J. Physiol. (1957) 138, 202–214

OBSERVATIONS ON THE CEREBROSPINAL FLUID PRESSURE IN THE PERFUSED CAT PREPARATION

By H. F. GRUNDY and F. HOWARTH

From the Department of Pharmacology, University of Cambridge

(*Received* 6 *May* 1957)

The studies of Howarth & Cooper (1949), Adams (1951), Sweet & Locksley (1953) and Sweet, Brownell, Scholl, Bowsher, Benda & Stickley (1954) suggest that after introduction into the subarachnoid space certain naturally occurring ions may pass into the general circulation via the local venous drainage. A similar route appears probable for spinal anaesthetics (Howarth, 1949; Helrich, Papper, Brodie, Fink & Rovenstine, 1950) and for even more abnormal substances (Howarth & Cooper, 1955). It thus becomes of interest to determine the relative parts played by the venae cavae and the azygos vein in the final venous drainage of the subarachnoid space. In the intact animal, however, a quantitative investigation of this problem is complicated by the recirculation of an absorbed test substance through these channels. It appeared that this might be avoided if, during an absorption experiment, the blood passing via each great vein was separately deviated into a container, while fresh blood was continuously supplied to the right side of the heart. In addition, by placing certain of the major cardiovascular variables under direct control, such a technique would be of value in an examination of the mechanisms for the maintenance and modification of the cerebrospinal fluid pressure.

To meet these requirements a perfused cat preparation was developed. An indication of the 'physiological state' of the perfused animals was obtained by comparing their total systemic blood flows with those of intact anaesthetized cats. This preparation was used for a study of the influence of certain circulatory changes upon the cerebrospinal fluid pressure.

METHODS

Apparatus

The general circuit and arrangement of components are shown in Text-fig. 1 and Pl. 1. Apart from the Perspex tap *P*, the apparatus was made of unsiliconed glass with connecting tubes of polyvinyl and unvulcanized rubber. The widest practicable thin-walled glass cannulae were used for the great vessels. This apparatus required approximately 400 ml. of blood which was in contact

with a total surface of about 900 cm². The thermostat maintained the blood input temperature at that within the rectum before perfusion.

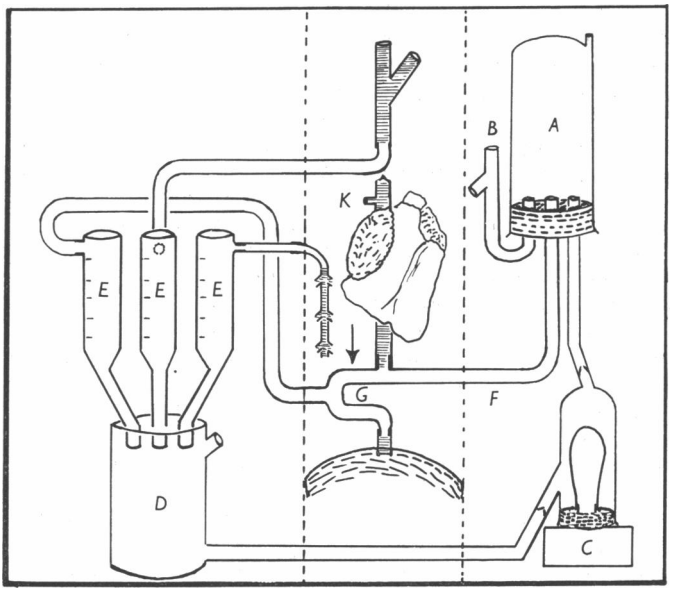
Perfusion blood. In the first three experiments, ox red cells washed in 0·9% sodium chloride solution and resuspended in cat plasma were used. In the remaining seventeen, the perfusate was cat blood. To obtain this, cats of 3–5 kg were anaesthetized with ether, venepuncture performed at a saphenous vein and a 0·75 mm bore polythene or nylon tube passed via the lumen of the needle into the inferior vena cava. Five mg heparin in 1 ml. saline was injected through the tube and blood was withdrawn as rapidly as possible into a lightly paraffined syringe. Periods of respiratory arrest or collapse of the inferior vena cava with blocking of the caval tube limited the volume of blood withdrawn, which was usually about 110 ml. This blood was set aside in a non-siliconed beaker containing 20 mg heparin, and 60–80 ml. 'Dextraven' (Benger, 6% dextran in 0·9% sodium chloride) or stored plasma was returned to the animal. Thirty cats were kept as blood donors. In later perfusions, cells and sera of donors and perfusion animal were compatible as previously determined by a simple tube-agglutination test. In this, one drop each of freshly prepared undiluted serum and 2% washed red blood cell suspension were mixed and results noted macroscopically and microscopically after standing at room temperature for 2 hr. Each test was duplicated. Appropriate controls of 0·9% sodium chloride solution and each red blood cell suspension were included.

Perfusion technique. The cat to be perfused was anaesthetized with intraperitoneal sodium pentobarbitone (Abbott Laboratories, 30–40 mg/kg), and received subsequent smaller doses as required. The caudal extremity of the spinal subarachnoid space was exposed and cannulated with a 0·5 mm bore nylon tube bearing numerous pin-hole orifices in its wall for a distance of 1 cm from the tip. The wound was closed round the cannula which communicated with a straight 1·0 mm bore manometer from which records of the cerebrospinal fluid pressure were obtained with the device shown in Text-fig. 2. During the course of some experiments the pressure was raised for predetermined periods by means of a burette, containing Ringer–Locke solution, attached to a T-piece connecting cannula and manometer.

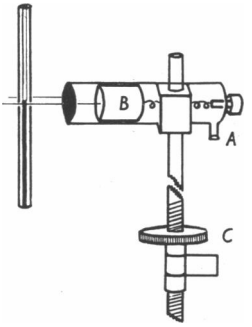
Positive pressure ventilation was applied and the chest opened to the right of the sternum through a J-shaped incision curving backwards over the lower ribs. All tissues were divided between ligatures, sparing the internal mammary vessels. At this stage the donor blood was introduced into the perfusion apparatus and a screw clamp on input tube *F* (Text-fig. 1) adjusted to obtain a delivery of about 100 ml./min. A blood-pressure cannula was introduced into the left femoral artery and 30 mg of heparin given intravenously. The azygos vein was divided, the clamped distal end cannulated and connected to a calibrated measuring tube *E* (Text-fig. 1). The proximal end of this vessel led to a saline manometer for the recording of right atrial pressure. Next, the inferior vena cava was divided between clamps, both ends cannulated within 90 sec and the long-circuit *G* established within the Perspex tap *P* (Pl. 1). The superior vena cava was now ligated just distal to the entrance of the azygos vein and a cannula introduced into the peripheral end. This cannula was connected to the Perspex tap which was then turned so as to break the long-circuit, deliver perfusion blood to the heart from the input reservoir *A* and connect the peripheral ends of both venae cavae with their respective measuring tubes. After this, the clamp on the azygos vein was removed. Finally, the clamp on the input tube was carefully opened till the blood pressure attained 110–150 mm Hg with an atrial pressure at, or slightly below, that found before perfusion. Sometimes only the distal end of the inferior vena cava was cannulated and led into a long-circuit established on the superior vena cava. In this case perfusion was carried out via the proximal stump of the latter vessel. At the end of each experiment the perfusate was centrifuged and the plasma stored at −20° C.

Cardiac output determinations

Direct Fick method. Cats were anaesthetized as for perfusion and received 30 mg of heparin intravenously. Blood-pressure records were taken from one femoral artery while the other carried a polythene tube for arterial blood samples. A wide silver T-tube was inserted into the trachea



Text-fig. 1. Essential components of the perfusion apparatus. The great veins, heart and diaphragm lie between the dotted lines. The head of blood in the input reservoir *A* was controlled by the height of the overflow pipe *B* which discharged into output receiver *D* whence blood was returned to *A* by the Dale–Schuster pump *C*. During perfusion the tap *P* (Pl. 1) occluded the long-circuit *G* at arrow. Blood was delivered to the heart by input tube *F* which contained a thermostat. The calibrated measuring tubes *E* conducted the venous return from each of the great veins into *D*. The proximal stump of the azygos vein *K* was used to record right atrial pressure.



Text-fig. 2. Cerebrospinal fluid pressure recorder. *A* was connected to an air-bulb, repeated compression of which moved spring-loaded piston *B* and its attached needle along the cylinder to mark a series of dots on moving smoked paper. A needle was also fixed to the cylinder and the saline meniscus levelled between these two needles before making a record. Fluctuations in cerebrospinal fluid pressure were followed by turning wheel *C*.

and its limbs connected to two 'water' valves containing saturated calcium chloride solution acidified with hydrochloric acid. The appropriate tube of each valve just made contact with the surface of the solution. Expired air samples were taken into a bag made of 0·25 mm thick polythene film ('Visqueen'). Mixed venous blood was obtained from a metal-tipped 0·5 mm bore polythene tube passed with X-ray control from a femoral vein to the orifice of the pulmonary artery. The arterial and venous blood samples were drawn into separate 2 ml. syringes connected to the appropriate cannulae by short, fine-bore, mercury-filled rubber tubes. Before sampling, 0·25 ml. of blood was drawn from side arms on these tubes and discarded. Each syringe was lightly paraffined and contained a trace of heparin and about 0·5 ml. of mercury. Sampling at equal rates was achieved by means of a brass plate fixed to the pistons of the syringes and moved by a vernier screw gauge. Blood was withdrawn continuously throughout the air collection period and replaced by a similar volume of 'Dextraven'. Sampling started after about 90 min and continued at intervals for some 6 hr. Analyses of expired air were carried out in a standard Haldane apparatus. The estimations of carbon dioxide and oxygen in blood (van Slyke & Neill, 1924) were begun immediately.

The additional effects upon cardiac output of thoracotomy and temporary caval obstruction were examined. After taking two or three blood and air samples the chest was opened, as in a perfusion experiment, then closed again with a moulded celluloid plate. When normal respiration had been re-established further samples were taken. During some of these experiments, the inferior vena cava was temporarily obstructed under direct vision by tightening a loop of thread passed round it. Animals were killed by the injection of pentobarbitone or chloroform or by excision of the heart after clamping the great vessels. Autopsies were performed immediately and the position of the venous sampling cannula checked. It was thought that chloralose might be preferable to pentobarbitone for anaesthesia during perfusion and consequently a similar series of observations was carried out during intravenous chloralose anaesthesia (0·08 g/kg, British Drug Houses Ltd.).

Serial analyses of blood and air samples served as checks on individual procedures but failed to reveal the relatively large variations in cardiac output values induced by minor analytical errors. To estimate the over-all precision of the method, adequate volumes of arterial and venous blood were drawn with concomitant samples of expired air and stored as in an actual determination. Successive analyses were then carried out and a series of cardiac outputs calculated. There were no detectable changes in the carbon dioxide and oxygen content of air samples stored in the polythene bag for periods comparable to those of the output determinations.

RESULTS

Behaviour of the perfused preparation

While the inferior vena cava was clamped to permit the insertion of the long-circuit, there was a fall of blood pressure to about 40 mm Hg and an increase in amplitude and rate of diaphragmatic movements. When the clamps were removed, the blood pressure returned to its original level after a brief hypertensive phase. Respiration was also restored to normal.

At the beginning of perfusion the blood pressure usually fell to about 80 mm Hg while the right atrial pressure, after an occasional sharp rise, fell to 5–10 mm saline below the pre-perfusion level. The subsequent increase of cardiac input was usually accompanied by a steady rise of arterial and right atrial pressures to the desired levels, which were then satisfactorily maintained for some hours (Table 1). During this stable period frequent measurements showed little alteration in the individual venous returns. The flow from the

inferior vena cava was most commonly between 2 and 3 times that from the superior vena cava and azygos vein combined, and the total flow showed no close relationship to body weight. The cerebrospinal fluid pressures remained constant in most animals but occasionally rose slowly towards the end of perfusion. The mean cerebrospinal fluid pressure, for the fourteen animals in which it was recorded, was 122 mm of Ringer–Locke solution, which agrees with the value (119 mm) found by Weed & Hughson (1921) for intact cats under ether anaesthesia. During the satisfactory perfusions there were active

TABLE 1. Data obtained from cats after long-circuiting the venous return to the heart through a perfusion machine

Expt. no.	Cat wt. (kg)	Duration of perfusion (min)	Range of B.P. (mm Hg)	Venous returns (ml./min) I.V.C.	S.V.C.	Azygos vein	Total	Total/wt. (ml./min/kg)	C.s.f. pressure (mm. saline)
1	2·7	157	80–125	120	69	—	189	70	—
2	2·8	115	70–112	148	67	11	226	81	—
3	2·8	95	80–140	158	102	—	260	93	140
4	3·9	170	98–120	172	63	24	259	66	—
5	2·8	120	68–110	175	62	21	258	92	120
6	1·5	179	115–140	120	36	8	164	109	125
7	2·5	236	130–170	149	47	13	209	84	120
8	2·3	202	118–125	106	38	7	151	66	80
9	2·0	151	57– 65	79	34	7	120	60	105
10	2·0	229	90–117	101	36	7	144	72	120
11	1·9	197	104–122	149	47	10	206	108	137
12	1·9	208	121–146	89	27	13	129	68	120
13	2·0	179	128–140	130	36	14	180	90	165
14	2·0	263	120–140	95	34	13	142	71	144
15	2·0	164	60– 90	82	28	—	110	55	—
16	2·2	333	114–138	145	41	3	189	86	125
17	1·8	345	108–131	118	38	10	166	92	93
18	2·0	225	105–135	130	24	19	173	87	—
19	2·4	364	115–137	87	29	17	133	55	110
20	2·0	269	46– 65	140	58	14	212	106	—

In Expts. 1 and 3 the azygos vein was ligated. In Expt. 15 this vein was not ligated but the flow was not measured. In Expts. 1, 2, 4, 15, 18 and 20 the lumbar subarachnoid space was not cannulated. Expts. 9, 15 and 20 are regarded as failures because of the low blood-pressure levels. The lowest value in the blood-pressure range was not necessarily found at the end of perfusion.

diaphragmatic movements and withdrawal of fore and hind limbs on pinching the foot pads. Frequently the cat spontaneously licked its chops and flicked its ears. Many animals became more active in the later stages of the experiments. It is noteworthy that despite perfusion with a large volume of blood containing a negligible anaesthetic concentration only two of the animals required further pentobarbitone within the first 30 min of perfusion. Only four animals died, the rest of the experiments being terminated voluntarily often with no previous sign of deterioration in the cat. The rate at which blood was lost from the perfusion apparatus into the animal was not measured, but an extra 50–100 ml. was usually needed during the course of a perfusion. In some of these experiments the initial increase of cardiac input caused a great

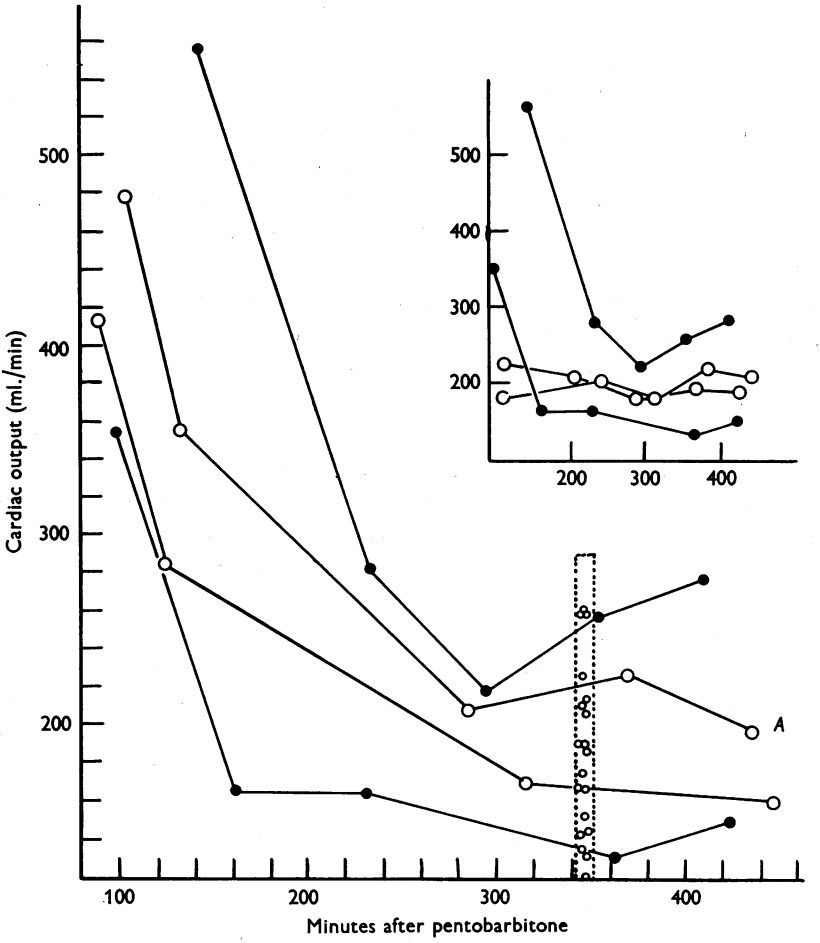
rise of right atrial pressure without a corresponding increase in arterial pressure. In these cases the input had to be reduced and then gradually increased again till the arterial pressure attained a satisfactory level. Despite these manipulations the blood pressure persisted at a low level in three of the twenty experiments recorded in Table 1, and in these only the knee-jerk gave clinical evidence of a surviving central nervous system.

Cardiac output studies

The cardiac outputs of twenty normal cats, under pentobarbitone anaesthesia, declined rapidly during the first 3–4 hr and then tended to become steady (Text-fig. 3). Neither the initial nor the later values were related in any precise way to body weight. The cardiac output curves of five thoracotomized cats still lay within the range determined for cats under anaesthesia alone. Similar results were obtained when, in addition to thoracotomy, the inferior vena cava was obstructed for a period comparable to that usually required to establish the long-circuit on this vessel. In one-third of all the above experiments the blood pressure remained steady throughout, in the remainder a slow fall was observed. The mean initial and final pressures of the whole series were 170 and 140 mm Hg respectively. Cardiac outputs were calculated from both carbon dioxide and oxygen data. In 87 of 114 determinations the values based on carbon dioxide analyses were higher than those based on oxygen, the average difference for all the determinations being +11%. In six estimations of cardiac output derived from analyses of common pools of expired air and arterial and venous bloods, the *maximum* deviations from the mean of the cardiac output figures were ±2·5 and ±15% for the oxygen and carbon dioxide series respectively. Thus oxygen-based values were used in Text-fig. 3. The total venous return via the great veins was known by direct measurement in twenty perfusions (Table 1), but these are less than the cardiac output chiefly by the exclusion of coronary flow. Nevertheless, when these stable values were plotted on the graph (Text-fig. 3) at the mean time of the start of perfusion after the injection of pentobarbitone, it was found that eighteen lay close to, or within, the cardiac output range of cats under anaesthesia alone. At this time the average cardiac output for the normal cats was 83 ml./kg/min, while the average total venous return (Table 1) for the perfused animals was 81 ml./kg/min. Of the three unsuccessful perfusions, one lay towards the upper limiting curve while the other two fell below the limits, although in one of these the azygos flow was not measured. In eight normal cats under chloralose anaesthesia of similar duration the cardiac outputs remained steadier than with pentobarbitone but started at a lower level (Text-fig. 3).

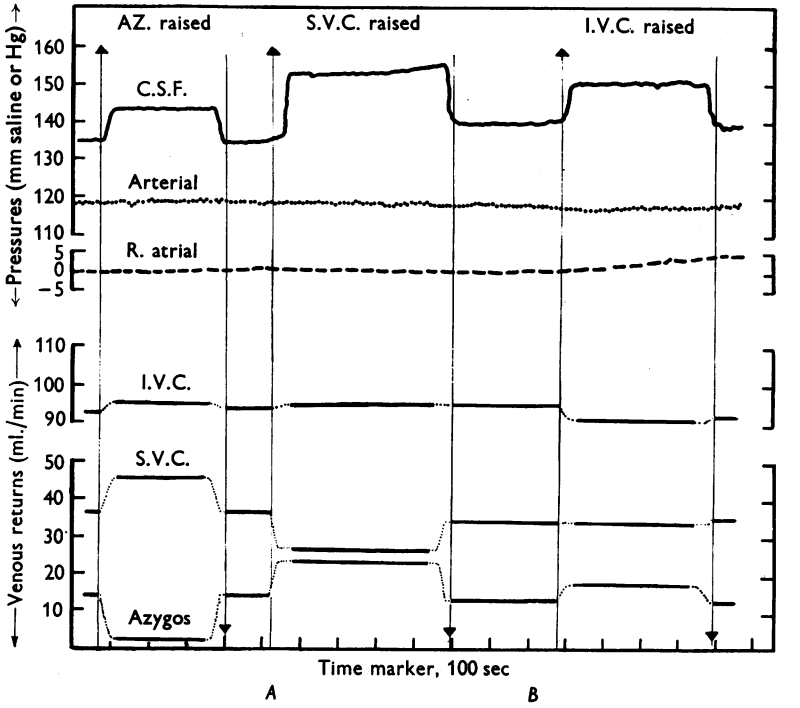
Studies on the cerebrospinal fluid pressure

Effects of change of venous pressure. The venous pressure in the superior vena cava, inferior vena cava or azygos vein was increased by successively raising the calibrated measuring tubes *E* (Pl. 1) by 5 cm. This manoeuvre caused a rapid rise of the cerebrospinal fluid pressure in each case (Text-fig. 4).



Text-fig. 3. Large figure. During the course of pentobarbitone anaesthesia in twenty normal cats the curves of cardiac output lay between those represented -●—●-, though most were clustered about *A*. Between the 2nd and 3rd observations of the two experiments shown -○—○- an extensive thoracotomy was performed and the chest closed again. In addition (curve *A*) the inferior vena cava was obstructed for 75 sec. The circles within the dotted rectangle indicate volumetric determinations of the total venous return via the great veins during nineteen perfusions. (Expt. 15, Table 1, falls below this scale.) The small figure repeats the pentobarbitone findings and shows (-○—○-) the behaviour of the cardiac output during chloralose anaesthesia.

This response was always greatest when the pressure in the superior vena cava was increased but inconstant comparative responses were obtained from the other two vessels. When the measuring tubes were returned to their original levels, the cerebrospinal fluid pressure returned at once to normal in the cases of the inferior vena cava and azygos vein but a delay was often noted in the case of the superior vena cava. When the pressure in either the superior vena cava or azygos vein was increased, there was a reduction in the flow through



Text-fig. 4. Cat, 2 kg, pentobarbitone anaesthesia. Venae cavae and azygos vein long-circuited through the perfusion machine. Between the arrow shafts the back pressure in the azygos vein (AZ.), superior vena cava (S.V.C.) and inferior vena cava (I.V.C.), was raised successively by 5 cm then restored to the initial value (see Pl. 1). The arrow shafts mark the beginning and end of the pressure alterations. The dotted parts of the venous return curves indicate their *probable* shape. During all these manoeuvres the total venous return was 142±2 ml./min. At *A* and *B* the drum was stopped for 260 and 172 sec respectively.

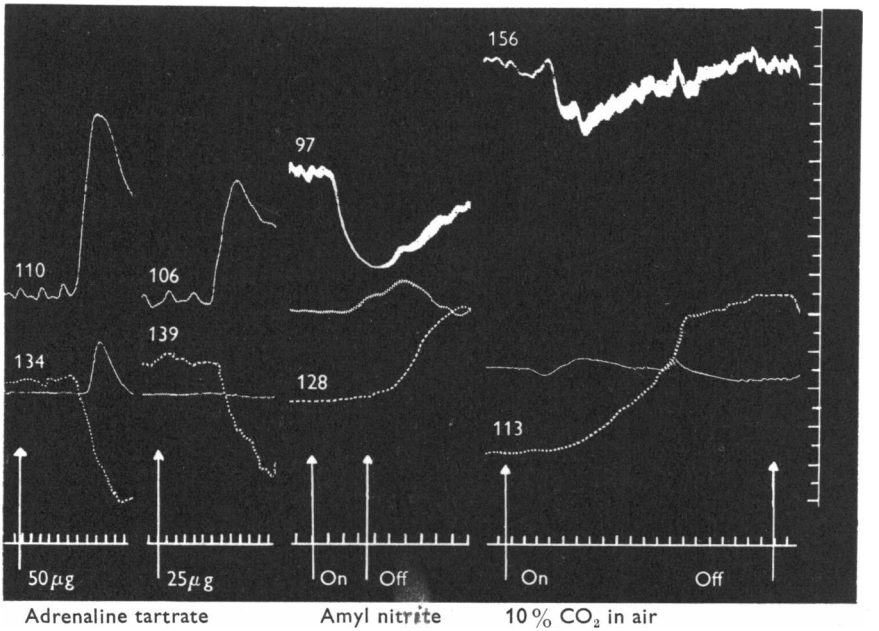
the raised vessel and a prompt and similar increase in the flow through the other. Sometimes the azygos stream was completely arrested when its tube was raised by 5 cm. When the pressure in the inferior vena cava was raised there was a very slight reduction in its blood flow, an increase in that from the azygos vein and a negligible change in the flow from the superior vena cava. Alterations in pressure were maintained for as long as 12 min and induced no significant change in the total venous return. Meanwhile there was

little modification of either the arterial or right atrial pressures, and the maximum variations observed are shown in Text-fig. 4.

Effects of change of cardiac input or cerebrospinal fluid pressure. When the cardiac input was increased by raising the head of blood in the input reservoir, the blood pressure and all the individual venous flows increased. The right atrial and cerebrospinal fluid pressures, however, usually remained constant, though on occasion variations of up to 4 mm were observed. The largest change studied was an increase in the total venous return from 125 to 208 ml./min. In this case the blood pressure rose from 120 to 176 mm Hg while the increments in the individual flows from the superior and inferior vena cava were 70% and that from the azygos 50%.

When the cerebrospinal fluid pressure was raised to approximately double its resting value, arterial and atrial pressures and individual and total venous returns showed no appreciable alterations. As an example of such an experiment, in which the blood pressure remained steady at 124 mm Hg and the atrial pressure 1 mm below the pre-perfusion level, an increase in the cerebrospinal fluid pressure from 131 to 251 mm of Ringer–Locke solution caused a drop of only 2 ml. in the total venous flow of 168 ml./min.

Effects of drugs. Adrenaline tartrate (Burroughs Wellcome), acetylcholine chloride (Roche), amphetamine sulphate (British Drug Houses), distilled water and hypertonic sodium chloride solution were added to the reservoir of the perfusion machine. Amyl nitrite (Savory and Moore), carbon dioxide and pure oxygen were administered by inhalation. Adrenaline (25 μg) caused a fall in cerebrospinal fluid pressure and a rise in arterial blood pressure. With a larger dose there was also a concomitant rise in right atrial pressure (Text-fig. 5). Amyl nitrite produced opposite changes in cerebrospinal fluid and arterial pressures to those initiated by adrenaline; the atrial pressure sometimes showed fluctuations but usually remained unchanged. Carbon dioxide (10% in air) produced a marked rise in cerebrospinal fluid pressure, but arterial and atrial records were disturbed by vigorous diaphragmatic movements (Text-fig. 5). Acetylcholine (10 μg) produced a marked rise in cerebrospinal fluid and atrial pressures and a fall in arterial blood pressure. Amphetamine (5 mg) produced rather erratic results; usually there was a rise in cerebrospinal fluid and blood pressures with little change in atrial pressure and an appreciable increase in motor activity. The responses to oxygen were unpredictable. A lasting fall and rise in the pressure of the cerebrospinal fluid followed the administration of 2–3 ml. of 30% sodium chloride solution and 15 ml. of glass-distilled water respectively. These changes persisted after the immediate vascular effects had subsided.



Text-fig. 5. Cats under pentobarbitone anaesthesia; great veins long-circuited through the perfusion machine. The upper and lower unbroken tracings are of femoral arterial and right atrial pressures respectively, recorded in mm Hg or saline. The broken line represents the cerebrospinal fluid pressure in mm of saline. The signal marks for the first two strips are 10 sec intervals and 9 min elapsed between them. For the last two strips the signal marks are 25 sec intervals. The scale on the right is marked in 5 mm divisions.

DISCUSSION

It is generally accepted that perfused whole animals deteriorate more or less rapidly and we claim no exception for our preparation. Inadequate blood flows and inimical substances in the perfusing blood may be factors in this decline. Certainly, in the dog, both Wégria, Rojas & Wiggers (1943) and Daly, Eggleton, Hebb, Linzell & Trowell (1954) found values for the systemic blood flow which they considered low. We found much variation in the cardiac outputs of different anaesthetized normal cats at comparable times after the injection of anaesthetic. Variations were also revealed in the stable values for systemic flows obtained from different perfused cats. Nevertheless, at comparable times the systemic flows of the two groups of animals cannot be considered strikingly different. In the perfusion experiments, the duration of stable blood pressure was not related to the determined value of the venous return, and modification of the cardiac input produced but a temporary amelioration of the progressive hypotension of failing preparations. It thus

appears that the ultimate decline of such preparations is determined by factors other than the value of the imposed cardiac input.

It is now proposed to discuss the observations made on the cerebrospinal fluid pressure. Though it has long been accepted that a rise of venous pressure is associated with a rise in the pressure of the cerebrospinal fluid (see Lups & Haan, 1954) the mechanism and course of the reaction remain uncertain. This is mainly due to the disturbance of vascular variables usually produced by the experimental alteration of the former component. These disturbances are widespread when the general venous pressure is raised but may apparently involve only the unknown factor of collateral venous circulation when selected vessels are obstructed (Bedford, 1935). The unknown influence of raised venous pressure upon the secretion and absorption of the cerebrospinal fluid is yet a further difficulty in the interpretation of the results of such experiments. Studies of the effects of arterial pressure alterations pose comparable problems. With the perfused cat it was possible to produce a physiological increase of venous pressure in the territories drained by the superior vena cava, inferior vena cava or azygos vein, and to maintain it constant without changing arterial or right atrial pressures. We have shown that such an increase of pressure in any of the great veins transferred a portion of its venous return to the others and brought about a sustained rise of cerebrospinal fluid pressure; but whereas the exchange of blood between superior vena cava and azygos vein was free, that between this circuit and the inferior vena cava was restricted. For this reason little change in the venous return from the superior vena cava followed an increase in the inferior caval pressure. The associated rise of cerebrospinal fluid pressure was thus produced by an increase of venous pressure involving the spinal but sparing the cranial region, which latter is generally agreed to be more important in the secretion and absorption of the cerebrospinal fluid. A more significant alteration in these factors may have occurred during a constant increase of venous pressure in the superior vena cava, for in this case the cerebrospinal fluid pressure slowly increased and failed to return at once on restoring the caval pressure. It is unlikely that this small increase in superior caval pressure would cause much change in cerebral blood flow (Forbes, 1940), which would therefore seem to be a minor factor in this response. Further, we have shown that changes of cardiac input did not greatly modify the cerebrospinal fluid pressure despite the concomitant large variations in arterial blood pressure which usually imply an alteration in the cerebral flow. It thus appears that, in the perfused cat, the cerebrospinal fluid pressure is more readily influenced by the venous pressure than by any of the other variables examined. In this preparation the great veins were not in connexion with the right atrium and changes in cardiac input had little effect upon the cerebrospinal fluid pressure. These considerations suggest that the changes in fluid pressure induced by the drugs used might be ascribed to

an action on the peripheral vascular bed. The free superior vena cava-azygos shunt appears to have wide implications. It might be initiated merely by cannulation and in this case the disparity in the azygos and superior vena caval concentrations of ions introduced into the lumbar sac is probably even greater than that recorded by Howarth & Cooper (1949). If such a by-pass exists in other species, it might account for the maintenance of cerebral blood flow reported by Ferris (1939) in cases of superior vena caval obstruction in man.

SUMMARY

1. A durable perfused cat preparation has been described and shown to possess a cardiac output similar to that of an intact animal anaesthetized for a comparable time.

2. With this preparation the relationships of cerebrospinal fluid pressure and certain major cardiovascular variables have been studied.

3. The shunts between the venae cavae and the azygos vein have been investigated quantitatively in the cat.

We wish to thank Dr R. R. A. Coombs and Dr G. S. Adair for their advice on serology and gas analysis, and are indebted to Professor J. D. Boyd for X-ray facilities and to Mr J. A. F. Fozzard for help with the screening. We are grateful to Mr C. Harbird for technical assistance and to the Royal Society for generous financial aid.

REFERENCES

ADAMS, J. E. (1951). Tracer studies with P^{32} on absorption of c.s.f. The problem of hydrocephalus. *J. Neurosurg.* **8**, 279–288.

BEDFORD, T. H. B. (1935). The effect of increased intracranial venous pressure on the pressure of the cerebrospinal fluid. *Brain*, **58**, 427–447.

DALY, I. DE B., EGGLETON, P., HEBB, C., LINZELL, J. L. & TROWELL, O. A. (1954). Observations on the perfused living animal (dog) using homologous and heterologous blood. *Quart. J. exp. Physiol.* **39**, 29–54.

FERRIS, E. B. (1939). The effect of high intracranial venous pressure upon the cerebral circulation and its relation to cerebral symptoms. *J. clin. Invest.* **18**, 19–24.

FORBES, H. S. (1940). Physiologic regulation of the cerebral circulation. *Arch. Neurol. Psychiat., Chicago*, **43**, 804–814.

HELRICH, M., PAPPER, E. M., BRODIE, B. B., FINK, M. & ROVENSTINE, E. A. (1950). The fate of intrathecal procaine and the spinal fluid level required for surgical anaesthesia. *J. Pharmacol.* **100**, 78–82.

HOWARTH, F. (1949). Studies with a radioactive spinal anaesthetic. *Brit. J. Pharmacol.* **4**, 333–347.

HOWARTH, F. & COOPER, E. R. A. (1949). Departure of substances from the spinal theca. *Lancet*, **257**, 937–940.

HOWARTH, F. & COOPER, E. R. A. (1955). The fate of certain foreign colloids and crystalloids after subarachnoid injection. *Acta anat.* **25**, 112–140.

LUPS, S. & HAAN, A. M. F. H. (1954). *The Cerebrospinal Fluid.* Amsterdam: Elsevier.

SWEET, W. H., BROWNELL, G. L., SCHOLL, J. A., BOWSHER, D. R., BENDA, P. & STICKLEY, E. E. (1954). The formation, flow and absorption of c.s.f.; newer concepts based on studies with isotopes. *Neurology and Psychiatry in Childhood.* Baltimore: Williams and Wilkins, Association for Research in Nervous and Mental Diseases, no. 34, pp. 101–159.

SWEET, W. H. & LOCKSLEY, H. B. (1953). Formation, flow, and reabsorption of cerebrospinal fluid in man. *Proc. Soc. exp. Biol., N.Y.*, **84**, 397–402.

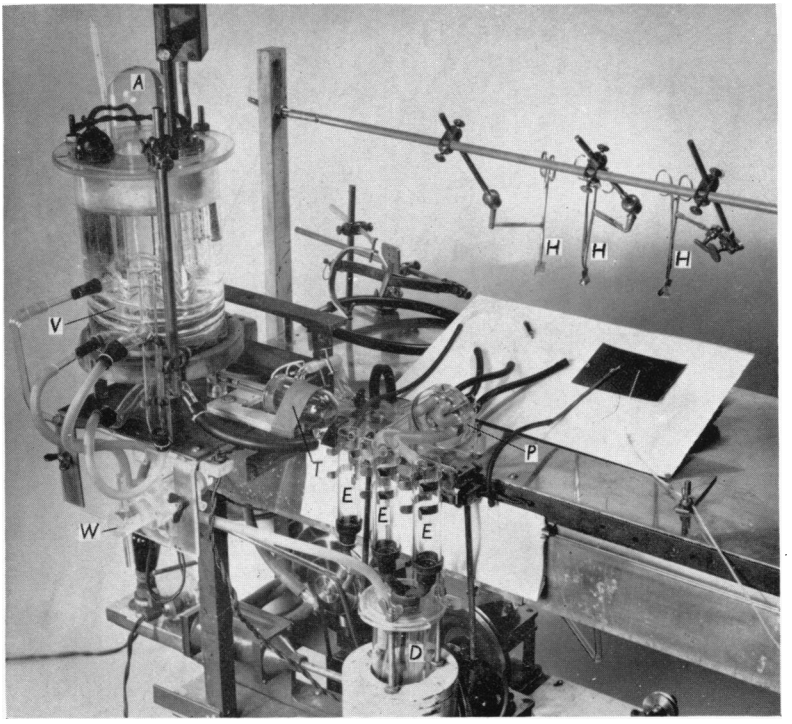
VAN SLYKE, D. D. & NEILL, J. M. (1924). The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. 1. *J. biol. Chem.* **61**, 523–573.

WEED, L. H. & HUGHSON, W. (1921). Systemic effects of the intravenous injection of solutions of various concentrations with especial reference to the cerebrospinal fluid. *Amer. J. Physiol.* **58**, 53–84.

WÉGRIA, R., ROJAS, A. G. & WIGGERS, C. J. (1943). A study of spontaneous fulminant shock in a heart-lung-dog preparation. *Amer. J. Physiol.* **138**, 212–229.

EXPLANATION OF PLATE

Perfusion apparatus. On the upper white card, from left to right, are the cannulae for the distal ends of the azygos vein and the superior vena cava, the proximal and distal ends of the inferior vena cava, the proximal stump of the azygos vein and the subarachnoid space. The clamps *H* held the cannulae in place. Perspex tap *P* contained the long-circuit *G* (Text-fig. 1) and was interposed between the cardiac input and both caval return circuits. Venous returns were measured by closing the lower end of the appropriate tube *E* and noting the time of filling between two graduations. These tubes could be raised or lowered in their clamps to change the pressure in the venous return channels. Heated water-jackets, controlled by the thermostat *T*, surrounded receiver *D* and input reservoir *A*. Before entering the reservoir, blood passed round the heating coil *V*. The by-pass tap *W* was not used in these experiments.



(*Facing p.* 214)