THE CEREBRO-SPINAL FLUID. II. CEREBRO-SPINAL PRESSURE.

By W. E. DIXON and W. D. HALLIBURTON.

(From the Physiological and Pharmacological Laboratories, King's College, London, and the Pharmacological Laboratory, Cambridge.)

CONTENTS.

Introductory. The present paper is the outcome of investigations which followed on those recorded in the first paper of this series[1]. Our object was to examine the cerebro-spinal pressure under various experimental conditions. It will be referred to in subsequent pages as the C.S. pressure.

This pressure has been measured by a manometer by numerous observers, and it will be seen from the following figures[2] that it varies within considerable limits. In the majority of cases the observations were made in dogs in the horizontal position and the pressure was taken in the lower dorsal region. Cybulski 72–90 mm. of water, Adamkiewicz 80–100, Axel Key and Retzius 160–200, Bergmann 80–160, Quincke 40–60, Schultzen 52–100, Kronig 125–150, Parisot 100–150, Boveri 170–200.

Among these observers Axel Key and Retzius noted differences caused by respiration, their figures being 100–200 mm. of water during

[1] This *Journal*, XLVII. p. 215. 1913.

[2] Taken from p. 85 of Mestrezat's book *Le liquide cephalo-rachidien normal et path.* Paris, A. Maline, 1912. See also Cavazzani, *Arch. ital. de Biologie*, p. 475. 1893.

inspiration, and 250–275 during expiration. H. Falkenheim and B. Naunyn[1] give nearly the same estimate (160–200 in inspiration, and 250–275 in expiration). They also made extensive observations in dogs under ether anæsthesia, and under these circumstances place the normal C.S. pressure with the cannula inserted into the lumbar region, at 30–38 mm. of water, but state that when the carotid blood-pressure is high the C.S. pressure rises a variable amount and may reach 140 mm. of water (= 10·5 mm. Hg). They adopt the view that the fluid is a true secretion, and that it is formed in all probability by the choroid plexuses.

They also state that changes of arterial blood-pressure are accompanied by similar changes in cerebro-spinal pressure; in strychnine convulsions the cerebro-spinal pressure rose but they incline to the view that this is mechanically produced and is not due to an increase of secretion. Compressing the veins leaving the central nervous system also raises the pressure in the cerebro-spinal fluid apparently by mechanical means. L. Hill[2] in his work on the cerebral circulation calls attention to the fact that variations in the cerebro-spinal pressure are closely related to alterations in venous pressure.

The present observations were made by connecting a cannula inserted into the subcerebellar cisterna, as described in Part I, with a manometer containing salt solution. The long arm of the manometer was connected by tubing to a Marey's tambour in which the rubber was so loose that within certain limits it recorded true volume changes. The tambour was calibrated before each experiment. Dogs anæsthetised with morphine and urethane were employed in all experiments.

It must be remembered that a manometer connected up in the manner described will transmit variations in pressure which may be due to many factors; increased secretion, or a block in the movement or absorption of the cerebro-spinal fluid, will obviously augment its pressure; but besides these, variations in the arterial blood-pressure transmitted through the brain substance, and in the venous pressure will also modify the result. Cerebral venous pressures were recorded by trephining over the torcula, removing the bone, and screwing in a brass tube connected with a manometer containing half saturated sodium sulphate or 10 % sodium citrate solution. A record was obtained by measuring the movements in the distal limb of the manometer. Indications of the changes in the cranial contents were also taken by a cup-shaped

[1] *Arch. exp. Path. u. Pharm.* XXII. p. 261. 1887.

[2] *The Physiology and Pathology of the Cerebral Circulation.* London, 1896.

oncometer, one inch in diameter which when applied over a trephine hole of the same diameter could be made air tight by a clamp. Respiration as we have pointed out in Part I always exerts a profound effect on the rate of secretion so that in observations on pressure it is important that respiration should remain unchanged, and in all the present experiments efficient artificial respiration was performed throughout.

1. Experiments on the dead animal.

Since the brain and its vessels and lymphatics are enclosed in a bony case it has generally been assumed that the brain and its vessels occupy the whole skull and that the brain being incompressible the total blood content is almost constant. This hypothesis is generally spoken of as the Monro-Kellie doctrine, and it has obtained general recognition. The advocates of this view suggest that the brain can increase its blood content only by turning out the cerebro-spinal fluid and that when this fluid has gone the brain comes in contact with the skull so that no further expansion of vessels can occur.

In order to test the validity of this hypothesis, experiments were performed in which the torcula pressure, arterial blood-pressure and C.S. pressure were recorded simultaneously, and sometimes the right auricle pressure was also recorded.

The first series of experiments were performed on the dead animal and in these the torcula pressure and C.S. pressure were recorded, a 20% solution of sodium citrate being used in both the manometer tubes. The death of the animal was caused by chloroform, hydrocyanic acid, or asphyxia. The artificial respiration was always kept up after death as the small oscillations in the pressures caused by this means served to facilitate movements of the fluid in the manometer tubes.

Although the circulation was stopped the blood remained fluid in the vessels, so that it was possible to test the effect of alterations of one pressure upon the other. Generally the two pressures were nearly equal, the venous being a little higher than the C.S. pressure. The venous pressure can be readily raised by injecting fluid into either the femoral vein or artery. Supposing that the initial artificial pressure in millimetres of 20% sodium citrate solution is between 50 and 60 mm. in each manometer, then raising the venous pressure to 130 mm. suddenly, causes only a gradual rise in the C.S. pressure of from 5 to 10 mm. which reaches its maximum after the venous pressure and falls only very slowly (see Fig. 1). A better method of

increasing the venous pressure consists in compressing the abdomen with the hand, this raises venous pressure suddenly 50 or 60 mm. and when the hand is removed the fall is equally sudden (see Fig. 2); the C.S. pressure however rises very gradually 8 or 9 mm. but falls again suddenly when the increased venous pressure is removed. In these cases the initial C.S. pressure was low and a relatively large increase of venous pressure produced very little influence on the C.S. pressure.

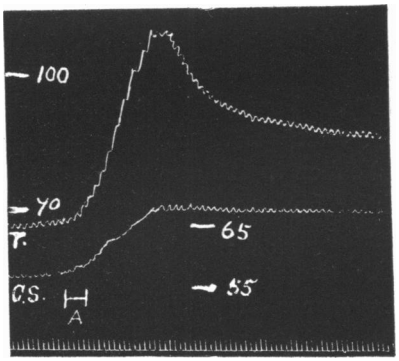

Fig. 1.

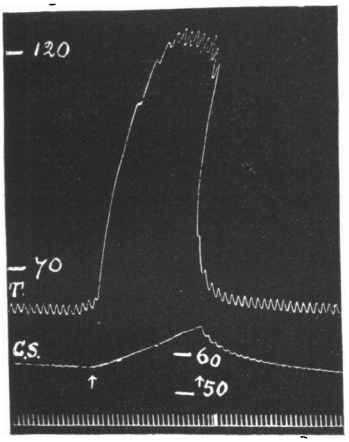

Fig. 2.

Fig. 1. Dog killed by chloroform. Torcula and C.S. pressures in 20 % sodium citrate solution. Shows the effect of injecting (at A) 45 c.c. normal saline solution into the femoral vein. Time = secs.

Fig. 2. Dog killed by chloroform. Torcula and C.S. pressures in 10 % citrate solution. Shows the effect of compressing the abdomen with the hand. Time = secs.

In another experiment the two pressures at the commencement were roughly equal and represented 120 mm. of 20 % sodium citrate solution. In this instance small changes of the venous pressure produced exactly similar changes of pressure in the C.S. fluid. In other words at this degree of distension in the dead animal the cerebral venous pressure exerts a decided passive influence on the C.S. pressure. It is clearly wrong then to imagine that the C.S. pressure must equal that of cerebral venous pressure. The ventricles of the brain hold an appreciable quantity of fluid and when this is at a relatively low pressure (such as 60 mm.) it is only with difficulty that the pressure can be increased passively by augmenting the venous pressure. If however the C.S. pressure is high to start with (100 mm. or more), so that the ventricles are distended with fluid, then this pressure is more sensitive to changes in venous pressure and within certain limits

these two pressures may run parallel courses. Furthermore it cannot be argued that the C.S. pressure does not rise because the fluid escapes along the natural channels, since if it is raised artificially by the direct introduction of fluid it becomes equal to and runs parallel with the venous pressure for an indefinite period, and in this state of high tension, absorption of the fluid if it occurred at all in a dead animal should be greater than at the lower pressure.

2. Normal pressure.

It has been pointed out already that after death the cerebral venous and C.S. pressures may or may not approximate to one another according to certain conditions. The same rule holds true during life. For example in one experiment on a dog the pressures at the commencement were; torcula 340, C.S. 190 mm. of 10 % sodium citrate solution. Ten minutes later the pressures measured; torcula 260, C.S. 170, and fifteen minutes later the venous pressure had fallen to 160 and the C.S. to 100. After the death of the animal one hour from the first record the two pressures were approximately equal at 65 mm. This is no exceptional condition. In other experiments the two pressures have remained roughly parallel throughout, unless experimental procedures have been adopted to alter them, but the venous was always higher than the C.S. pressure. Perhaps the most remarkable feature of the C.S. pressure viewed from the physical side is the fact that relatively small circulatory changes as determined by the general arterial and venous pressures may cause large changes in the cerebral venous pressure but have very little effect on the C.S. pressure.

The normal pressure of the cerebro-spinal fluid is variable as previous observers have noted, but in most of the present experiments in which the animals were anæsthetised in the manner mentioned and in which sodium sulphate was used in the manometer tubes the normal pressure was nearer the lower than the higher limits of the figures already given, a rough average being 40–70 mm. of salt solution.

In the case of one dog the pressures which were taken with similar manometers using a 10% citrate solution varied during the experiment as follows:

Observations at 5-minute intervals.

Arterial blood-pressure	140—120—110—140—150—170—165—130—140—100—120—110—115—115—120—120 mm. Hg.
Venous pressure	350—294—280—260—280—260—300—415—225—230—220—230—260—330—240—255 mm. citrate solution.
C.S. pressure	95— 25— 30— 35— 55— 25— 80— 65— 65— 75— 70— 60— 55— 50— 80— 90 mm. citrate solution.

These figures are typical of numerous other experiments. The venous and arterial pressures in the above experiment are higher than normal, but the C.S. figures are typical. It is quite evident that no simple relationship can be obtained between any of these, which may vary quite independently of one another. One law always holds, however, under all ordinary conditions; the arterial blood-pressure is always higher than the venous pressure, and the venous pressure than the C.S. pressure.

The use of citrate solution in the manometer tubes is more satisfactory than sulphate as regards prevention of clotting, but it has disadvantages. If much of the solution reaches the general circulation, the deficiency of ionic calcium in the body renders the central nervous system hyperactive so that the arterial pressure, venous pressure and C.S. pressure are all high and natural respiration is very difficult to paralyse with anæsthetics. In the present experiments half saturated solution of sodium sulphate was used in the torcula manometer and normal saline in the C.S. manometer unless it is stated otherwise.

3. Effect of changes in arterial blood-pressure.

(*a*) *Hæmorrhage.* The simplest method adopted for lowering blood-pressure was bleeding; in one typical experiment during natural respiration 100 c.c. of blood was removed from the femoral artery of a dog, after two minutes a second 100 c.c. and still later a third 100 c.c. The blood-pressure and cerebro-spinal pressure fell together at each withdrawal of blood but the first bleeding produced much the greatest effect. The animal was then bled to death, but no further fall in C.S. pressure was registered, and at the moment of death when respiration ceased, the pressure rose 20 mm. In another experiment the effect of drawing off from the femoral artery 200 c.c. of blood was to cause a fall in the C.S. pressure of 30 mm. saline. The curves of systemic blood-pressure, cerebral venous pressure, and C.S. pressure showed in their broad features similar outlines but the relative amount of fall was very much greater in the case of the arterial and

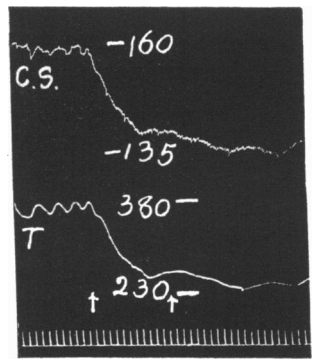

Fig. 3. C.S. and torcula pressures in 10% citrate solution. Shows the effect of withdrawing 75 c.c. blood from the femoral artery. Time = 2 secs.

venous pressures. At the end of one experiment (Fig. 3) 75 c.c. of blood was withdrawn, this caused a fall in torcula pressure from 380 to 230 mm. of 10% citrate solution and a fall in C.S pressure from 160 to 135 mm. of the same solution. In these cases the fall in C.S. pressure should be regarded therefore as passive, the direct result of the altered vascular conditions.

(*b*) *Compressing blood vessels.* Compression of the aorta is a simple and uncomplicated way of raising the arterial pressure in the cerebral region. The aorta had a ligature passed round it just below the diaphragm and drawn through the abdominal wound which was

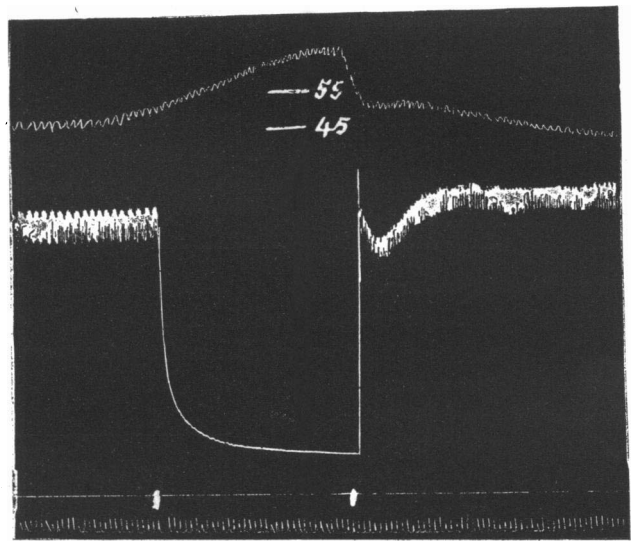

Fig. 4. C.S. pressure in normal saline and blood-pressure in femoral artery. Shows the effect of compressing the abdominal aorta. The blood-pressure in the carotid artery rose 45 mm. Hg. Time = secs.

then closed: by putting some tension on this ligature the lumen of the artery was blocked completely. In one dog on which this experiment was tried the original pressure of the cerebro-spinal fluid was equal to 50 mm. of salt solution: the aorta was compressed for brief periods of 10 or 20 seconds and the C.S. pressure rose in successive compressions, 8·5 and 15 mm. (see Fig. 4). On ceasing the compression the pressure rapidly fell to the normal, and then more slowly until a subnormal pressure was reached: the fall below normal after compression usually approximated to the rise above normal during the compression. In the

experiment quoted the falls of pressure following on the rises of 8·5 and 15 mm. were 7·3 and 22 mm. saline respectively. The "brain volume" showed a corresponding slight increase and the venous pressure in the brain measured by taking the pressure in the torcula a much more considerable effect. Any such rise in the carotid blood-pressure then is associated with a corresponding rise in (1) venous pressure (relatively large), (2) in C.S. pressure (relatively small), and (3) increase in the brain volume. If the C.S. fluid is free to escape from an open cannula during the rise in pressure, then after the first slight gush due to the increased vascular volume in the cranium, secretion either ceases or goes on at its normal rate. In other words such vascular changes do not augment the C.S. secretion. The rise in pressure is entirely the result of the altered vascular conditions. This being so it is natural to expect that the pressure would fall after a time even whilst the altered vascular conditions obtain, on the assumption that there is a free outlet for the escape of fluid. That the outlet is free is easily shown by puncturing the theca lower down and placing a second cannula in the mid-dorsal region; if 20 c.c. of saline are injected into this cannula the C.S. pressure as measured by the cannula in the subcerebellar cisterna rises but the extra fluid is soon absorbed and the pressure falls again to normal. So long, however, as the aorta is clamped the C.S. pressure remains up within the limits of experiments which extended for some two or three minutes. On two occasions the pressure was continued for a quarter of an hour; in these instances the pressure gradually fell but came to rest before the normal was reached. These facts suggest that the increased C.S. pressure is due to the altered vascular conditions and that these conditions either prevent the free absorption or facilitate the secretion of fluid and so keep the pressure high. The fact, which is well recognised clinically, may be pointed out here that sudden rises in blood-pressure in man such as may occur for example in acute nephritis are associated with augmented pressure in the C.S. fluid. This subject will receive further consideration in a later paper.

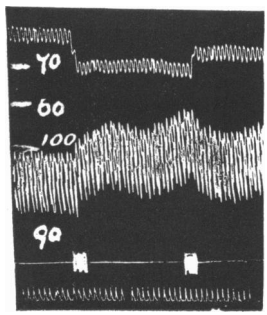

Fig. 5. C.S. pressure and blood-pressure in femoral artery. Shows the effect of compressing both carotids. Time = secs.

(*c*) *Clamping both carotid arteries* is another method of interfering with the circulation so as to induce purely passive effects on the C.S.

fluid. The effect is shown by a relatively great fall in venous pressure, a relatively small fall in C.S. pressure 5–7 mm. of saline (Fig. 5), and a diminution of "brain volume." If the two vertebral arteries are tied first, clamping the carotids exerts a more decided action but even this procedure only causes a fall of 10–15 mm. in the C.S. pressure.

(*d*) *Stimulation of the vagus and sympathetic nerves.* Excitation of the central end of the vagus is yet another means of causing a considerable rise of both arterial and cerebral venous pressures; the C.S.

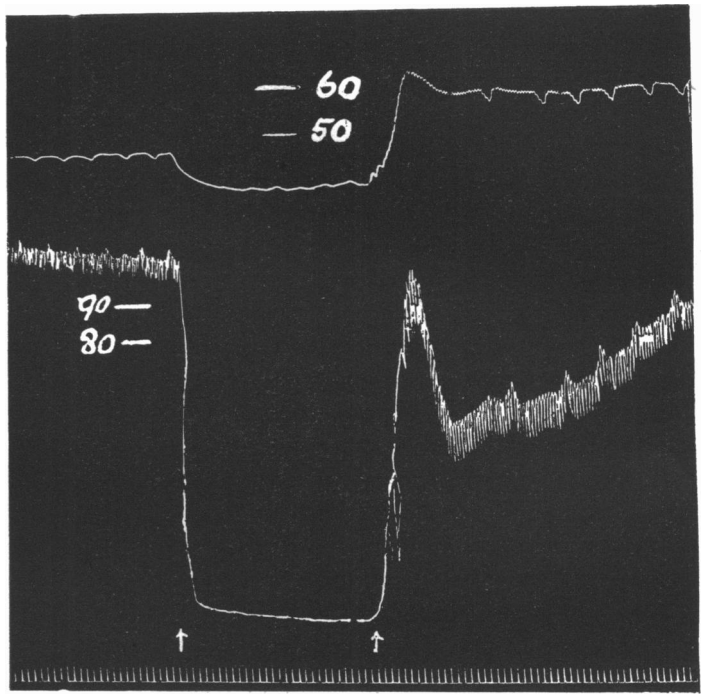

Fig. 6. C.S. pressure and arterial blood-pressure. Shows the effect of exciting the right vagus with the secondary coil at 10 cms. Time = secs.

pressure rises also to a small extent. The character of the rise is very similar to that which is caused by compressing the aorta and may be regarded as the result of the altered vascular conditions. In these experiments it was noted that the C.S. pressure often begins to fall and even reaches normal during a stimulation lasting only 40 or 60 seconds. A subnormal pressure then invariably occurs before the constant normal level is reached. Stimulation of the peripheral end of the cervical sympathetic which had been carefully separated from

the vagus never produced changes in the C.S. pressure nor in the torcula pressure.

Excitation of the peripheral end of the vagus causes both immediate and delayed effects. The immediate effects are, of course, a fall in carotid blood-pressure; less blood passes to the brain and therefore the brain volume diminishes. The cerebral venous pressure is dependent upon the systemic arterial blood-pressure and the right auricular pressure: the former drops almost to zero whilst the latter rises very considerably. The torcula pressure therefore varies according to these two factors. Usually whilst the stimulus lasts (say for 30 seconds) a small fall in the torcula pressure is recorded but when the stimulation ceases the arterial pressure rises before the veins can efficiently empty themselves; therefore a very considerable increase in the torcula pressure may occur at this time (Fig. 8). The C.S. pressure would not be influenced directly by cardiac inhibition but as both the arterial and venous cerebral pressures fall it might be expected that some passive diminution would occur, and this is frequently the case (see Fig. 6). Thus in one experiment a short vagal stimulation lasting 20 seconds, and which produced decided cardiac slowing and fall of blood-pressure equal to 50 mm. of mercury, also caused a fall in torcula pressure equal to 40 mm. of sodium sulphate solution and a fall of C.S. pressure equal to 15 mm. of saline.

When the stimulation ceased the C.S. pressure rose immediately 35 mm. that is 20 mm. above the normal and then slowly regained the normal condition.

We have pointed out in Part I that stoppage of the circulation tends to increase, at least for two or three minutes, the secretion of C.S. fluid so that during a long stimulation of the vagus (after the initial passive fall) the C.S. pressure begins to rise very slowly at first, but more rapidly later, and when the stimulation of the vagus is stopped and the blood-pressure recovers, the C.S. pressure rises considerably above the normal. After cessation of the stimulus and especially if the carotid pressure rises much above the normal the brain volume and torcula pressure will be increased correspondingly but the rise of C.S. pressure is greater than can be accounted for by any such passive effect. Furthermore in some experiments in which vagal stimulation caused complete cardiac inhibition and in which the secretion of the fluid was especially active it was found that the cardiac inhibition (which produced a fall of carotid pressure to zero and a correspondingly large fall in torcula pressure) was unable to reduce passively the C.S. pressure; this commenced to rise

immediately gaining acceleration with each second of the stimulation (Fig. 7): for example during one experiment in which electrical stimulation of the right vagus with the secondary coil at 10 cms. caused a rise of 20 mm. of saline in the first 10 seconds, the continuation of the same stimulus caused a rise of 50 mm. in the next 20 seconds. This effect then must be due to increased secretion of fluid or to some failure of the fluid to escape; the former must be the more important factor since if the fluid is free to escape from an open cannula cardiac inhibition may cause a considerable increase in the rate of flow.

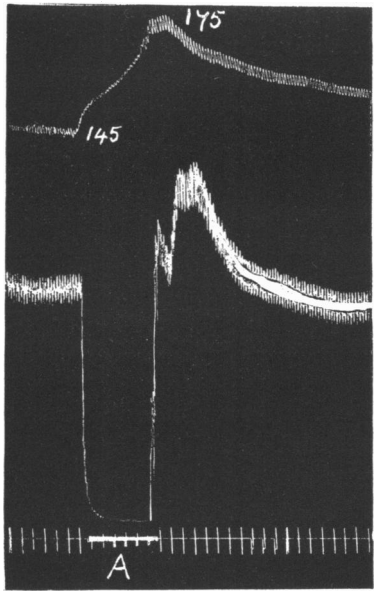

Fig. 7.

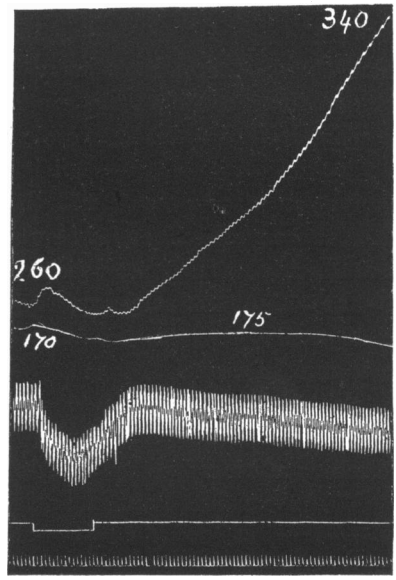

Fig. 8.

Fig. 7. c.s. pressure and arterial blood-pressure. Shows the effect of stimulating at 'A' the right peripheral vagus with the secondary coil at 10 cms. The torcula pressure is not recorded but it fell during the period of inhibition, but subsequently rose 40 mm. of sodium sulphate solution. Time = 5 secs.

Fig. 8. Torcula (upper line). c.s. and arterial pressures. Shows the effect of exciting the left vagus with the secondary coil at 15 cms. Time = secs.

From this it is clear that stimulation of the peripheral end of the vagus may cause (1) when the fall of blood-pressure is small a slight passive diminution of the c.s. pressure without any subsequent rise even though the torcula pressure rises greatly (Fig. 8); (2) an initial passive fall in pressure followed by a rise which commences whilst the

arterial and venous pressures are still low (Fig. 6); or (3) an immediate rise in C.S. pressure which may be regarded as being caused by increased secretion due to deficient oxygenation or collection of carbon dioxide in the brain (Fig. 7).

4. Passive effects of the C.S. pressure on cerebral venous pressure.

It becomes necessary now to examine how far these two pressures may influence one another by passive means. If the two cannulæ in the torcula and subcerebellar cisterna respectively are connected to two manometers, it is an easy matter to raise the pressure of the C.S. fluid and note the effect on the venous pressure. Such a rise always produces a passive increase in the cerebral venous pressure but not to the extent of the additional increase of C.S. pressure. Thus if the two pressures to start with are approximately 70 and 140 mm. then raising the C.S. pressure 100 mm saline increases the venous pressure only by about 40 mm. (Fig. 9): the rise is steep but not so steep as the fall when the pressure is removed If the pressure is increased to 200 mm. the rise in venous pressure is 75 mm. These figures are given for a rise of pressure lasting 45 seconds. At the end of this period the venous pressure was still actively rising and if the increased C.S. pressure is allowed to continue till no further change occurs in the venous pressure it is invariably found to be higher than the C.S. pressure, provided that the latter pressure has not been raised artificially more than a few hundred millimetres. It is evident therefore from the direct experiment that alterations in the C.S. pressure exert a marked passive action

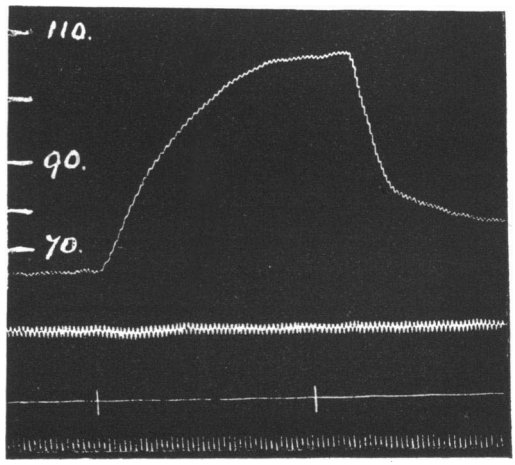

Fig. 9. Torcula and arterial blood-pressure. Shows the effect of raising the C.S. pressure 100 mm. of saline solution. Time = secs.

on the venous pressure, and provided no greater pressures than 100 or 200 mm. of saline are employed no material alteration occurs in the arterial blood-pressure. This factor requires careful consideration when investigating the action of chemical substances, as those which cause an increase of C.S. pressure from augmented secretion must cause secondarily some, though not a corresponding, increase in the cerebral venous pressure. It might be imagined that when the C.S. pressure exceeds the venous pressure as in the experiment quoted that so much pressure would be exerted as to partly block the venous circulation. This is not however the case. Measurements of the blood flow from the internal jugular vein during these conditions show no appreciable diminution in blood flow. If the C.S. pressure is raised still higher so that a serious block might be placed on the outflow of blood from the brain then in order to compensate for this condition the arterial blood-pressure also rises, but a consideration of these cases we defer to Part III. In all these pressure effects it is desirable to bear in mind that the vessels connecting the arteries to the veins are not under effective vaso-motor control, so that any rise of arterial blood-pressure is associated necessarily with a rise in venous pressure.

5. Passive effects of changes in cerebral venous pressure on the C.S. pressure.

This of course cannot be investigated by injecting fluid into the torcula since the fluid immediately drains away and the pressure remains at the same height. The injection of 50 or even 100 c.c. of saline into the torcula cannula within the space of 20 seconds exerts no decided influence on the C.S. pressure. The obvious method of increasing the cerebral venous pressure is to clamp the veins from the head as near to the right auricle as possible but without opening the thorax. Ligatures can be placed round these veins and the wound stitched up so that by gentle tension on the ligatures the lumina of the vessels are occluded. This procedure raises the pressure in both the torcula and cerebro-spinal fluid (see Fig. 10). By this means in three experiments the following figures were obtained:

	Exp. 1		Exp. 2		Exp. 3	
Torcula pressure	190	215	170	215	190	280
C.S. pressure	150	155	150	160	155	180

The first figure in each case represents the normal pressure and the second the maximum height to which the pressure rose as a result of

compression. It will be noted that in each instance the rise in C.S. pressure is only about one quarter that which occurs in the torcula. It may be pointed out also that in all these experiments the two series of pressures are very high. When they are lower, as is more usual, compressing the veins has little or no effect on the C.S. pressure. It follows therefore that the effect of C.S. pressure on cerebral venous pressure is considerably more important than the effect of cerebral venous pressure on C.S. pressure and that when the two pressures are low the passive effect of increasing the venous pressure is negligible.

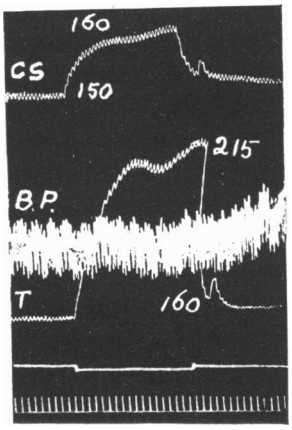

Fig. 10. C.S. pressure, arterial blood-pressure and torcula pressure. Shows the effect of compressing the veins in the neck. Time = 2 secs.

Compression of the abdomen with the hands is another means by which venous pressure may be raised but in this instance the experiment is not clean, for arterial blood-pressure may be materially altered, and the activity of the heart is changed, so that the significance of figures obtained by this method is not great. In three experiments the following figures were noted:

	Exp. 1		Exp. 2		Exp. 3	
Torcula pressure	245	260	240	255	120	130
C.S. pressure	180	190	80	90	60	65

The first figure represents the normal pressure and the second that obtained during compression. When the compression was stopped the venous pressure occasionally showed a secondary rise of from 50 to 100 mm. but this had relatively little effect on the C.S. pressure. The first effect is due to passive venous congestion brought about in the same way as ligaturing the veins, the second and delayed rise in venous pressure we think is due to increased cardiac output; at all events in these cases an increased cardiac output occurs and it is remarkable that this has very little or no effect on the C.S. pressure.

The torcula pressure may be raised by two principal means (1) passively, due to back pressure, (2) actively, due to increased cardiac output. When the pressure rises as a result of the former method it affects passively the C.S. pressure to a greater extent than when it rises as the result of increased cardiac output.

If the arterial and venous pressures are lowered, as for example by bleeding, the drop in the C.S. pressure is relatively small. It is certain then that the C.S. pressure is not greatly affected by circulatory changes except perhaps when it happens to be very high; it is an independent pressure and the factors determining its height are dependent on the rate of secretion and the rate of absorption of the fluid.

6. The effect on cerebro-spinal pressure of substances which increase the cerebro-spinal secretion.

The conclusion stated in the preceding sentence, that C.S. pressure is an independent secretory pressure (although it may be influenced passively by circulatory changes) received abundant confirmation when we proceeded to investigate the effects upon it which are exercised by substances which our previous work had shown us increase the flow of the fluid. Under this head, observations have been specially directed to three substances, choroid extract, chloroform and carbonic acid gas. The first was administered by intravenous injection and the two latter by inhalation.

The effect upon arterial blood-pressure of the first two is to cause a fall: it might therefore be anticipated that were this circulatory factor the only one concerned a simultaneous fall of C.S. pressure would occur; but in all cases the C.S. pressure rises and it is obvious that the change in arterial pressure cannot produce that effect. It is, however, important to remember that all three substances increase the cerebral venous pressure, and so it is necessary to prove that this vascular change is not the cause of the rise in C.S. pressure.

(*a*) *Choroid extract.* We have already shown that extracts of the choroid gland increase the rate at which the C.S. fluid is excreted from an open cannula: the injection of this substance should therefore increase the C.S. pressure, and as a matter of fact the injection of 5 c.c. of a 1% solution into a vein always causes an increase in the pressure. Usually the rise commences at once and is synchronous with the fall in arterial blood-pressure (Fig. 11), but sometimes a latent period of half a minute or longer may follow the injection, and during this time the pressure either remains constant or may fall slightly. The rise in C.S. pressure is generally about 20 or 30 mm. of saline, and lasts two or three minutes. The venous pressure usually falls a trifle immediately after the injection probably on account of the diminished output from the left ventricle but when the arterial blood-pressure rises the cerebral venous pressure rises more rapidly and may rise as much as 20 mm. of

sulphate solution above the normal. This rise in the torcula pressure is associated with a small rise in the right auricular pressure, and similar effects can be obtained with numerous other substances (such as the choline group) which slightly depress the heart and cause a fall in systemic blood-pressure.

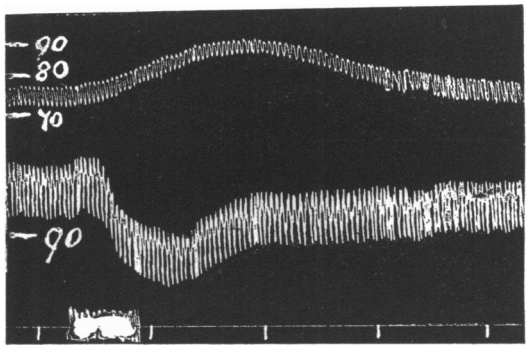

Fig. 11. c.s. pressure and arterial blood-pressure. Shows effect of injecting 5 c.c. 1 % solution of boiled choroid extract into femoral vein. Time = 30 secs.

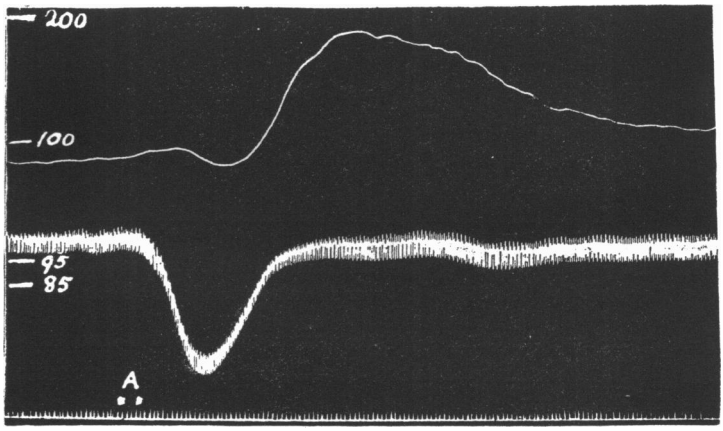

Fig. 12. Torcula pressure and arterial blood-pressure. Shows effect of injecting at 'A' 5 c.c. 1 % solution of boiled choroid extract into femoral vein. Time = secs.

The curves of c.s. and venous pressures do not run parallel with one another, as the former generally rises immediately after injection, whilst the latter rises only when the arterial blood-pressure commences to rise (Fig. 12). It may be noted that in one instance in which no change in the arterial blood-pressure was registered as the result of an

injection, the rise in C.S. pressure was nevertheless well marked. The increase in C.S. pressure is therefore specific and due to increased secretion of fluid.

(*b*) *Anæsthetics and hypnotics.* Chloroform inhalation generally produces a much more decided increase in C.S. pressure than choroid extract: a rise of 40 mm. is no uncommon effect. The cause of this must be due to one of three conditions. It may be that some cause is damming up the secretion so that its natural outlet is blocked: this however cannot be the explanation since we have shown already in

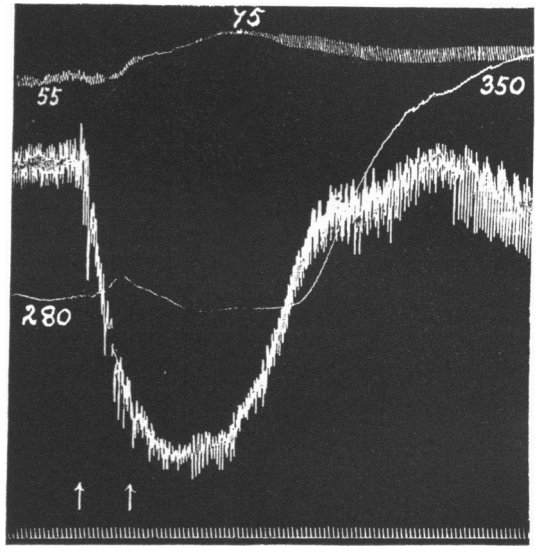

Fig. 13. C.S. pressure (top line), arterial pressure, and torcula pressure. Effect of chloroform inhalation (between the arrows). Time = 2 secs.

Part I that chloroform causes a greatly increased flow of secretion. The effect might be caused by altered circulatory conditions pressing upon the channels in which the C.S. fluid lies. The arterial blood-pressure certainly cannot effect this since it always falls whilst the C.S. pressure rises. The venous pressure does not always behave in the same way during the inhalation of chloroform. Usually after relatively small doses the torcula pressure rises and this rise occurs soon after the arterial blood-pressure begins to fall but neither its height nor length corresponds with the fall in arterial blood-pressure. This rise must be due to the increased right auricular pressure since it occurs at a time when the output of blood through the carotids is diminished. Larger doses of chloroform

which lower the arterial blood-pressure to a great extent still cause the immediate rise in C.S. pressure, but now the torcula pressure also falls and may remain subnormal often until the arterial blood-pressure has reached its normal height. The venous pressure now begins to rise rapidly often going up 100 mm. of sulphate solution, but even this sudden rise exerts no effect on the C.S. pressure (see Fig. 13). The venous pressure is dependent on two factors (1) cardiac output and (2) resistance on the right side of the heart, that is right auricular pressure: the fall which occurs first is due to diminution in the cardiac output and the second effect (the rise) to increase in right auricular pressure. From this it is certain that the C.S. pressure is completely independent of cerebral venous pressure so that only one explanation remains which can account for the phenomenon, namely that it is due to an entirely independent secretory pressure. Other anæsthetics and hypnotics produce similar types of effect to those described. Urethane injected slowly into the circulation may cause an increase in the C.S. pressure without influencing either the systemic blood-pressure or torcula pressure. Ether given by inhalation also causes very little fall in arterial blood-pressure or rise in venous, and alcohol often none, and yet both of these cause some increase in the C.S. pressure though not to the same extent as chloroform.

(*c*) *Carbon dioxide.* It has been shown already that an excess of carbonic acid in the blood increases the rate of flow of the C.S. fluid from an open cannula placed in the cisterna, and this at a time when the blood-pressure is not materially raised. It might be expected then that this gas when inhaled should increase the C.S. pressure. This expectation has been confirmed. The gas has been administered by the respiration pump freely diluted with air in amounts varying from 2 to 20 %; though usually 3 or 4 % produced a decided effect yet 10 % produced a better result in the short period during which it was administered. In these experiments the animal must be anæsthetised sufficiently deeply to prevent spontaneous respiratory efforts. The effect begins a few seconds after the inhalation commences; the C.S. pressure rises steeply whilst for a time the venous pressure remains unchanged. Then the venous pressure also slightly rises and its contour closely follows the curve of the C.S. pressure except that the degree of change is much smaller (see Fig. 14). When the inhalation ceases the C.S. pressure falls, but more slowly than it rises and takes perhaps two or three times as long to reach the normal as it takes to rise to its maximum height. The rise in venous pressure is

insignificant and can be explained by the passive effect of the rise in C.S. pressure and perhaps also by the rise in arterial pressure when this occurs. The reasons for this view are that the changes in venous pressure always follow accurately those of the C.S. pressure and because the pressure in the right auricle often remains unchanged at a time when the torcula pressure is maximal. The increased C.S. pressure then must be regarded as a pure secretory rise and the changes in venous pressure as partly at least a passive effect the direct result of this.

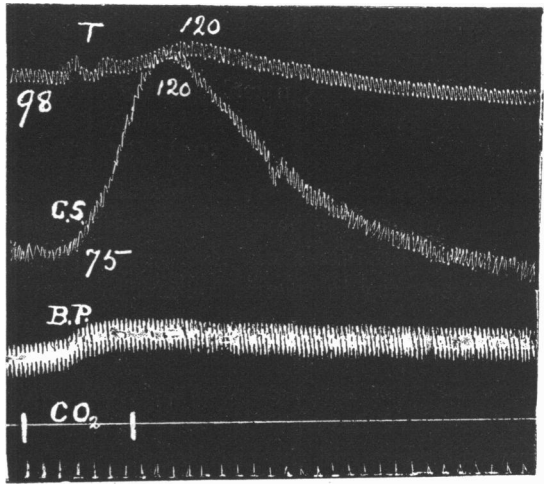

Fig. 14. Shows effect of inhaling 5 % CO_2 in the air. Time = 5 secs. (T = torcula pressure; C.S. = C.S. pressure; B.P. = arterial pressure.)

7. Asphyxia.

The changes in the C.S. pressure during asphyxia were studied in animals so deeply anæsthetised that the medulla had lost its respiratory action. At the instant artificial respiration is stopped, in typical experiments the torcula pressure first falls a trifle, it then gradually rises with the rise in arterial pressure and continues to rise when the arterial pressure begins to fall, rising much more steeply when the heart fails (see Fig. 15). These changes closely correspond with the changes of pressure in the right auricle though the sudden rise in torcula pressure during cardiac failure is more marked than the corresponding increase in pressure which occurs in the right auricle.

The C.S. pressure rises almost immediately, slowly at first but more rapidly later and often goes up as much as 100 mm. of saline (Fig. 15). This pressure commences to fall before the arterial blood-pressure has reached its maximum height and long before there is any decided increase in venous pressure. During the sudden rise in torcula and general venous pressures the C.S. pressure is rapidly falling and when the venous pressure is not far from its maximum the C.S. pressure may be down far below its normal.

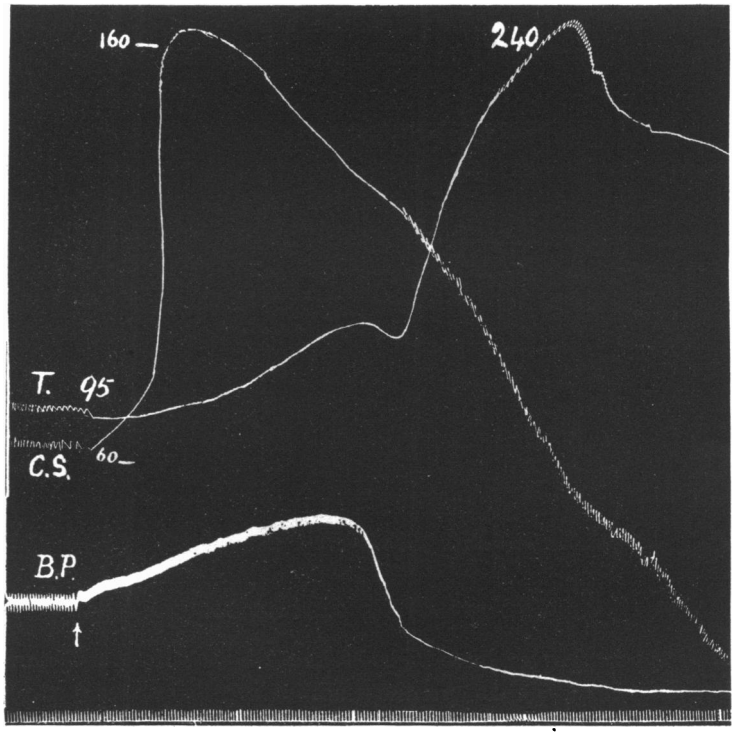

Fig. 15. Asphyxia. Time = secs.

Clearly then the changes in C.S. pressure cannot be accounted for by vascular conditions, but they can be explained on the assumption that carbonic acid which collects in the blood during asphyxia excites the secretory epithelium to activity and produces a secretory pressure which is entirely independent of all vascular changes. The general appearance of the curve is the same as that which is obtained when an excess of carbonic acid is inspired at a time when a plentiful supply of oxygen is

reaching the blood. The final fall in the C.S. pressure must be referred to the circulatory failure, and no very decided fall occurs until the heart has nearly ceased beating.

If the animal has been receiving other substances which influence secretory activity and if the asphyxia is performed at the end of an experiment devoted to other objects the typical effect of asphyxia is often lacking, that is the sudden rise in C.S. pressure whilst the arterial and venous pressures are almost constant. In these instances the C.S. pressure may closely follow the curve of the arterial blood-pressure, gradually rising to a maximum at the time when blood-pressure is maximal and falling during cardiac failure (Fig. 16).

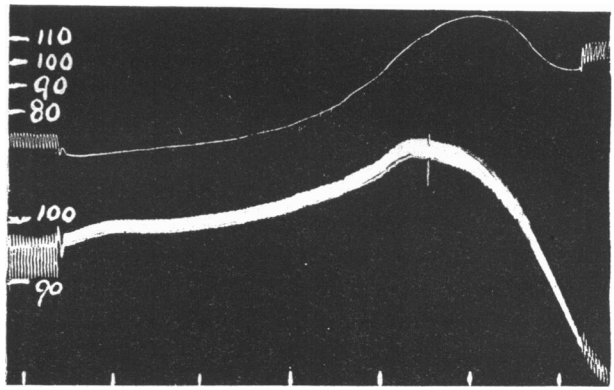

Fig. 16. C.S. pressure and arterial blood-pressure. Asphyxia. Time = 30 secs.

8. THE EFFECT OF CERTAIN DRUGS.

Three typical drugs have been taken to illustrate the effect of vascular changes on the C.S. pressure, adrenaline to represent a typical vaso-constrictor, amyl nitrite to represent a vaso-dilator, and pilocarpine to represent the group of drugs which induce cardiac inhibition.

(*a*) *Adrenaline.* The rise of arterial pressure produced by this substance is always accompanied by a rise in the fluid of the manometer connected with the cranio-spinal space (see Fig. 17). This begins with the rise in systemic pressure and follows it until a maximum is reached but after this the two curves no longer run parallel. The C.S. pressure tends to fall much more rapidly than the blood-pressure so that when the blood-pressure is normal the C.S. pressure may register 20 or 30 mm. of saline below normal. The rise in C.S. pressure is

apparently mechanical, the direct result of the filling of the cerebral arteries and veins and the transmission of the increased pressure through the C.S. fluid to the manometer.

The pressor action is associated with increased torcula pressure and increased "brain volume," but the increase in these pressures is not comparable with that which obtains during cardiac failure, asphyxia, or after chloroform inhalation: these two curves run a course roughly parallel with the systemic arterial pressure and must be regarded as the direct outcome of it. It may even be stated in general terms that all drugs which increase blood-pressure cause a corresponding increase in the cerebral venous pressure, and as may be seen if a cerebral vein is opened, a greatly increased flow of blood occurs, which is roughly proportional to the rise of blood-pressure, an additional proof if one were needed that the cerebral vessels possess no efficient vaso-motor nerves. The C.S. pressure then does not follow the blood-pressure except during the rise. It is not uncommon to notice in the atropinised dog that the C.S. pressure may be increased 40 mm. of saline and in the normal dog 15 to 20 mm. after the injection of 0·1 mgrm. adrenaline. During the increase in systemic blood-pressure the C.S. fluid is under increased pressure and it is probable that this leads to a temporary increase in the rate of the flow of the fluid to its natural outlets from the brain, and therefore as soon as the blood-pressure begins to fall a subnormal pressure is established. It appears then that adrenaline affects the C.S. fluid only indirectly through the vascular system. Pituitary extract, nicotine, tyramine and other pressor bases act similarly to adrenaline.

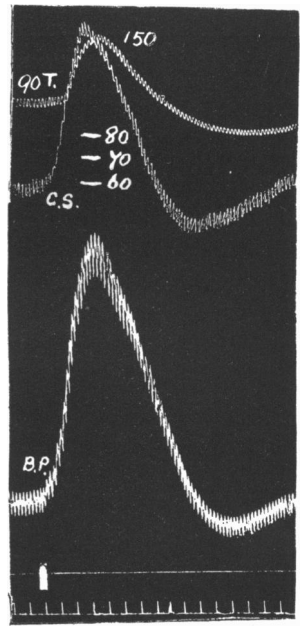

Fig. 17. Shows the effect of injecting into the jugular vein 1 c.c. 1 in 20,000 adrenaline. Atropine had been given previously. Time = 5 secs.

(*b*) *Amyl nitrite.* This drug given in moderate doses, such as the inhalation of three or four drops, increases the secretion of C.S. fluid[1],

[1] In Part I we attribute the increase of cerebro-spinal flow produced by this drug as due to interference with the due oxygenation of the blood.

and hence should tend to increase C.S. pressure. A rise in C.S. pressure is the rule (see Fig. 18); it comes on immediately the arterial pressure falls and assumes the normal position again about the same time as the arterial blood-pressure. This effect is often associated with a general rise in venous pressure including torcula pressure. Frequently the C.S. pressure falls a little at first with the initial drop in arterial blood-pressure but soon recovers and shows an augmented pressure even while the blood-pressure is at its lowest. Now amyl nitrite by lowering systemic resistance causes the output of blood from the heart to be increased. This factor and the small rise which occurs in the right auricular pressure are sufficient to account for the effect on torcula

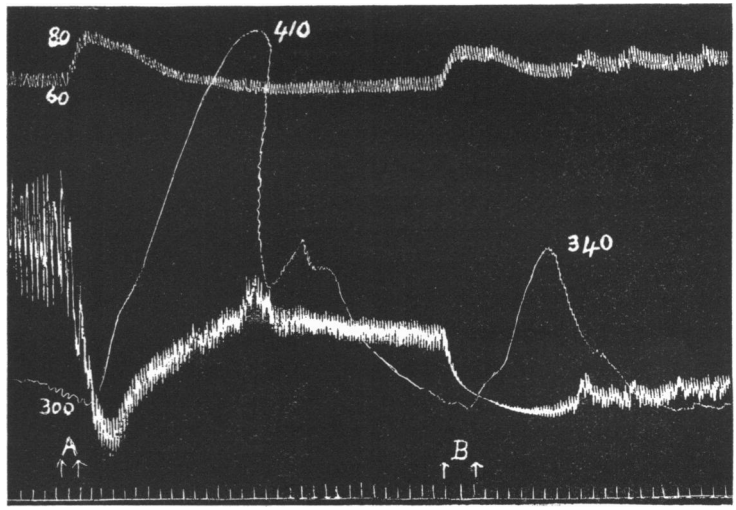

Fig. 18. C.S. pressure, arterial pressure, and torcula pressure (top line). Shows the effect of two inhalations of amyl nitrite at 'A' and 'B.' Time = 5 secs.

pressure; and the two curves representing cardiac output as measured by the cardiometer and torcula pressure run a roughly parallel course. The "brain volume" also increases whilst the C.S. pressure is high. The rise in C.S. pressure cannot be regarded as secondary to alterations in the venous pressure because it begins and reaches its maximum before the rise in venous pressure, often five to ten seconds before. In those cases when the increased cardiac output is decided the torcula pressure may rise considerably, 100 to 150 mm., but it was noticed that this large increase coming on when the C.S. pressure is already maximal is without any appreciable effect on this pressure. Furthermore it is by no means

very uncommon to note that the venous pressure is unaltered by nitrites in the doses under consideration, or even that it falls whilst the C.S. pressure is actively rising. Thus in one experiment the torcula pressure fell 35 mm. of sulphate solution whilst the C.S. pressure increased 10 mm. and in another the torcula pressure fell 10 mm. whilst the C.S. rose 30 mm. The rise in C.S. pressure has certainly all the characteristics of an independent factor. It might of course be argued that the rise in torcula pressure is the passive effect of the rise in C.S. pressure, and no doubt this may be one of the determining factors in the rise and sometimes may be the sole one, but in such cases the rise would be very slight.

(*c*) *Pilocarpine,* as has been noted in Part I, has a double action on the C.S. secretion of which the more important factor is its action upon respiration. It has in addition a true secretory effect. If this alkaloid is injected into an anæsthetised dog with natural respiration it causes a great increase of C.S. pressure, 70 to 100 mm. saline, which falls again when atropine is administered in spite of the sudden and great rise in arterial blood-pressure. This rise in pressure is associated with a large and corresponding rise in the general venous pressure and in torcula pressure and these three curves run a more or less parallel course and all three slowly assume the normal condition when the cardiac inhibition is removed by atropine. If the animal is subjected to forcible artificial respiration sufficiently strong to counterbalance any moderate degree of bronchial constriction the effect on the C.S. pressure is not quite the same. Here a gradual rise in C.S. pressure occurs of about 20 to 30 mm. saline, which is further increased, though only temporarily, to double or treble that amount when atropine is given on account of the sudden increase of the vascular cerebral volume. The torcula and general venous pressures on the contrary are not influenced by the artificial respiration, they rise in just the same way as before and fall when the atropine is administered. That is to say atropine causes an immediate and great rise in C.S. pressure and an immediate and great fall in torcula pressure (Fig. 19).

It is noticeable that the general venous pressure and torcula pressure rise immediately and steeply; the C.S. pressure, however, falls, the degree and amount of fall depending on the extent of the venous rise. Thus if the rise in venous pressure is great, 50 to 80 mm., the fall of C.S. pressure is slight and is followed by a moderate rise in pressure apparently passive, and largely dependent on the rise of venous pressure, because if the rise in venous pressure is slight the rise in C.S. pressure

may not occur for a minute or even longer. In the latter instance, this delayed rise is clearly not passive; it is entirely independent of venous pressure and should be regarded as a secretory rise, and we have shown that pilocarpine has such an action.

If whilst the heart is beating very slowly atropine is given the arterial blood-pressure bounds up to normal and the general venous and torcula pressures rapidly drop to normal. The C.S. pressure on the contrary

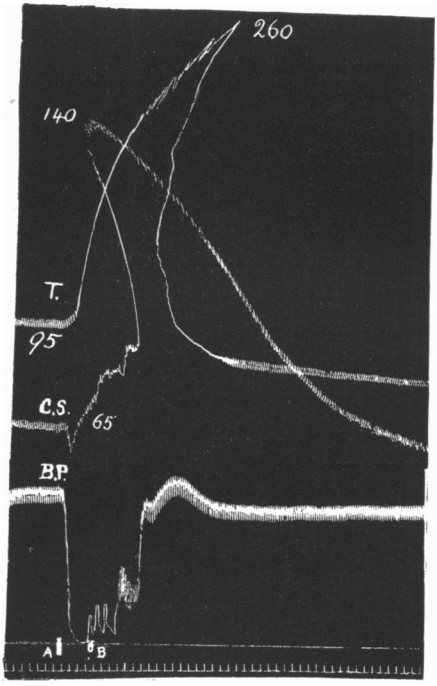

Fig. 19. Shows the effect of injecting into the femoral vein 20 mgms. pilocarpine nitrate (A) followed by 3 mgms. of atropine (B). Time = 5 secs.

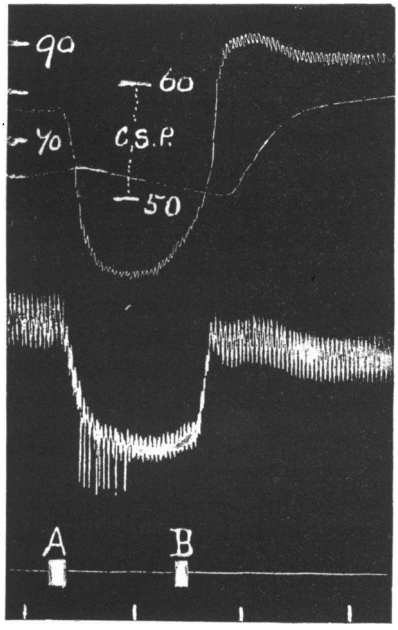

Fig. 20. Torcula (top line), C.S. and arterial pressures. Shows the effect of injecting 5 mgms. pilocarpine nitrate into femoral vein (A) followed by 1 mgm. atropine (B). Time = 30 secs.

rapidly and decisively rises to two or three times the height it was when the torcula pressure was maximal. This sudden rise in C.S. pressure cannot then be due to passive venous effects, indeed it rises in spite of the rapid venous fall. And arterial passive effects we have pointed out already have relatively little effect on C.S. pressure. The effect must be ascribed to a secretory pressure. During the

inhibition of the heart the cerebral circulation is almost at a standstill and oxygenation is deficient: the return of the circulation causes activity in the choroid gland with the resulting increase of pressure. Small doses of pilocarpine, arecoline, choline and other members of this group which produce a depressor effect without any marked effect on the rate of the heart, and many of which owe their depressor action largely to vaso-dilatation, show another picture. In these cases the injection of the drug causes the three curves, torcula, C.S. and blood-pressures, to assume a similar type; all three fall together, but the fall in C.S. pressure is insignificant compared with that of the torcula (Fig. 20). When the blood-pressure rises after atropine the torcula and venous pressures also rise and assume a level considerably above the normal.

CONCLUSIONS.

This investigation has shown that the cranial contents cannot any longer be regarded as a fixed quantity without the power of expanding or contracting in volume. The C.S. pressure is influenced passively to a small extent by changes in the arterial and venous pressures but such alterations are insignificant compared with the independent changes in pressure which occur as the result of secretory activity. Of all the conditions which influence the C.S. secretion we attach the most importance to deficiency of oxygen or excess of carbon dioxide in the blood.

We are indebted to the Government Grant Committee of the Royal Society and to the Science Committee of the British Medical Association for grants towards the expenses of this research.