertebral canal and not from the brain. In Roy and Sherrington's method, and also in ours, it is extremely probable that the venous outflow would sometimes, from experimental interference with the head, become impeded.

We have abundant evidence that these vagus effects are entirely mechanical in origin, and for the sake of making this quite clear, we will once again recapitulate our position.

Upon producing cardiac inhibition the rise of general venous pressure is simply caused by the pressure in the whole circulatory system reaching one dead level or mean pressure; the pump ceases to

work, the pressure in the arteries runs down and in the veins runs up until the mean is established throughout the system. There is no need to invoke the aid of any hypothetical vaso-motor nerves. In those cases in which the cerebral venous outlet is impeded and a marked rise of intra-cranial pressure occurs when the heart again begins to beat, the explanation is also mechanical.

A more lucid way of stating this is as follows:—

(i) When the heart ceases to beat the brain cannot empty itself of blood because the cranium is a closed cavity.

(ii) When the heart again begins to beat, the brain is full of blood.

(iii) If the venous exit be impeded the force of the heart-beat will be transmitted from the large arteries at the base of the brain on to the venous sinuses, directly through the brain substance. Hence there is a great rise in the pressure of the torcula Herophili.

(iv) Finally as the blood again slowly forces open exits from the venous sinuses, the pressure in the torcula once more falls to the normal.

3. *Pressure on the abdomen.* Pressure on, or bandaging of the abdomen, by reducing the total capacity of the circulatory system, causes a rise in the general arterial and venous pressures, and the cerebral venous pressure passively follows this rise. The effect on the cerebral venous pressure is as large as in Fig. 3.

4. *Excitation of a sensory nerve.* Stimulation of any sensory nerve causes a rise of general arterial pressure and the intra-cranial or cerebral venous pressure passively follows this rise. The general venous pressure rises slightly or remains unaltered.

5. *Asphyxia.* On producing asphyxia in the curarised animal by stopping the artificial respiration, the general venous pressure, owing to the mechanical effect of stopping the respiratory movements, at first falls. The cerebral venous pressure passively follows this fall (Fig. 6).

During the subsequent rise in arterial pressure, the general venous pressure does not vary while the cerebral venous pressure passively follows this arterial rise.

During the last stage of asphyxia, when the arterial pressure is falling the general venous pressure is rapidly rising, owing to the failure of the heart coupled with the diminution of the capacity of the circulatory system produced by the vaso-constriction. The cerebral venous

pressure is now the resultant produced by the arterial and general venous pressures.

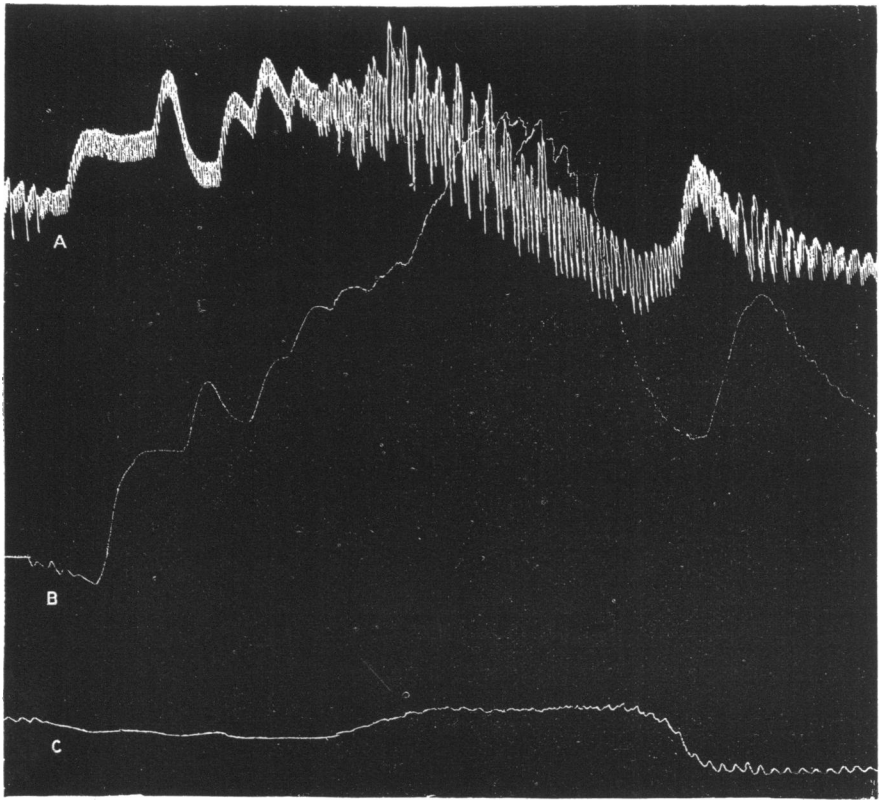

Fig. 6. A. Carotid. B. Torcula Herophili. C. Right Auricle.

Thus it is seen that when the arterial pressure has returned to the normal level, the cerebral venous pressure is far above the normal owing to the large rise that has, at this time, taken place in the general venous pressure[1].

We have never obtained the slightest evidence in our numerous experiments on asphyxia of any change in the cerebral vessels which could not be explained passively. Roy and Sherrington obtained evidence of expansion of the brain volume which could not be explained by them as being due to any rise in the arterial or general venous side.

[1] In this tracing the general venous effect was larger than it appears, owing to the venous tambour being less delicate than the torcula tambour.

These authors did not record all the effects of asphyxia on the volume of the brain, on the arterial, and on the general venous pressure simultaneously.

We have noticed in the case of an animal if insufficiently curarised, that the slightest attempt at respiration on its part, especially if it cause movements of the neck muscles which compress the jugular veins, will raise the cerebral venous pressure, and this unless carefully guarded against may possibly be a source of error. Dean noticed the preliminary fall in the pressure of the cerebro-spinal fluid in an animal in a condition of asphyxia, and ascribed this effect to the possible existence of vaso-constrictor action on the cerebral vessels. This preliminary fall is, we believe, entirely due to the fall in general venous pressure, which is itself occasioned mechanically by the cessation of respiration.

6. *Influence of anæsthetics.* Administration of chloroform produces a fall of arterial pressure and a rise in the general venous pressure. Following the greater effect of the arterial fall, the cerebral venous pressure also falls. In the later stages of chloroform poisoning, as in asphyxia, there is a rapid rise in the cerebral pressure following the now greatly increased pressure in the right auricle. The general venous pressure rises because of the failure of the heart. In this case again as the pump ceases to act the arterial pressure falls to the mean and the venous pressure rises to the mean. Gaertner and Wagner found an increased flow of blood from the lateral sinuses during the stages of chloroform poisoning, this they ascribed to active dilatation of the cerebral vessels. We explain it on the other hand mechanically as due to the rise of general venous pressure consequent on the increasing cardiac paralysis. We have obtained no evidence of active dilatation of the cerebral vessels taking place during the inhalation of chloroform.

Ether produces a slighter fall of arterial pressure and a slight rise of pressure in the right auricle. The cerebral venous pressure follows the greater effect of the arterial fall.

7. *Curare.* By damaging the vaso-motor tone and increasing the capacity of the circulatory system the injection of curare causes a fall in all three pressures.

8. *Injections of acids, alkalies and brain extracts.* Roy and Sherrington write that the "intra-venous injection of free acid—sulphuric

or nitric or lactic were the acids chiefly used by us in small doses freely diluted with ·75 % salt sol. and injected slowly—produced in all our experiments on the subject, great and immediate expansion of the brain. The extent of the congestion resulting from the administration of 1–2 minims of Acid Sulph. or Acid Nitric. sometimes approaches in intensity that produced by strychnia."

We have used lactic, hydrochloric, sulphuric and nitric acids in weak and strong solutions. We have injected these acids freely diluted with ·75 % saline, and we have injected them scarcely diluted at all. We have injected them into the central end of the jugular vein and into the peripheral end of the carotid artery. We have found that if the injection is followed by convulsive and increased respiratory movements, as is often the case, the general venous pressure from purely mechanical causes rises, and the cerebral venous pressure or intra-cranial pressure passively follows this rise. Muscular movements compress the veins and diminish the total capacity of the circulatory system and produce the same effect as compression of the abdomen.

Again if the contents of the circulatory system are increased by the injection of a quantity of saline sufficient to produce hydræmia, then the general venous pressure rises and the cerebral venous pressure passively follows this rise.

We have been entirely unable to confirm the results that Roy and

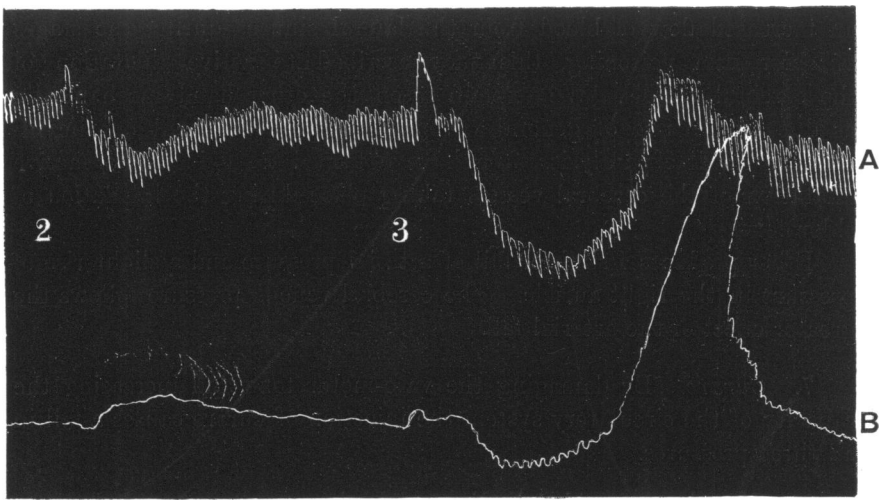

Fig. 7. A. Carotid Artery. B. Torcula Herophili.

Sherrington obtained with acids and have not found the slightest evidence of active dilatation of the cerebral vessels.

In Fig. 7 is shown the effect of injecting sulphuric acid. In this experiment 1·5 grm. of sulphuric acid diluted with saline were injected in successive doses until the death of the animal occurred. On injecting the contents of the first syringe there was practically no effect. On injecting the second a slight fall of arterial pressure followed with very slight convulsive movements and consequent slight rise of cerebral venous pressure. On injecting for the third time marked convulsive movements occurred, the arterial pressure fell and the cerebral venous pressure rose. This was owing to the effect of the muscular contractions on the general venous pressure and especially on the jugular veins.

The injections of acids we found almost always caused a fall of arterial pressure, and lactic acid as has been previously noted by others seems to be especially apt to excite the respiratory centre.

The injection of *alkalies* causes a fall in arterial pressure and the cerebral venous pressure passively follows this fall. On this point we confirm the results of Roy and Sherrington.

Brain Extracts. Roy and Sherrington found that a saline extract of the brain produced in the brain a marked expansion, when through a cannula tied in the submaxillary artery the extract was injected into the carotid artery. The brain of a dog taken four hours after death and rubbed up in a mortar with 250 c.c. of saline made the necessary extract. The filtrate from this extract was used and was found to be faintly acid. On injecting 3 c.c. of this extract "the brain expanded immediately so greatly that the point of the oncograph lever was rapidly carried off the drum, there being no corresponding rise of either the arterial or venous blood-pressures." These authors concluded from this experiment "that the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels; that in this reaction the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity."

We have prepared the extract of brain according to the method of Roy and Sherrington and have injected it both into the peripheral end of the carotid and into the central end of the external jugular vein. We have many times injected it and into many animals, in small doses and in large amounts. We have also injected a solution of the dry

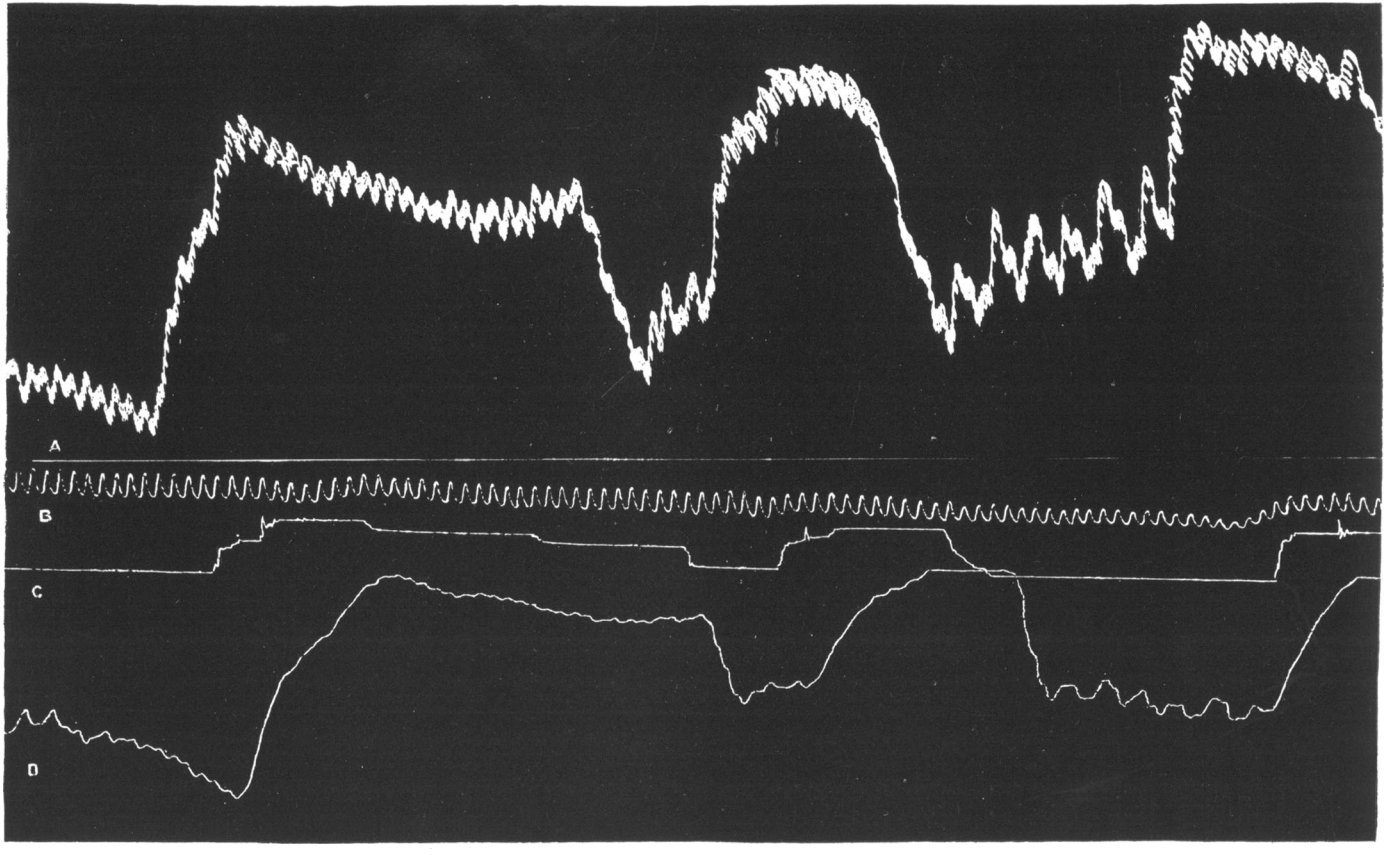

Fig. 8. A. Carotid Artery. B. Right Auricle. C. Intra-cranial pressure. D. Torcula Herophili.

powdered grey matter of the brain prepared by Messrs Willows, Francis and Butler. In no case have we been able to observe any active effect on the cerebral circulation or intra-cranial pressure. If a large amount of fluid is injected, or if convulsive movements are produced, the cerebral venous pressure rises. Again if while making the injection into the peripheral end of the carotid, the veins of the neck should be accidentally compressed, a marked rise of cerebral venous pressure occurs from simple mechanical reasons.

If none of these contingencies arise the effect of injecting brain extract is nil. In our hands therefore neither acids nor brain extracts have yielded any active results on the cerebral circulation, and we have been unable to find evidence of any such local vaso-motor mechanism in the brain as has been indicated by Roy and Sherrington.

9. *Epileptic fits.* In an uncurarised animal an epileptic fit produced by excitation of the cortex owing to its convulsive movements produces a rise in general venous pressure. The cerebral venous pressure follows this rise. During the course of the fit the arterial pressure may both fall and rise. In the curarised animal the arterial pressure rises to a high degree, and the cerebral venous pressure follows this rise.

10. *Absinthe.* On injecting absinthe into the *curarised* animal a succession of intense spasms of the arterioles ensues, general venous pressure remains practically unaltered, and intra-cranial or cerebral venous pressure follows exactly the arterial trace (Fig. 8).

Strychnine. During the strychnine spasms arterial pressure rises enormously, cerebral

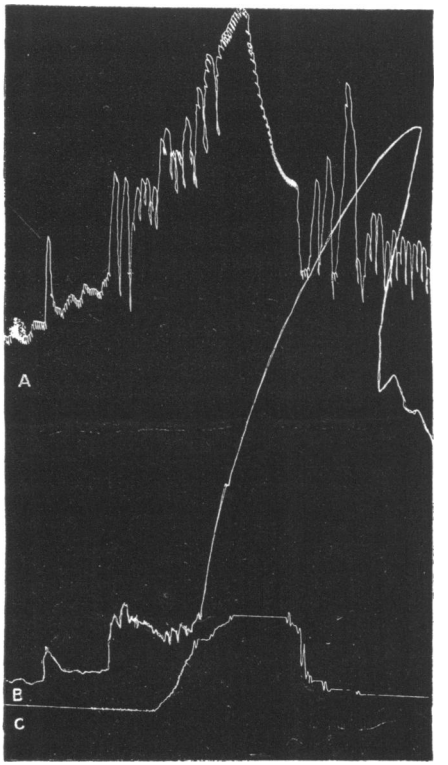

Fig. 9. A. Carotid. B. Torcula Herophili. C. Intra-cranial pressure.

venous or intra-cranial pressure follows this enormous rise, and that of the general venous pressure which also rises largely owing to the convulsive movements (Fig. 9). Roy and Sherrington found great expansion of the brain, and Gaertner and Wagner a great increase in cerebral venous flow during strychnine spasms.

11. *Supra-renal extract.* Oliver and Schäfer have demonstrated the tremendous effect which an extract of the medulla of the supra-renal gland has on the arterioles and they have proved that the extract acts on the muscular walls of the vessels, for it is not lessened by section of the spinal cord or vaso-motor nerves. On the suggestion of Prof. Schäfer we have employed the supra-renal extract in a final effort to obtain constriction of the cerebral vessels.

On injecting supra-renal extract the arterial pressure rises greatly, the general venous pressure also rises, and the cerebral venous pressure passively follows the rise in the general pressures.

In order to eliminate the overwhelming effect of the splanchnic constriction we have attempted to tie the aorta and inferior vena cava, and so restrict the circulation to the upper part of the body.

In ten successive experiments on cats and dogs, ligaturing the arch of the aorta just beyond the left innominate artery has proved fatal in the course of a few minutes, although the vena cava inferior was tied immediately afterwards. The heart passed into delirium cordis. If the vena cava inferior was not tied, death resulted still more rapidly. We take the opportunity of recording this fact, which requires further investigation in the future.

In four animals we have ligatured the aorta just above the diaphragm, and also the vena cava inferior, and the result has not been a fatal one. In these four experiments we have been unable to obtain any decided evidence of constriction in the cerebral vessels. On injecting the extract, the arterial rise is much smaller, but the cerebral venous pressure or intra-cranial pressure still passively follows this rise.

There is undoubtedly muscular tissue in the vessels of the pia-mater, and it may well be asked—why is there muscle present, if it does not constrict?

We at any rate are assured that if there is constriction, it is overcome passively by any rise in the general pressures. The splanchnic area is predominant, and functionally the muscle of the cerebral vessels appears to be of no importance. The muscle may be a vestigial structure, or it may be a supporting structure capable of slight constriction, but as far

as the principles of the cerebral circulation are in question it may be neglected.

Conclusions.

Such being our experimental results it now remains for us to attempt to answer the questions which at the beginning of this paper we set before ourselves to solve.

We find that the volume of the brain is in the closed cranium almost an invariable quantity and agree with the doctrine of the younger Monro whom we have already quoted. This conclusion follows on the results of researches (Hill) on intra-cranial pressure. If a foreign body be introduced into the sub-dural space in the parietal region of a dog, complete compensation only takes place to the extent of 2–3 c.c.; that is to say a foreign body 2–3 c.c. in volume can be introduced without raising the intra-cranial pressure or affecting the cerebral circulation.

The compensatory mechanism is provided for by the exit of the small quantity of cerebro-spinal fluid which lies in the ventricles and in the arachnoidal spaces at the base of the brain. This fluid passes out into the vertebral canal.

If the foreign body be of greater volume than 2–3 c.c., the venous sinuses are compressed, the cerebral capillaries are obliterated, the intra-cranial pressure rises, and the cerebral circulation is disordered.

Similarly when the arterial pressure rises, the expansion in cerebral volume can take place only to an insignificant amount. For as soon as the cerebro-spinal fluid has been driven out from the cranium, the brain is everywhere in contact with the rigid wall of the skull, while the foramen magnum is blocked by the descent of the pons and cerebellum.

Any further expansion of the arteries and capillaries can now alone take place by an equivalent compression of the venous sinuses, for the semi-fluid brain matter is practically incompressible.

The reservoirs of blood in the sinuses will therefore be so far emptied, until the intra-cranial pressure and the cerebral venous pressure are again equalised, and then the whole circulatory system of the brain will have assimilated itself to a scheme of rigid tubes. Thus the velocity of the blood-flow will be increased and the relative distribution of the blood in the arteries, capillaries and veins will be changed.

A rise of arterial pressure does not by any means—through compression of the cerebral capillaries—produce an anæmia of the brain, but rather it causes an increased velocity of the current.

Gaertner and Wagner found that this was so in experiments on the outflow of blood from the lateral sinuses, and their results have been lately confirmed by Hill and Nabarro in a research on the exchange of gases in the brain. We found that during the intense vaso-motor spasms produced by absinthe, the outflow of blood from the torcula Herophili increased twice to six times.

It was Grashey who enunciated the doctrine that the intra-cranial pressure depends in origin on the tension of the cerebral arteries and that consequently a high pressure in these arteries must lead to decrease in the amount of blood flowing through the brain. Geigel went so far as to declare that every expansion of the cerebral arteries causes an anæmia and every constriction a hyperæmia of the brain. This view cannot be accepted. The intra-cranial pressure has been found by us in all physiological conditions, to be the same as the cerebral venous pressure. It does not depend *directly* on the tension of the cerebral arteries, but is an expression of the tension of the cerebral capillaries and veins.

The intra-cranial pressure is in fact that tension which remains after the force of the heart has been expended in driving the blood through the cerebral arterioles. It is therefore the same as the pressure in the venous sinuses.

If the intra-cranial pressure becomes pathologically greater than the pressure in the venous sinuses, the cerebral circulation is disordered. This is what has been found experimentally (Hill).

On introducing foreign bodies of a larger volume than 2–3 c.c. within the cranium of a small dog, the venous sinuses and capillaries are compressed and as the capillaries are obliterated the intra-cranial pressure rises to the arteriole tension, and to the arterial tension as the arterioles are obliterated. It must be borne in mind that the cerebro-spinal fluid is not a secretion, that is to say in the same sense as the saliva which is poured out at a higher tension than the arterial pressure. In all physiological conditions the tension of the cerebro-spinal fluid is the same as the pressure in the venous sinuses. One of us (Hill) has found that normal saline can be driven through any part of the dura mater by a pressure of 10–20 mm. Hg. At this pressure the fluid like beads of sweat exudes through the membrane from numberless pores. The sinuses at the base of the skull are roofed

over by very thin and tense dura mater, and filtration here takes place at a still lower pressure. When saline coloured with methyl blue is driven into the subdural space the blue rapidly passes into the blood, and these basal sinuses are found to be most intensely coloured. From these facts it is clear that the cerebro-spinal fluid cannot be secreted at a pressure much above that of the venous sinuses, and physiologically it is never found to be so.

If we now turn to the consideration of the cerebral effects of a fall of arterial pressure, we again reach the conclusion that the volume of the brain is almost an invariable quantity. So long as the cranium is closed to atmospheric pressure, the blood vessels of the brain cannot empty unless cerebro-spinal fluid pass into the skull in equivalent amounts. One of us (Hill) has investigated this point. If the spinal cord be divided in the upper dorsal region, and the animal be placed in the vertical feet down position, the intra-cranial or cerebral venous pressure is from the influence of gravity and the vaso-motor paralysis of the splanchnic area reduced to its lowest point.

If the animal be now trephined in the parietal region, there is no evidence of any marked increase of cerebro-spinal fluid within the cranium, but the brain under the atmospheric pressure immediately collapses for the cerebral capillary pressure has in these conditions fallen below that of a column of blood reaching from the heart to the brain. It seems indeed highly probable that the secretion of cerebro-spinal fluid entirely depends on the cerebro-capillary pressure. When the capillary pressure rises in the central nervous system, the cerebro-spinal fluid presses against the soft parts of the walls of the vertebral canal, and room for increased transudation of fluid may thus be found. On the other hand when the capillary pressure falls, the elastic rebound of the walls of the canal will come into play, and fluid will tend to pass into the venous sinuses either by means of the Pacchionian bodies or directly through the dura mater. Other modes of exit exist such as the root sheaths of the nerves. Key and Retzius injected these from the arachnoid space. These however are subsidiary channels, for saline coloured with methyl blue, and driven into the cranium passes into the blood far more rapidly than into the lymphatic system.

Naunyn and Falkenheim found that, when tapped off from the vertebral canal of the dog, in twenty-four hours were secreted 36–240 c.c. of cerebro-spinal fluid. They also found that injection of saline into the venous system increased the amount of secretion by 50 p. c.

If the above opinions are correct it would follow that any patho-

logical obstruction of the cerebral veins would lead to increased secretion of cerebro-spinal fluid. For example if by some pathological condition the veins of Galen be compressed, the pressure in the capillaries of the choroidal plexuses would rise to that of the arteries, the vascular walls would be damaged and increased transudation of cerebro-spinal fluid into the ventricles would follow. Similarly any lack of normal rigidity in the walls of the cranium or vertebral canal might permit increased transudation of cerebro-spinal fluid. The pathology of meningocele, spina bifida, etc. may thus find an explanation, but on these points further investigations are needed.

There is undoubtedly a certain tidal amount of cerebro-spinal fluid which sets in and out of the cranium with the fall and rise of the cerebral blood-pressure. This amount is however very small. The essential function of the cerebro-spinal fluid is probably that of a water cushion for the spinal cord. It has not the important duty which has been attributed to it, for it is entirely insufficient in quantity to keep the intra-cranial pressure constantly yielding to the expansion of the brain. Thus during the large rise of arterial pressure that occurs in the spasms of strychnia and absinthe, we have recorded a rise of intra-cranial pressure from some few millimetres to fifty or sixty millimetres of mercury. These experiments prove that there is no compensatory mechanism by which the brain matter can be protected from great changes of circulatory pressure. Men remain conscious in the spasms of strychnia, when the intra-cranial pressure must be equal to some 50–60 mm. Hg. On the other hand one of us (Hill) found that the intra-cranial pressure was slightly below zero in a patient, when standing upright, the influence of gravity on the circulation being at its greatest. This patient had been trephined by Dr Claye Shaw for symptoms of lunacy. It is therefore clear that the functions of the brain can continue at any circulatory pressure varying from below zero to 50–60 mm. Hg.

It may be as well to here insist again that in all physiological conditions the intra-cranial pressure is entirely circulatory in origin, and that the flow of blood is greatly accelerated in absinthe and strychnine spasms. Intra-cranial pressure produced by a foreign body blocking the venous exits and diminishing the blood flow has an entirely different effect on the brain. That is to say the cerebral matter does not suffer from pressure, but from anæmia. Turning to the question of the existence of vaso-motor nerves, we are convinced from our experiments that the cerebral vessels are free from any such control. Under every

condition of experiment, the cerebral circulation passively follows the changes in the general circulation. We have reached the same general conclusion as Roy and Sherrington, and have by our records of the general venous pressure explained some results obtained by these authors and by Dean which were in a contrary sense.

We have been unable to find any evidence of the local vaso-motor mechanism which Roy and Sherrington sought to establish on the grounds of experimental results which followed in asphyxia and after injection of acids and brain extract. These results we have been entirely unable to confirm. The cerebral circulation passively follows every change in the general circulation. Every change in the position of an animal from the influence of gravity on the vascular system affects the cerebral circulation. Every variation in respiration, and every muscular movement is followed by passive changes in the circulation of the brain.

Every heart-beat and every respiratory undulation is exhibited on the tracings of the cerebral venous or intra-cranial pressures. Compression of the jugulars or of the abdomen causes a marked rise in cerebral venous pressure, and muscular movements of the neck, by pressure on the jugular veins, are sufficient to affect the cerebral circulation. Every stimulus that attacks the organism, and affects the general vaso-motor system, produces a passive effect on the cerebral circulation. Each pleasurable emotion raises the general blood-pressure and increases the blood flow through the brain, and each painful emotion brings about the opposite result.

It is by means of the splanchnic area that the blood supply to the brain is controlled. The overwhelming importance of the splanchnic mechanism in maintaining the circulation and life has been especially shown by the influence of gravity on the circulation. By abolishing the splanchnic control and placing the animal vertically feet down, the circulation of the brain ceases and the animal dies. An anæmia of the central nervous system excites the vaso-motor centre, and if the splanchnic vessels constrict the blood-pressure rises, and more blood is driven through the brain. The same result is produced by asphyxia. As Roy and Sherrington pointed out, we have in the vaso-motor centre a protective mechanism, by which blood can be drawn at need from the abdomen and supplied to the brain. At the moment that excitation from the outside world demands cerebral response, the splanchnic area constricts and more blood is driven through the brain. On the other hand after the taking of food, the abdominal vessels dilate,

the brain circulation is slow, and the organism is unwilling to respond. The low cerebral metabolism that has been found by one of us (Hill) and Nabarro helps to explain how the brain can functionate with so varying a blood supply.

To sum up we are in a position to state that the brain has no direct vaso-motor mechanism, but that its blood supply can be controlled indirectly by the vaso-motor centre acting on the splanchnic area.

The vaso-motor centre is part of the central nervous system, and feels the same needs, and is stimulated by the same centripetal impulses as affect the rest of that system, and thus it maintains a supply of blood to the central nervous system which corresponds to its functional activity. We have by experimental methods reached the same conclusions as those Lewy has obtained by an exhaustive mathematical examination of the conditions of the cerebral circulation. In the brain as in other organs of the body arterial dilatation will increase and arterial constriction diminish the blood flow. (But the dilatation and constriction are always passive there.) Venous obstruction produces anæmia. Any acute compression of the brain such as that which would be caused by the presence of a foreign body, produces anæmia. Extensive inflammation and dilatation of the cerebral vessels in any particular part, will tend to produce anæmia of other parts. Extensive blocking of the capillaries in any part will also, whenever the arterial pressure rises, tend to produce anæmia in other parts of the brain.

In both these cases arteriole or arterial pressure will be manifest in the injured part of the brain, and this will overcome the capillary pressure in other parts and produce anæmia, for in the closed cranium filled with the semi-fluid brain matter, pressure is transmitted in all directions equally. Thus pathologically in the brain situated as it is in the closed box of the skull, a circulus vitiosus may be established, for either extensive inflammation or obliteration of capillaries will lead to anæmia of the rest of that organ.

It is important to note that the spinal bulb is partially protected from severe intra-cranial pressure, by the descent of the base of the brain into the foramen magnum. It thus comes about that the bulb lies in the upper part of the vertebral canal, and is cut off from intra-cranial pressure by the blocking of the foramen magnum. It seems possible that the circulation may yet continue through the bulb after it may have been brought to a stop in the brain by any pathological condition producing increased intra-cranial pressure.

On the above grounds we cannot agree with Roy and Sherrington that the rise of blood-pressure in pathological conditions of increased intra-cranial pressure is protective in function. For it does not, as these authors affirm, help to maintain the cerebral circulation. If a large area of cerebral capillaries be obliterated by a foreign body as in cases of hæmorrhage, a rise of arterial pressure will not only increase the hæmorrhage, but will cause progressive anæmia of other parts of the brain.

In our opinion the old method of producing low arterial tension by depletion and purgation is the right treatment in these pathological cases of increased intra-cranial pressure.

SUMMARY.

Method. The simultaneous record of general arterial pressure, general venous pressure, intra-cranial pressure, and cerebral venous pressure.

Experimental results.

1. No evidence has been found of the existence of cerebral vaso-motor nerves; either by means of stimulation of the vaso-motor centre or central end of the spinal cord, after division of the cord in the upper dorsal region; or by stimulation of the stellate ganglion, and that is to say the whole sympathetic supply to the carotid and vertebral arteries.

2. Evidence is not forthcoming of the existence of any local vaso-motor mechanism such as that indicated by Roy and Sherrington. The injection of acids and extract of brain have produced in our hands no active dilatation of the cerebral vessels.

3. In every experimental condition we find that the cerebral circulation passively follows the changes in the general arterial and venous pressures.

4. The intra-cranial pressure is in all physiological conditions the same as the cerebral venous pressure.

5. The volume of the brain is practically invariable.

6. There is no compensatory mechanism by which the intra-cranial pressure is kept constant. The intra-cranial pressure, which in all physiological conditions is circulatory in origin, may vary with the circulatory pressure from zero to 50–60 mm. Hg. The functions of the brain matter continue in this varying condition of pressure.

7. In all physiological conditions a rise of arterial pressure accelerates the flow of blood through the brain, and a fall slackens it.

8. In pathological conditions where there is occlusion or inflammatory dilatation of large capillary areas in the brain, the opposite effects occur. In these conditions a rise of arterial pressure diminishes the cerebral blood flow and a fall accelerates it.

9. Any foreign body in the cranial cavity will obliterate capillaries, raise the intra-cranial pressure, and produce cerebral anæmia.

10. The brain matter does not suffer from pressure alone, but from pressure producing anæmia.

11. The rise of arterial pressure that occurs in pathological conditions of increased intra-cranial pressure, is not protective but tends to increase the extent of the cerebral anæmia.

12. The right direction of treatment therefore in such conditions is to lower the blood-pressure.

REFERENCES.

Bayliss and Starling. This Journal. 1894.
Dean. Journal of Pathology. 1892.
Donders. Onderzoekingen ged. in het phys. Lab. Utrecht. 1850.
Falkenheim and Naunyn. Arch. f. exper. Path. u. Pharm. 1886–7.
Gaertner and Wagner. Wien. med. Wochenschr. 1887.
Geigel. Arch. f. pathol. Anat. 1891.
Grashey. Festschr. für L. A. Buchner. 1892.
Hill. Pr. Roy. Soc. 1893. This Journal. 1895.
Hill and Nabarro. This Journal. 1895.
Kellie. Edin. Med. Chir. Soc. Trans. 1824.
Key and Retzius. Studien in der Anatomie des Nervensystems. 1875.
Knoll. Sitzber. d. kais. Akad. d. Wiss. 1886.
Lewy. Arch. f. pathol. Anat. 1890.
Monro, Alex. Observations on the structure and functions of the Nervous System. 1783.
Roy and Sherrington. This Journal. 1890.
Salathé. Trav. du labor. de Marey. 1876.
Schäfer and Oliver. This Journal. 1895.

PART II. BY G. LOVELL GULLAND.

ABOUT two years ago, I began, at Dr Batty Tuke's suggestion, to examine the question as to whether there were or were not vaso-motor nerves in the brain, or, to speak more exactly, whether it was possible to demonstrate nerve-fibrils in the walls of the intra-cranial blood vessels. The results I obtained then, and on the subsequent occasions when I examined the matter, were entirely negative. In view of the experimental results obtained by Hill and Bayliss it is perhaps worth while to put my histological observations on record.

The methods I employed were the usual Golgi methods with various modifications and Ehrlich's methylene-blue method. The brains examined were those of cats and rabbits, adult, young and embryonic, and a number of human brains obtained as fresh as possible from the post-mortem room.

As regards the Golgi methods, in some cases the brains were examined by sections cut either with the free hand, by freezing, or under alcohol in a microtome after superficial enclosure in paraffin. In other cases portions of the pia mater were stripped off and a number of intra-cerebral vessels were of course pulled out with them. These portions of pia mater were rolled up as Cajal recommends in the case of the retina, and impregnated as usual. In addition to the ordinary osmium and bichromate of potash mixture used for hardening in the rapid process, I have tried Berkley's mixture, and a number of others such as solutions containing bichromate and chromic acid in varying proportions, Flemming's solution, Erlicki's fluid, Kultschitzky's solution, &c. In order to avoid, if possible, the precipitate of chromate of silver on the surface,—of the pia mater especially—I have tried the addition of formic acid to the silver solution, and also Lehrwald's plan of superficial enclosure in gelatine before the silver bath. Neither of these methods were, in my hands, of any use at all, and I got the best results, in this respect, from rapidly washing the pieces of tissue in distilled water, after they had been removed from the bichromate solution, and then rinsing them in $\frac{1}{4}$ p.c. nitrate of silver solution, renewed several times, before putting them definitely into the silver bath. This, in my opinion, is best used of $\frac{3}{4}$ p.c. strength.

It has been known empirically for some time that nerve-fibres were often impregnated alone in those pieces of tissue which had remained

for several days in the bichromate solution, and Ramon y Cajal[1] has recently pointed out that this is due to overhardening. Berkley[2] utilized the fact in his work on nerve-fibres in the liver by hardening, after treatment with picric acid, in a fluid rich in bichromate and osmic acid for a relatively long time, and by hastening the process by heat. His method does very well for such tissues as the liver, and I have found it show vascular nerves beautifully in the bladder, for example. The cerebrum becomes too brittle however and the sections fall to pieces very readily. I have varied the time of hardening with all the solutions I have mentioned. Golgi's and Cox's sublimate methods were also tried.

The methylene blue was used generally in the proportion of 1 to 1000 of salt solution. As it was of importance to see as much of the process of impregnation as possible I did not inject the methylene blue into the blood vessels, but immersed small portions of pia mater or of the cerebral vessels in the solution, and watched the process under the microscope. I used the cornea and iris in all cases as a control and had no difficulty in staining the nerve-fibrils in them in this way, nor in fixing them with picrate of ammonium.

The net result of all these observations was that neither by the silver, the mercury, nor the methylene blue method could I succeed in demonstrating any nerve-fibres in the walls of the pial vessels nor of the intracerebral vessels.

In the Golgi preparations the blood vessels, especially the smaller ones, are often impregnated as a whole, and sometimes a partial impregnation of this sort gives an appearance like a nerve plexus. Again in the larger vessels especially, the longitudinal network of elastic fibres is often impregnated, but it is quite easy to distinguish this from the nerve plexus of ordinary arteries. The processes of neuroglia cells attached to an artery and running along it as they often do, for a little way, might also give rise to error.

[1] *Les nouvelles idées sur la structure du système nerveux.* Paris. 1894. p. 183.

[2] "Studies in the histology of the liver." *Anat. Anz.* VIII. 1893.