The Influence of Volatile Anaesthetic Drugs on the Blood Flow and Oxygen Uptake of the Cerebral Cortex and on Cerebrospinal Fluid Pressure

by

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SUMMARY OF THESIS

This thesis, after a general introduction, is divided into two parts.

Part I Studies of the Influence of Volatile Anaesthetic Drugs on the Blood Flow and Oxygen Uptake of the Cerebral Cortex

(1) This Part begins with a detailed account of the methodology of the techniques used for measuring the blood flow and oxygen uptake of the cerebral cortex in the dog including discussion of relevant anaesthetic, anatomical and surgical details.

(2) It is demonstrated that halothane dilates the blood vessels of the cerebral cortex, producing increases in cerebral cortical perfusion. The intensity of cerebral vasodilatation increases with increasing concentrations of halothane so that cerebral cortical blood flow is greater with 2% halothane than with 0.5%. Also with the higher concentration the flow increase is maintained for at least one hour while with 0.5% halothane it lasts only about 20 minutes. These increases in cerebral cortical blood flow with 0.5% and 2% halothane occur despite the lowering of systemic arterial blood pressure produced by these concentrations of halothane. However in the case of 2% halothane, the increase in cerebral cortical blood flow is greater when the mean arterial pressure is above 90 mm.Hg. With the highest halothane concentration studied (4%) the fall in blood pressure is such that flow is not above control (nitrous oxide-oxygen) levels. By administering a vasopressor drug the underlying vasodilatation produced by 4% halothane is revealed. Finally it is demonstrated that blood flow over

the cortical surface is uniform within the reproducibility of the method, during anaesthesia with 0.5% and 2% halothane.

Halothane depresses the oxygen uptake of the cerebral cortex and the amount of the depression is greater with 2% than with 0.5% halothane. The E.E.G. patterns present at the times of these changes in cerebral metabolic activity are illustrated.

As a result of the changes in the blood flow and oxygen uptake of the cerebral cortex, the oxygen saturation of cerebral venous blood rises and the arterio-venous differences across the cerebral cortex for oxygen, carbon dioxide and hydrogen ion concentration are narrowed. The consequent changes in mean tissue oxygen and carbon dioxide tensions are calculated.

(3) It is shown that trichloroethylene, in concentrations of less than 1%. increases blood flow through the cerebral cortex in the first 20 minutes of its administration but that thereafter flow tends to return to control values.

These concentrations of trichloroethylene reduce the oxygen uptake of the cerebral cortex by approximately the same amount as does 0.5% halothane.

As with halothane, trichloroethylene increases venous and tissue oxygen tensions, especially in the first 20 minutes of its administration.

(4) The findings with 1% chloroform are similar to those with halothane, cerebral cortical blood flow increasing despite a fall in mean blood pressure. The depression noted in oxygen uptake with this drug does not however reach statistical significance.

(5) Finally in Part I, it is shown that cerebrovascular sensitivity to alterations in $Paco_2$ is fully maintained during anaesthesia with these drugs provided that due allowance is made for the concomitant fall in mean blood pressure.

(6) At the conclusion of each of the above sections, the relevant literature is fully reviewed and previous findings compared with the present results.

(7) Part I of the thesis concludes with an extended discussion of the possible mechanisms by which the observed changes may be produced. The most likely explanation would appear to be that these anaesthetic drugs relax by a "direct" action the normal tone of the cerebral arterioles and it is postulated that they do this by inhibiting the enzymatic reaction responsible for the generation of energy for vascular smooth muscle tone.

The interrelationships between the actions of these drugs and the effects of alterations in blood pressure and in arterial Pco_2 are considered.

From the clinical point of view, these findings are used to describe the sequence of changes in cerebral blood flow and metabolism which occur with commonly employed anaesthetic techniques. The possible use of volatile anaesthetic agents to increase the tolerance of the brain to temporary regional or total ischaemia is then discussed in relation to the common clinical problems of induced hypotension, cerebral arteriosclerosis and deliberate circulatory arrest. It is concluded from this that the demonstrated depression of cerebral oxygen requirements, especially with deep anaesthesia, may render partial protection to the brain during ischaemia and an attempt

is made to make a quantitative prediction of the possible extension of the period of safe circulatory arrest by this means.

Part II Studies of the Influence of Volatile Anaesthetic Drugs on Cerebrospinal Fluid and Cerebral Venous Pressures

(1) The methodology of cerebrospinal fluid, cerebral venous and central venous pressure measurements in dogs is first critically discussed. Cerebral venous pressure is measured in the superior sagittal sinus and c.s.f. pressure in the cisterna magna. Ventilation is controlled to maintain a constant $Paco_2$.

(2) It is demonstrated that halothane and chloroform increase cerebrospinal fluid pressure and that, in the case of halothane, the extent of the increase in c.s.f. pressure is greater with 2% than with 0.5% inspired concentration. It is also noted that the changes in c.s.f. pressure with halothane are not maintained with time but reach a peak value in from 3-9 minutes and then begin to fall towards the initial control value. With halothane administration, c.s.f. and cerebral venous pressures both increase together and to the same degree. Significant changes in central venous pressure do not occur.

(3) In some of the experiments of Part I, cerebral venous pressure in the superior sagittal sinus was measured and the results are displayed and discussed at this point. It is observed that halothane, chloroform and trichloroethylene in the first 20 minutes of its administration increase

cerebral venous pressure and that the changes in cerebral venous pressure are closely correlated with increases in measured cerebral cortical blood flow.

(4) A clinical study of lumbar c.s.f. pressure changes in patients anaesthetised for surgical treatment of lumbar disc protrusions follows. It is demonstrated that halothane and trichloroethylene increase c.s.f. pressure despite careful maintenance of a constant $Paco_2$. The observed changes are not the result of changes in central venous pressure. The extent of the c.s.f. pressure rise is greater with 1% than with 0.5% halothane but, at the same halothane concentration, the increase is smaller in patients who are first hyperventilated. There appears to be no important difference between the extent of the c.s.f. pressure increase with 0.9% trichloroethylene as compared with 0.5% halothane.

(5) These findings are discussed and related to the previous literature on this subject. It is argued that the most likely explanation of the changes observed is that the increases in cerebral blood flow seen in Part I result in increases in the pressure within the superior sagittal sinus because this vessel has relatively rigid walls and therefore a low compliance. This pressure rise is transmitted back to the thin walled cerebral veins which thereby become more distended. The blood volume on the venous side of the cerebral circulation therefore increases and because of the low compliance of the intracranial theca, pressure rises within the skull and throughout the c.s.f. space. In this way the findings of the two Parts of the thesis become mutually corroborative.

SUMMARY (6)

(6) Finally intraventricular c.s.f. pressure is measured in 4 patients undergoing surgical treatment of intracranial tumours and it is shown that considerably greater increases in cerebrospinal fluid pressure occur in this group as compared with patients without intracranial space occupying lesions.

(7) It is pointed out that this finding could be clinically important if differentials of pressure are established within the central nervous system or if the perfusion pressure of the brain (mean arterial - mean intracranial pressure) falls below the critical level required to sustain adequate cerebral perfusion. It is calculated that during halothane administration in these patients with cerebral tumours, cerebral perfusion pressure is lowered to a level at which others have demonstrated reductions in cerebral blood flow. While not necessarily damaging in itself, this situation is one in which the normal reserves of cerebrovascular compensation are exhausted and cerebral ischaemia may occur at a level of blood pressure which would not normally be considered inadequate. It is demonstrated in one patient that prior hyperventilation avoids this potentially hazardous position.

CONTENTS

PART II

STUDIES OF THE INFLUENCE OF VOLATILE ANAESTHETIC DRUGS ON CEREBROSPINAL FLUID AND CEREBRAL VENOUS PRESSURES

INTRODUCTION

"It is then useful to study it (General Anaesthesia) not only from the point of view of surgical operations but by itself and for its own sake.... only thus could we safely, and with a clear conscience, apply it to man."
Magendie, F. (1847). C.R. Acad. Sci. Paris. 24,137.

This thesis was planned in 1963 and the work for it began then. At that time there was virtually no knowledge of the action of commonly used volatile anaesthetic drugs on either cerebral circulation or cerebral metabolism. The position at that period is best illustrated by quoting from the authoritative and exhaustive review by Sokoloff (1963) on the effects of anaesthetic agents on cerebral blood flow:-
"Although the barbiturates are hardly representative, it is likely that most general anaesthetic agents have similar effects on the cerebral circulation and metabolism. All reduce cerebral metabolic rate in anaesthetizing doses. With the possible exception of ether, which appears to have specific vasodilator properties, there is little evidence that any of them exert any greater direct action on the cerebral circulation than the barbiturates. Any influence they may have is also probably chiefly secondary to their effects on blood pressure, cerebral metabolic rate and the respiratory gas tensions in the blood."

It is clear from this account that experimental evidence on the effects of all the commonly employed anaesthetic drugs, except the barbiturates and ether, was scarce. In fact even this cautious summary slightly overstretches

the evidence when it states that "all (anaesthetics) reduce cerebral metabolic rate" for this had only been established for the barbiturates and, on the basis of one unpublished account, for ether.

More investigative work had been done on the changes produced by anaesthetic drugs on cerebrospinal fluid pressures but the results of these studies, which will of course be reviewed in detail subsequently, were contradictory in the extreme. On the one hand, it was said that anaesthetic drugs had no important effects on cerebrospinal fluid pressure provided they were administered skilfully (Stephen, Woodhall, Golden, Martin and Nowill, 1954), while on the other Woringer, Brogly and Dorgler (1954) considered that all volatile anaesthetic drugs elevated cerebrospinal fluid pressure. In 1960, Small, Weitzner and Nahas concluded that clinically undetected hypercapnia was the cause of the c.s.f. pressure increases sometimes reported to occur after administration of various anaesthetics.

It therefore appeared necessary to attempt to add to the available evidence on the effects of volatile anaesthetic drugs on cerebral blood flow, cerebral metabolism and cerebrospinal fluid pressure. It also seemed important to investigate this subject for practical reasons. The clinical questions which this thesis set out to answer were:-

(See Overpage

(1) is cerebral perfusion adequate to avoid cerebral hypoxia during anaesthesia with these drugs? If cerebral blood flow is adequate, does it remain so when hypotension accompanies anaesthetic administration? Does the cerebral circulation respond to hypocapnia during anaesthesia with these drugs? (The last question appeared important in relation to the clinical use of hyperventilation techniques in neurosurgical anaesthesia.)
(2) is the aerobic metabolism of the brain depressed by volatile anaesthetic drugs and, if so, by how much? If depression of cerebral oxygen requirements occurs, is it of a degree which could influence cerebral neuronal survival during periods of cerebral ischaemia? Do different volatile anaesthetics produce similar degrees of cerebral metabolic depression and is the degree of any depression which occurs related to the concentration of the anaesthetic administered?
(3) how does administration of these drugs affect operating conditions for neurosurgery? Is the brain rendered more vascular and is the intracranial pressure increased so that brain herniation may occur? If the intracranial pressure does increase with these drugs, does it help to hyperventilate the patient? Under what circumstances is it safe to administer volatile anaesthetic drugs to patients with intracranial tumours?

In order to answer these questions, it was obviously necessary to measure cerebral blood flow, cerebral oxygen consumption and intracranial or cerebrospinal fluid pressures. In order to measure cerebral blood flow and to derive cerebral oxygen consumption, measurements of radioactive gas clearance from the cerebral cortex were made by a technique to which I was introduced by Dr. A. Murray Harper. For the measurements of intracranial and cerebrospinal fluid pressures, I was most fortunate in obtaining the

interest and cooperation of Mr. W. Bryan Jennett and Dr. John Barker. The planning and direction of all this work was of course my own as was the collection and processing of all the data presented in this thesis.

Since as indicated above, this work was closely connected with important clinical problems, some of the studies have been published in order to make the information quickly and readily available to clinicians. Reprints of these publications are attached. In this thesis, all the studies which I have carried out in the past 4 years in this field are presented in detail and are considered with reference to one another. The thesis is divided into two Parts:-

Part I consists of a full account of the blood flow and oxygen uptake of the cerebral cortex during anaesthesia with halothane, trichloroethylene and chloroform.

Part II deals with the changes in intracranial and cerebrospinal fluid pressure produced by these three drugs.

The thesis particularly discusses three clinical aspects of these investigations. Firstly a quantitative assessment is made of the oxygenation of the brain during anaesthesia in terms of cerebral venous and cerebral tissue oxygen tensions. Secondly the relationship of the findings to clinical situations of general and local cerebral ischaemia is explored and finally the question of the safety of anaesthetic administration to patients with intracranial tumours is discussed.

(Tables referred to in Text with prefix App. before the table number will be found in the Appendix which starts on p. 232).

AUTHOR'S WORK

PART I

Studies of the Influence of Volatile Anaesthetic Drugs on the Blood Flow and Oxygen Uptake of the Cerebral Cortex

CHAPTER 1

General Description of the Methodology of Blood Flow and Oxygen Uptake Measurement

The studies were carried out on unpremedicated, unselected mongrel dogs. Anaesthesia was induced with a sleep dose of thiopentone just sufficient to produce unconsciousness and a cuffed endotracheal tube was inserted. Muscular paralysis was obtained with suxamethonium chloride and ventilation was controlled with nitrous oxide-oxygen using a constant volume ventilator. Either one or two additional supplements of thiopentone of 50-100 mgs. were given during the surgical preparation to ensure that anaesthesia was adequate.

The femoral artery was cannulated to allow sampling of arterial blood and measurement of mean arterial blood pressure. The femoral vein was also cannulated for the administration of increments of suxamethonium as required to maintain control of ventilation. A cannula was placed in either the superior thyroid or the lingual branch of the common carotid artery so that its tip lay just at the entrance of this branch into the main artery. Through this cannula, krypton 85, dissolved in saline, was injected for the flow measurements.

The skin and subcutaneous tissues of the scalp were reflected and the temporalis muscle on one side of the skull was removed. A trephine hole was made and the dura reflected to expose an area of parietal cortex. This was covered with a thin plastic membrane (6 u polyethylene teraphthalate - "Melinex I.C.I.) to prevent dessication of the brain surface. In some animals the superior sagittal sinus was exposed and was

cannulated to allow sampling of cerebral venous blood. In those animals in which the sinus was cannulated the bone overlying the sinus was removed as far anteriorly as the frontal air sinuses in order to sever as many emissary veins as possible.

A Geiger Muller tube was mounted 2-5 mms. above the membrane covering the exposed area of cortex and the surrounding brain and bone shielded from the counting field by lead foil. The Geiger Muller tube was attached to a ratemeter and linear direct writing recorder.

To measure flow, krypton 85, dissolved in saline, was injected at a rate just sufficient to maintain a constant level of radioactivity in the monitored area of cortex for 2-3 minutes. During this time equilibrium was reached between arterial and cerebral tissue tensions of krypton in even the most slowly perfused areas of the cortex. At the end of this equilibration period, the injection was suddenly stopped and the rate of clearance of the radioactive krypton recorded. The linear record was subsequently plotted on semilogarithmic graph paper, of which the y axis was logarithmic and the x axis was linear. Radioactivity in arbitrary units was plotted on the y axis and time in seconds on the x axis. The best straight line fit to the initial slope of this clearance plot was drawn and the time to half clearance in seconds measured from this. Mean cortical blood flow was then calculated by substituting this value for $T\frac{1}{2}$ in the following equation:-

$$\text{Flow (ml/G/min)} = \frac{\log_e 2 \times 60}{T\frac{1}{2}}$$

(Lassen & Ingvar; 1961)

The values used for the blood-brain partition coefficient (λ) were obtained from the work of Glass & Harper (1962). The particular value used depended on the arterial blood haematocrit existing at the time of the flow measurement.

A number of measurements of flow were made during unsupplemented nitrous oxide-oxygen anaesthesia and then the volatile drug under study (halothane, trichloroethylene or chloroform) was introduced into the same nitrous oxide-oxygen mixture from a calibrated vaporiser and further measurements of flow carried out.

During each flow measurement arterial blood was sampled for measurement of arterial pH, Pco_2 and oxygen saturation. In many animals cerebral venous blood from the superior sagittal sinus was also obtained and analysed for pH, Pco_2 and oxygen saturation. Arterial Pco_2 was maintained constant by adjusting the stroke volume of the ventilator when necessary.

The oxygen uptake of the cerebral cortex was calculated as the product of the measured cortical blood flow and the arterio-venous oxygen content difference across the cerebral cortex.

Cerebrovascular resistance (C.V.R.) was calculated as the ratio of cerebral cortical blood flow to mean arterial blood pressure and expressed, as is customary, in arbitory units. Since cerebrovascular resistence is really an expression of the relationship between flow and perfusion pressure, cerebral venous pressure should theoretically be subtracted from the mean arterial pressure in calculating this ratio. However the values obtained for cerebral venous pressure were so low (approximately 4 mm.Hg. - see Part II) in relation to the values for the arterial blood pressure that it was decided not to include cerebral venous pressure in these calculations. It was felt that this was a reasonable decision since the error involved was almost certainly less than that involved in assessing the arterial perfusion pressure of the brain from measurements of aortic blood pressure.

The above was the standard protocol of the experiments but many variations were made to elucidate particular points and these will be described as they arise.

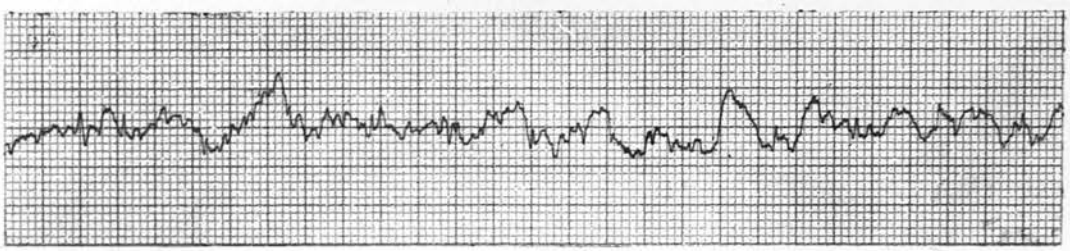
CHAPTER 2

Detailed Discussion of Methodology

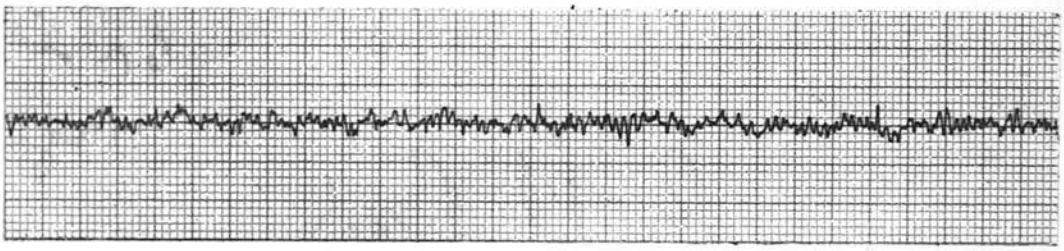
(a) Anaesthetic Technique

Thiopentone in a 5% solution was used for the induction of anaesthesia. The dose used was carefully adjusted to be just sufficient to produce sleep; this averaged 20 mgs./kg. This is considerably in excess of the dosage required to produce sleep in man but is in agreement with the figures given in the veterinary anaesthetic literature (Westhues & Fritsch, 1965; Hall, 1966).

In addition to the fact that higher dosage is required, the dog metabolises thiopentone at a considerably slower rate than does man. Brodie, Mark, Papper, Lief, Bernstein & Rovenstine (1950) have shown that man reduces the level of thiopentone in his plasma by 15% per hour but that the dog lowers his plasma thiopentone concentration by only 50% in 24 hours. However these authors also showed that, after a normal anaesthetic dose of thiopentone, there is an initial very rapid drop in plasma concentration of thiopentone in both dog and man which is due, not to metabolic breakdown, but to redistribution of the drug away from organs such as the brain and towards neutral fat stores. It is this initial redistribution which accounts for the rapid recovery of consciousness after thiopentone administration in normal dosage. It was on account of this rapid redistribution within the first 5-30 minutes after administration that it was deemed necessary to give one and occasionally two supplements of thiopentone during the performance of necessary surgery. Usually one



RESIDUAL THIOPENTONE



1 hour later

Figure 1 The lessening of thiopentone depression of the E.E.G. The lower record was obtained 1 hour after the upper and shows the E.E.G. activity present at the time of control flow measurements.

supplementary dose was given 30 minutes after induction, and the surgery was completed (except for reflection of the dura) in 1-1½ hours after induction. If, in any particular animal, the surgery was progressing slowly, a second supplement was given one hour after induction. After the final completion of the preparation which, including reflexion of the dura, would be about 2 hours after the start, a pause of one hour was made to allow the brain level of thiopentone to fall to very low levels and to allow the brain surface to stabilise after the surgical interference. In many of the animals, the E.E.G. was recorded and it was always found that, employing this dose-time schedule, only minimal barbiturate activity remained in the E.E.G. at the time of the first flow measurement. Figure 1 consists of two E.E.G. records obtained from one animal, the lower being recorded one hour after the upper. The upper record, taken approximately 1 hour after the induction of anaesthesia with 30 mgs./kg. thiopentone and during nitrous oxide-oxygen anaesthesia, shows delta activity with some superimposed fast activity in the beta range. One hour later the record is devoid of delta waves though barbiturate fast activity is still evident. This latter type of barbiturate effect is equivalent to barbiturate sedation and not anaesthesia (anaesthesia in these animals being maintained with nitrous oxide) and this degree of barbiturate depression would not be sufficient to affect cerebral blood flow or metabolism itself though it may have potentiated the effect of nitrous oxide (see below). The control measurements of flow in the experiments to be described were obtained when the E.E.G. resembled the lower one in Fig. 1. (Nitrous oxide itself has little effect on the E.E.G.; Clutton-Brock, 1961)

The relatively slow metabolic breakdown of thiopentone in the dog was an advantage because it meant that any residual effect on the brain after

TIME	BLOOD FLOW	Pa_{co_2}	BLOOD PRESSURE	C.V.R.
- 35 mins.	0.76	36	120	1.58
- 15 mins.	0.72	37	120	1.67
Zero	I.V. 12.5 mgs./kg. Thiopentone			
+ 20 mins.	0.55	40	105	1.91
+ 1 hr.	0.58	37	110	1.90
+ 1 hr. 15 mins.	0.49	38	105	2.14
+ 1 hr. 35 mins.	0.72	35	105	1.46
+ 2 hr. 15 mins.	0.78	37	110	1.41

Table 1 The effect on cerebral cortical blood flow and cerebrovascular resistance of I.V. thiopentone (12.5 mgs./kg.) in one dog (6/8/64).

(Blood flow in mls./G./min; $Paco_2$ in mm.Hg; Blood pressure in mm.Hg. and cerebrovascular resistance (C.V.R.) in arbitory units)

the initial rapid fall in thiopentone concentration would remain fairly constant throughout the time occupied by these experiments.

These points are, of course, important to this study because thiopentone is known to have profound effects on cerebral blood flow and metabolism. The evidence in favour of a reduction in cerebral metabolic rate by anaesthetic doses of this drug is overwhelming (Schmidt, Kety & Penner, 1945; Homburger, Himwich, Etsten, York, Maresca & Himwich, 1946; Geiger & Magnes, 1947; Himwich, Homburger, Maresca & Himwich, 1947; Wechsler, Dripps & Kety, 1951; McCall & Taylor, 1952; Fazekas & Bessman, 1953; Schieve & Wilson, 1953; Wilson, Odom & Schieve, 1953; Gleichmann, Ingvar, Lassen, Lubbers, Siesjo & Thews, 1962; Pierce, Lambertsen, Deutsch, Chase, Linde, Dripps & Price, 1962) and recent studies in which arterial Pco_2 has been controlled have shown that this depression of metabolic rate is accompanied by a proportionate reduction in cerebral blood flow. (Landau, Freygang, Rowland, Sokoloff & Kety, 1955; Gleichmann et al, 1962; Pierce et al, 1962)

In order to determine the effect of thiopentone on cerebral cortical blood flow as measured in these experiments repeated blood flow measurements were made in one animal under nitrous oxide-oxygen anaesthesia before and after one intravenous injection of 12.5 mgs./kg. thiopentone. The results are given in Table 1 from which it will be seen that blood flow fell by about 25% immediately after thiopentone injection and returned to control values in approximately 1½ hours. The blood pressure fell slightly with the thiopentone injection. The reduction in blood flow was however not due to this reduced perfusion pressure since cerebrovascular resistance increased indicating active cerebral vasoconstriction following thiopentone.

The amount of the reduction in cerebral metabolic rate for oxygen (C.M.R.o_2) and in cerebral blood flow (C.B.F.) is proportional to the dosage of thiopentone administered (or more correctly to the depth of anaesthesia) (Homburger et al, 1946). Gleichmann et al.(1962) have shown that a close correlation exists between C.B.F., C.M.R.o_2 and E.E.G. frequency under barbiturate anaesthesia. Furthermore, Landau et al.(1955) have demonstrated that not only is flow reduced by thiopentone but that the PATTERN of flow over the cerebral cortex is altered in that those areas which have the highest flow during consciousness (sensorimotor, visual and auditory cortex) show the greatest reductions during light thiopentone anaesthesia. Flow therefore becomes more uniform over the cerebral cortex during barbiturate anaesthesia than during consciousness. This can be correlated with Roth's demonstration (1963) that thiopentone, immediately after administration, is distributed throughout the brain in accordance with the rate of local blood flow existing at the moment of barbiturate injection so that areas with the highest flows receive and take up the greatest thiopentone concentrations.

From the above, it is clear that it was essential in these studies to allow sufficient time for the brain concentration of thiopentone to fall below the level which produces anaesthesia and the accompanying alterations in cerebral blood flow. The evidence for believing that this condition was satisfied is as follows:-

(1) the time-dose schedule was such that the animal would have recovered consciousness long before the first flow measurement was made had anaesthesia not been maintained with nitrous oxide-oxygen. To be certain on this point, a 13.5 kgs. dog was anaesthetised with 30 mgs./kg. thiopentone, allowed to breath air spontaneously for 30 minutes, then given

a supplementary dose of 100 mgs. thiopentone (which was the maximum supplement used in the experiments discussed in this thesis). 1 hour after induction of anaesthesia, the eyelash reflex had returned. At 1½ hours, the dog's eyes were open and he cocked his ears in response to auditory stimuli. At 2 hours he was lifting his head to look round and at 2¼ hours was walking, though still ataxic;
(2) in all animals in which the E.E.G. was monitored, the pattern was devoid of slow wave activity by the time of the first flow measurement. Delta and theta activity due to residual thiopentone were, of course, seen during the earlier stages of preparing the animal (see Figure 1).
(3) there was no tendency for the values for flow to increase during the control period of measurement under unsupplemented nitrous oxide-oxygen anaesthesia which would have occurred if the animal were still recovering from thiopentone at this time.

It is none the less certain that detectable thiopentone would still be present in the blood of these animals throughout these experiments though the concentration would be below the level required for anaesthesia. Since it has been shown that below anaesthetic dosage thiopentone has no influence on cerebral blood flow or metabolism (Kety, Woodford, Harmel, Freygang, Appel & Schmidt, 1948), the residual thiopentone could not by itself affect the results obtained. However, it cannot be denied that some potentiation of the action of both nitrous oxide and of the volatile agents may have been produced by the low concentrations of thiopentone still circulating and indeed evidence will be presented subsequently which shows that this was the case. Fortunately, due to the slow metabolic breakdown of thiopentone in the dog, this factor would be reasonably constant throughout these experiments.

The only other drugs used constantly in these experiments were

suxamethonium chloride and nitrous oxide.

The influence of suxamethonium chloride on cerebral blood flow is unknown though it has been shown that this relaxant drug elevates cerebrospinal fluid pressure (Halldin & Wahlin, 1959). It is not clear from the literature whether these increases in c.s.f. pressure are the result of changes in central venous pressure consequent upon chest wall muscle fasciculations or are due to increases in cerebral blood flow. Halldin & Wahlin (1959) concluded that the latter was the correct explanation and therefore it was deemed wise to avoid administration of suxamethonium immediately before or during measurement of cerebral blood flow.

In all this work it was necessary that the animals be anaesthetised and for this purpose nitrous oxide and oxygen in the ratio of at least 2:1 were administered throughout these studies. It was therefore not possible to elucidate the effects of nitrous oxide itself on C.B.F. and C.M.R.o_2. The possibility of making control measurements under nitrous oxide and then administering the volatile agent in oxygen enriched air was considered and in fact a group of experiments was performed in this way. This technique was abandoned however because it involved the alteration of two variables between the control and study measurements. In all the experiments reported here the volatile agent under study was added to the same nitrous oxide-oxygen mixture as had been used for the control measurements so that any influence exerted by nitrous oxide would be constant. Wollman, Alexander, Cohen, Smith, Chase & Molen (1965) have shown that in man anaesthetised with nitrous oxide total cerebral blood flow is very close to that in conscious man but that cerebral metabolic rate is depressed by about 23%. It may be therefore that the values given here for C.M.R.o_2 are lower than in the conscious dog but any such depression must have been

DATE OF EXPERIMENT	FRONTAL CORTEX	PARIETAL CORTEX
6/8/64	1.08	0.93
9/8/64	1.09 0.95	0.93 0.84
14/8/64	0.96 1.12	1.09 0.93
28/12/64	0.72 0.79	0.93 0.82
Means	0.96 $\pm$0.15	0.92 $\pm$0.09

Table 2. Blood flow in different areas of cerebral cortex under constant conditions during nitrous oxide-oxygen anaesthesia.

(Blood flow in mls./G./min.)

equal in control and study measurements.

More urgent questions in the present discussion are however (1) what was the relationship between the flow measured in the area of parietal cortex studied to flow in other areas of the cortex, and (2) was the flow in the monitored area constant under unchanged nitrous oxide-oxygen anaesthesia?

A comparison of flow through different areas of cortex under nitrous oxide-oxygen anaesthesia was made in four dogs and the results are shown in Table 2. Because of limitations in available equipment, flow measurements in different areas could not be made simultaneously; they were however made as close to one another as possible, i.e. between five and ten minutes apart, this being the time required to establish the clearance curve of the preceding flow. The measurements were made over various parts of the supralateral surface of the frontal and of the parietal cortex. In each case the area measured from had a diameter of approximately 1 cm.

It will be seen from Table 2 that with only one exception (the first pair of flows on 28/12/64) there was excellent correlation between flow in the different areas. In considering these results it is necessary to bear in mind that this method of flow measurement has a 10% coefficient of variation for multiple measurements in any one area under constant conditions (Harper, Glass & Glover, 1961). Furthermore Betz (1967) has shown that spontaneous fluctuations in cerebral blood flow of up to 25% occur frequently. It can therefore be concluded that there is no systematic difference in flow between these different areas of cerebral cortex. This point is further verified by the close agreement of the two mean values for frontal and parietal flows. Harper et al. (1961), using the same method, have also found that there is little regional variation in blood flow

	0 - +1 hr.	+1 - +2 hrs.	+2 - +3 hrs.	+3 - +4 hrs.	+4 - +5 hrs.	+5 - +6 hrs.
3/5/65		0.88 (42) 0.84 (44) 0.80 (47)	0.82 (44) 0.80 (47) 0.66 (43) 0.82 (42)	0.71 (47)		
14/5/65	1.02 (33)	0.97 (41) 0.88 (40) 1.11 (40)	0.82 (37) 0.80 (40) 0.79 (43)			
17/5/65	0.92 (42) 0.77 (40)		0.64 (40)	0.63 (37) 0.63 (40)	0.60 (40) 0.71 (40)	0.69 (38)
5/4/66			0.72 (41)	0.70 (46)	0.74 (46) 0.68 (39)	0.79 (44) 0.71 (44)

Table 3. Repeated measurements of blood flow through the cerebral cortex of dogs under constant conditions of anaesthesia (nitrous oxide-oxygen), arterial carbon dioxide tension (shown in brackets) and temperature.

(Zero time is time of reflecting the dura).

(Blood flow in mls./G./min.)

between different areas of cortex under nitrous oxide-oxygen anaesthesia. This subject of flow variation between areas of cerebral cortex will arise again in connection with the study of halothane anaesthesia.

Was the flow in the single monitored area of cortex constant under unchanged nitrous oxide-oxygen anaesthesia? As already stated, Betz (1967) has shown that spontaneous fluctuations in regional cerebral blood flow do occur under apparently constant conditions. Such spontaneous changes last up to 2 minutes and so could introduce variability in individual flow determinations in the present experiments. Such fluctuations apparently occur randomly and therefore would not affect the conclusions of the present thesis which are based on comparisons between the means of multiple measurements. The question which is more vital to the present work is whether there was any progressive trend either upwards or downwards in regional cerebral blood flow with time during these experiments. Such time dependent trends would if present complicate the interpretation of the studies of the volatile anaesthetic drugs.

Four animals were studied during continuous nitrous oxide-oxygen anaesthesia at constant arterial Pco_2 within the eucapnic range and repeated blood flow estimations were performed. The results are given in Table 3 from which it is apparent that there is no evidence of any time dependent flow trend except that there is a suggestion that in the first hour after opening the dura, cerebral blood flow was greater than in the second or subsequent hours. This rapid flow after reflection of the dura probably resulted from slight mechanical irritation of the cortical surface during the exposure. This early vasodilatation did not influence any of the results to be reported since no flow determinations were made during this first hour. Harper et al. (1961) also reported no change in regional

DATE OF EXPERIMENT	MEAN CENTRAL VENOUS PRESSURE	MEAN ARTERIAL PRESSURE
30/4/63	-1.0 cms.H_2O	170 mm.Hg.
20/6/63	0 " "	145 " "
20/12/63	+4.0 " "	160 " "
30/12/63	+3.2 " "	150 " "
19/2/64	+1.8 " "	165 " "
25/3/64	+3.4 " "	150 " "
26/2/65	0 " "	150 " "
17/3/65	+1.0 " "	150 " "
16/8/65	+2.2 " "	145 " "
17/12/65	+3.5 " "	160 " "
Means	+1.8 $\pm$1.7	155 $\pm$9

Table 4. Mean central venous pressure and mean arterial blood pressure during controlled ventilation with the Starling ventilator in dogs anaesthetised with nitrous oxide-oxygen.

cerebral blood flow during prolonged nitrous oxide-oxygen anaesthesia.

The last question to be considered in connection with anaesthetic technique is that relating to the use of prolonged positive pressure ventilation. Firstly, did this mechanically elevate venous pressure and so influence the flow determinations and, secondly, did it result in progressive deterioration in respiratory gas exchange?

The ventilator used throughout was the Starling respiratory pump which is a constant volume, time cycled ventilator. The ratio of inspiratory to expiratory/
/time is fixed at 1 : 1 and the respiratory rate used was 24/minute. In order to determine the influence of this ventilatatory pattern on the haemodynamics of the dog, a number of measurements of central venous pressure were made following 3 - 5 hours of nitrous oxide-oxygen anaesthesia and controlled ventilation. The results are given in Table 4, from which it will be seen that in most instances the mean intrathoracic venous pressure was rendered positive with respect to atmospheric pressure by this technique of intermittent positive pressure ventilation (I.P.P.V.). However the absolute values for central venous pressure were well below those necessary to affect cerebral cortical blood flow as determined by Jacobson, Harper & McDowall (1963). From Table 4 it can also be seen that this technique of I.P.P.V. did not produce arterial hypotension.

As regards possible deterioration of respiratory gas exchange, this could affect flow via alterations in arterial carbon dioxide and oxygen tensions. In these studies such alterations in blood gas tensions did not occur because $Paco_2$ and Pao_2 were measured with each flow measurement and necessary adjustments in the tidal volume and inspired oxygen content were made.

However impaired lung function in the form of increased pulmonary venous

admixture could also influence the results by increasing the recirculation
(See Technique of Flow Measurement p. 33)
of the isotope. / Such increases in venous admixture have been shown to occur during prolonged anaesthesia in the dog by Finley, Lenfant, Haab, Piiper & Rahn (1960) and by McDowall (1964). No attempt was made in the present study to quantitate venous admixture but at the end of the experiment a large dose of krypton was administered intravenously and the beta emissions from the cortex were counted. In this way it was possible to determine the efficiency of lung clearance of the isotope and hence the danger of increased arterial recirculation. A significant beta count from the cortex after intravenous injection was obtained in only two animals and these animals were therefore excluded; in all other experiments significant increases in isotope recirculation following prolonged anaesthesia did not occur.

(b) The Surgical Preparation

The cannulation of the femoral vessels and the carotid artery have already been described.

The trephine used for removing the segment of skull over the area of flow measurements was of 2.5 cms. diameter. After the bone segment had been detached, bleeding from the bone edges was stopped with bone wax. The dura was then opened in a cruciate fashion. Large dural arteries were divided and ligated. Diathermy was not used to coagulate dural vessels lest the underlying cortical surface be damaged. The opening in the dura was usually of a diameter of 2 cms.

Immediately the brain was exposed, it was covered with a 6 u layer of polyethylene teraphthalate ("Melinex" I.C.I.). Great care had to be taken in laying the membrane on the brain to avoid trapping air bubbles. Even the smallest air bubble under the membrane resulted in fallacious underestimates of flow because krypton quickly entered the trapped air from the blood and was only slowly cleared (because of its high gas-blood partition coefficient).

The purposes served by the "Melinex" membrane were (1) to reduce heat loss from the cerebral cortex, (2) to limit diffusion of CO_2 from the brain into the atmosphere and (3) to limit diffusion of krypton from the brain. Because of its high blood flow, exposed cerebral cortex is close to blood temperature except for the most superficial layer. By covering this surface layer with a membrane and thereby trapping a layer of c.s.f. it is believed that cooling of the brain was avoided. Certainly whenever the temperature of the brain surface was measured, it was very close to blood temperature.

Loss of CO_2 from the brain surface is a more serious difficulty and of course unless CO_2 loss is prevented, measurements of cerebral cortical flow may be fallacious. The Pco_2 of the exposed brain quickly falls due to the rapid diffusion of CO_2 from the brain into the air. When a CO_2 electrode is first applied to the brain surface the reading obtained is at first very low but rises over a period of 10 - 15 minutes since the electrode itself prevents further loss of CO_2 to the atmosphere. Similarly when a pH electrode is applied to the brain which has been exposed for a few minutes to the air, a very alkaline pH of about 7.8 is recorded and this falls over 10 - 15 minutes to the normal brain pH of 7.25 - 7.33 due to the arrest of CO_2 escape by the electrode (personal unpublished observations). Loss of CO_2 from the exposed and uncovered cerebral cortex has also been reported by Meyer, Gotoh, Tazaki, Hamaguchi, Ishikawa, Nouailhat & Symon (1962).

The permeability of "Melinex" to CO_2 has been tested by comparing its behaviour with that of "Teflon" when used as the outer membrane on a CO_2 electrode ("Teflon" is relatively permeable to CO_2). It was found that after a step change in Pco_2 at the electrode surface , from 40 to 20 mm. Hg., the "Teflon" covered membrane registered 95% response in 24 seconds while the "Melinex" covered electrode required more than 15 minutes. It can therefore be stated that the "Melinex" membrane on the brain surface greatly reduded the escape of CO_2. This together with the high blood flow of the cerebral cortex ensured that the tissue Pco_2 in the area of flow measurement was similar to that in areas of cortex not exposed.

The membrane in addition to stopping the loss of CO_2 from the brain surface also prevented the escape of krypton to the atmosphere. This was important since krypton leaving the brain in this way would lead to a

fallacious overestimation of blood flow.

Over the membrane was placed a thin sheet of lead with a central aperture of 1 cm. diamater through which the G.M. tube "looked at" the area of exposed cerebral cortex. This lead sheet shielded out radioactivity coming from non cerebral sources and cut down the background effect of Bremsstrahlung (Glass, Harper & Glover, 1961).

Cerebral venous blood was sampled from the superior sagittal sinus. The blood in the sagittal sinus of the dog has drained mainly from the cerebral cortex but also there are a number of large emissary veins which enter it. These veins may bring into the sinus blood which has drained from the diploe and from extracranial muscle, skin and subcutaneous tissue. At its anterior end, the sagittal sinus in the dog commences as the union of several small veins draining the anterior ethmoidal air sinuses. These then constitute a source of non cerebral blood which could be removed only by the most radical surgery. As the sinus passes caudalward there are two further important sources of "contamination"; the first is the frontal air sinuses and the second is the parietal emissary vein (Hegedus & Shackelford, 1965).

The problem was to decide how radically the sinus should be cleared of these extra cerebral connections. Gleichmann et al. (1962) found that, in order to get good correlation between cerebral venous Pco_2 and cerebral tissue Pco_2, it was necessary to completely deroof the sagittal sinus to avoid extracranial contamination. This however is a very extensive surgical procedure involving considerable trauma and blood loss. It is after just such traumatic procedures that normal cerebrovascular control tends to be lost (Harper, 1965). Consequently, in the experiments to be discussed in this thesis, the sinus was deroofed as far anteriorly as the

frontal air sinuses and no further. This resulted in complete interruption of the two major sources of contamination, i.e. the frontal and the parietal emissary veins and was decided upon as a result of latex injection studies of the cerebral venous system. In addition the sampling cannula was placed as far caudalward in the sinus as possible since the ratio of extracerebral to cerebral blood becomes progressively smaller the further posteriorly the samples are obtained after deroofing the sinus as described above. Finally, the sampling of venous blood was always carried out very slowly, i.e. 2 ccs. over 2 minutes to avoid any tendency to aspirate extracerebral blood into the sinus. Evidence that these measures were successful in yielding venous blood almost entirely of cerebral origin is as follows:-

(1) the arterio-venous oxygen difference and the calculated cerebral cortical oxygen uptake were high. The values obtained for the oxygen uptake of the cerebral cortex under nitrous oxide-oxygen anaesthesia in the various studies to be described in this thesis varied from 0.060 to 0.070 ml. 02/G/min. This range is in agreement with the values obtained by others in the dog (Homburger et al., 1946; Gleichmann et al., 1962). If significant contamination of the sagittal sinus with non-cerebral venous blood had occured then the calculated oxygen uptake would have been low because of the relatively low oxygen extraction of extracranial tissues.

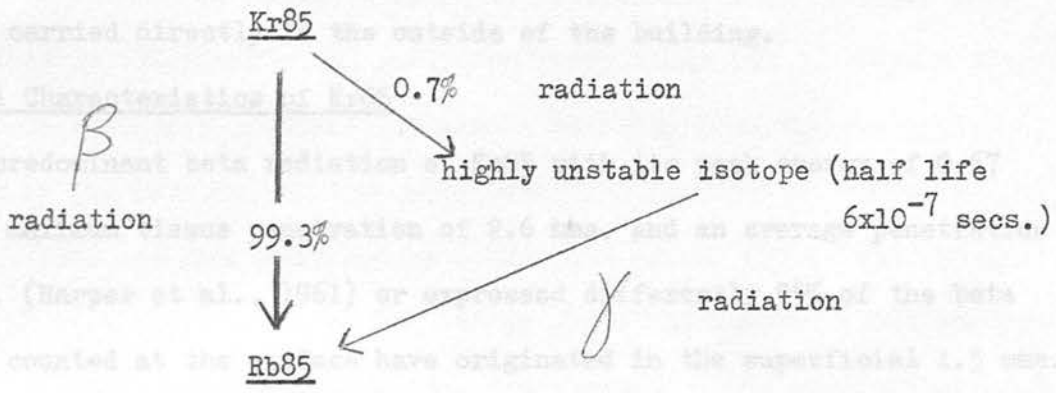
(2) the arterio-venous carbon dioxide tension difference was large. Further support for the use of this technique of venous sampling comes from the studies of Hegedus and Shackelford (1965). These authors state that in the dog "the posterior third of the (sagittal) sinus is the site to obtain cerebral venous blood specimens with minimal admixture of extracerebral blood"and that surgical exposure of the sinus "interrupts the

frontal and parietal emissary veins and the connecting dipoic veins and thereby only a small and constant contamination by extracerebral blood through the anterior ethmoidal veins will occur".

(c) The Technique of Flow Measurement

The technique used has been fully described by Lassen and Ingvar (1961) who introduced it. Like the Kety-Schmidt technique (1948) it relies on study of the rate of uptake or removal of an inert gas by the brain.

Krypton was the inert gas used in the form of its radioactive isotope krypton 85. This isotope disintegrates in the following manner:-



From this schema, it can be seen that 99.3% of the krypton 85 atoms disintegrate directly to Rb85 with the emission of beta radiation. The other 0.7% of the Kr85 emits beta radiation of lower energy to form a highly unstable intermediate isotope which disintegrates almost at once to Rb85 with the emission of gamma radiation. Kr85 therefore emits both beta and gamma radiation but approximately 150 times as much beta as gamma. The gamma radiation of Kr85 is however of relatively high energy and therefore the isotope has to be handled with some care.

Handling of the Isotope

Kr85 has a physical half life of 10.6 years. It was received in sealed glass ampoules from the Radioisotope Centre at Amersham; each

ampoule contained 1-2 curies of radioactivity. The Kr85 was transferred to an evacuated metal box and the remainder of the vacuum filled with saline. The box was left for 24 hours during which time the krypton gas dissolved in the saline; thereafter the saline containing dissolved krypton was drawn off as required. The box in which the krypton was stored was heavily shielded with lead.

During the animal experiments a wide bore tube was attached to the expiratory port of the ventilator so that the krypton excreted from the lungs was carried directly to the outside of the building.

Biological Characteristics of Kr85

The predominant beta radiation of Kr85 with its peak energy of 0.67 MeV has a maximum tissue penetration of 2.6 mms. and an average penetration of 0.7 mm. (Harper et al., 1961) or expressed differently 95% of the beta emissions counted at the surface have originated in the superficial 1.5 mms. of brain (Lassen, 1965). Since the thickness of the dog's cerebral cortex over the fronto-parietal area is approximately 2 mms. (Ingvar & Lassen, 1962) virtually all the activity recorded by the Geiger Muller tube mounted above the cortex must have emanated from the cortex with insignificant contribution from the subcortical white matter.

Krypton is poorly soluble in blood and therefore its clearance by the lungs is efficient. Chidsey, Fritts, Hardewig, Richards and Cournand (1959) found that only 5% of an intravenously injected bolus reached the arterial blood while with more prolonged injection (over 2 minutes) 15% reached the arterial blood. However the total body dose of krypton in the present experiments was smaller because the isotope was introduced only into the carotid circulation. It was therefore diluted with the entire venous return before passing through the lungs. Under these circumstances

Ingvar and Lassen (1962) have shown that arterial recirculation amounts to only 1% of the administered dose. The problem of increasing arterial recirculation with prolonged anaesthesia has been dealt with above. It is not necessary that the arterial concentration of krypton should fall to zero at the end of krypton injection but it is important that the arterial krypton concentration be constant for if it is not then arterial blood clearance of krypton will appear to be brain clearance and therefore result in a calculated blood flow higher than the true flow.

The next biological characteristic of krypton which is of importance to the method is its brain-blood partition coefficient (λ). Since the recorded beta radiation is emanating almost entirely from the cerebral cortex, it is the cerebral cortex-blood partition coefficient which is relevant. This has been measured by Ingvar and Lassen (1962) who obtained a λ of 0.92 at a haematocrit of 50% and by Glass and Harper (1962) who reported a value of $0.91 \pm 6\%$ at the same haematocrit. The exact value of λ varies with the blood haematocrit and in all the results to be presented the λ used was that appropriate to the haematocrit existing at the time of the measurement using the formula of Lassen and Munck (1955).

Saturation and Desaturation

The krypton 85 dissolved in saline was injected for between 2 and 3 minutes into the common carotid artery. The isotope was carried by the carotid circulation to the brain where its concentration was monitored by a Geiger Muller tube placed over the parietal cortex.

During the period of injection, the radioisotope concentration in the monitored area of the brain was held constant by varying the rate of injection. A fast rate was required at first to obtain the desired level, thereafter the rate of injection was decreased progressively. The isotope

on reaching the cortex diffused into the cortical tissue according to its blood-brain partition coefficient. At first the most rapidly perfused components of the counting field had the highest concentrations and the more slowly perfused components lower concentrations; consequently a disproportionate amount of the total radioactivity measured at the surface was originating from the fast components. During the subsequent 2 to 3 minutes of injection, the krypton concentration in the slowly perfused components rose and the concentration in the fast components fell until at the end of the injection time all components were at equal concentration. At this time arterial and venous concentrations of krypton were equal since the cortex had been saturated for the existing blood tension of krypton. The tissue concentration at this time was uniform and equal to arterial or venous concentration x partition coefficient.

The injection of krypton into the carotid artery was then suddenly stopped. Since arterial recirculation was small (see above) the arterial concentration fell to a low value relative to the brain concentration on cessation of the injection. The krypton in the cerebral cortical tissues then diffused back into the blood and was carried away in the venous drainage to the lungs where it was almost entirely excreted. Since krypton is an inert gas, the rate of fall in krypton concentration was dependent only on the volume of blood washing it out of the cortical tissues; consequently the rate of fall of radioactivity bore a relationship to the cerebral blood flow.

If blood flow through the counting field (i.e. the volume of cortex "seen" by the G.M. tube) were uniform then the clearance of krypton would be a monoexponential function. Replotting the clearance curve on semil-logarithmic paper (y axis = beta counting rate and x axis = time) would

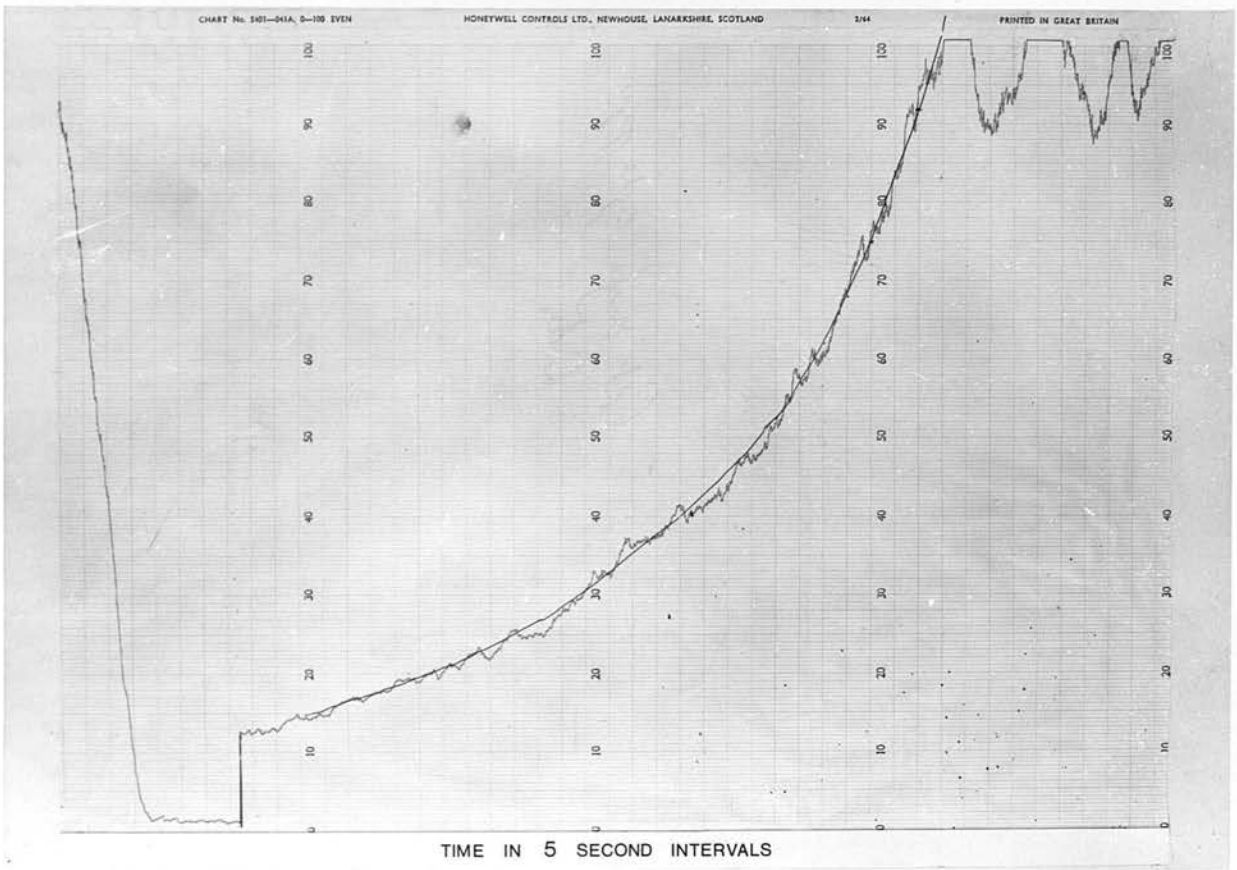


Figure 2 A typical record of the clearance of krypton 85 from the cerebral cortex.

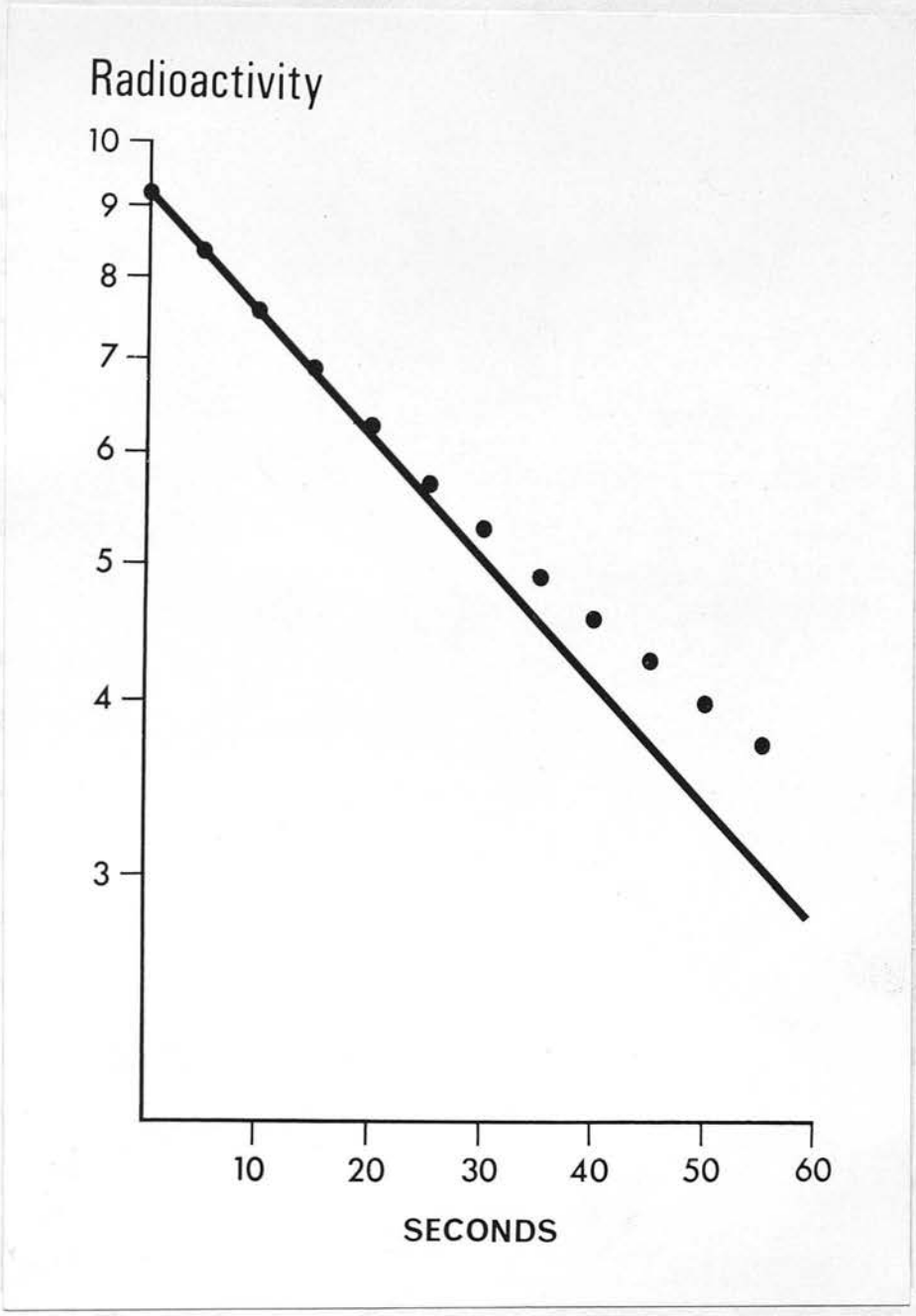


Figure 3 This figure is the plot of the clearance curve shown in Figure 2. The y axis is logarithmic and depicts beta counts in arbitrary units and the x axis is arithmetic and registers time.

give a straight line; the time taken for this line to fall to half of its initial height would give the $T\frac{1}{2}$, from which flow could be calculated.

However, cerebral cortical flow does not appear to be uniform but to consist of several compartments of flow (Harper et al., 1961; Lassen, 1965). Consequently the clearance curve is multiexponential and the plot on semilogarithmic paper is not a single straight line. However Ingvar and Lassen (1962) have shown that, provided all the compartments in the counting field have equal krypton concentration at the beginning of the clearance, then the slope of the first part of the clearance curve gives the mean blood flow through the area studied, i.e. the mean of all the different rates of blood flow through the cortical volume seen by the counter weighted in proportion to their actual weights. These points are illustrated in Figures 2 and 3; Figure 2 shows a typical clearance curve recorded from the cerebral cortex and Figure 3 is the plot of this clearance curve transposed onto semilogarithmic paper. The best straight line fit to the initial part of this plot yields a value for mean blood flow through the area of cortex monitored. It is clear however that slower rates of cerebral perfusion are also present as evidenced by the departure of the plot from the initial slope.

For this derivation of mean cortical flow to be valid it is essential that even the most slowly perfused component in the counting field be saturated with krypton at the start of the clearance. If it were not then the flow value obtained would be too high since the unsaturated slow component would be underrepresented in the clearance curve. Harper et al. (1961) have shown, by calculating flows after different times of injection, that equilibrium is reached after an injection time of 100 seconds. The 2 - 3 minutes of injection used in the following studies were therefore

more than adequate to saturate the counting field with krypton.

The reasons why this equilibration time is so much shorter than that reported by Alexander, Wollman, Cohen, Chase & Behar (1964) to be necessary for brain saturation with krypton administered by inhalation are:-

(1) there is no lag in the rise of the arterial concentration,

(2) a large volume of krypton is introduced at the beginning of the injection so that the krypton tension gradient into the cortex is at first very high,

and (3) cerebral cortical flow is 5 times as high as blood flow through white matter (Landau et al., 1955) and therefore equilibrium is reached more readily in the cortex than in whole brain.

Before leaving the subject of the injection of krypton the possibility that the intracarotid injections themselves might have altered cerebral blood flow has to be considered. Betz (1965) has shown that rapid intracarotid injections can in fact readily affect cerebral blood flow. I therefore went to Betz's laboratory to carry out a study on the effect of injections of saline given into the common carotid artery on cerebral blood flow in the dog. Flow on the cortical surface was measured by the heat clearance technique (Betz & Hensel, 1962) while intracarotid injections of saline at various rates were made. Rapid injections, i.e. more rapid than 1 ml. in one second certainly produced large alterations in flow but when saline was infused in the same way as in the experiments under discussion, i.e. at a rate of less than 6 mls. per 2 minutes, there was no alteration in cerebral cortical flow.

The last methodological question requiring consideration is the possible influence on the measured flow of cerebral arteries and veins in the counting field. Since at the cessation of the injection the arterial

concentration falls almost to zero, the presence of a large volume of arterial blood in the field might be expected to lead to an initial very rapid drop in counting rate. However the time constant of the arterial washout phase is so rapid that it was not registered by the recording system used which had a time constant at least 5 times as great.

Cerebral veins containing blood only from the counting field would have little effect on the calculated flow because the krypton concentration in them would be close to that in the tissue and would fall at the same rate. Unfortunately large cerebral veins in the counting field would certainly be carrying blood from areas of cortex other than that under study. However because cerebral cortical flow is relatively uniform under nitrous oxide-oxygen anaesthesia the influence of such venous blood on the calculated flow would be negligible. Nonetheless, the G.M. tube was placed to avoid the largest cortical arteries and veins.

Since there are several components of flow in any area of cortex, it is important that the geometry of the counting field be maintained constant so as to avoid changes in the weighting of different components from one flow measurement to another. Constant geometry was maintained as far as possible in the experiments to be discussed.

(d) Associated Measurements

Temperature

The pharyngeal temperature was measured with a mercury in glass thermometer. Heating by infra red lamps was applied to the animal to maintain the pharyngeal temperature close to 38°C. No measurements of cerebral blood flow were made if the temperature fell below 36.5°C. The electrodes for blood gas and pH measurement were maintained at 38°C.

Blood Pressure

The mean arterial blood pressure was measured continuously with a damped mercury manometer connected to the cannula in the femoral artery.

The Electroencephalograph

The E.E.G. was recorded either with an Offner recorder or with the equipment produced by Elema Schonander. The electrodes used were needles, which were inserted into the subcutaneous tissues of the scalp, one just anterior to and the other just posterior to the area of exposed brain.

Blood Gases

Arterial and cerebral venous pH were measured with the pH electrode no. G297/G2, and the pH meter 22 produced by Radiometer Ltd. The pH electrode was calibrated with two known buffers of pH 6.841 and 7.381.

Arterial Pco_2 and cerebral venous Pco_2 were measured by the interpolation technique of Andersen, Engel, Jorgensen & Astrup (1960). In the case of the venous Pco_2 the correction factors given by Andersen & Engel (1960) for haemoglobin desaturation were applied.

In the later experiments arterial Pco_2 and cerebral venous Pco_2 were measured with the direct CO_2 electrode produced by Electronic Instruments Ltd. and amplified by a pH meter 22 of Radiometer Ltd. The CO_2 electrode

was calibrated with three gases of known CO_2 concentration.

Oxyhaemoglobin Determination

The oxygen saturation of arterial and cerebral venous blood was measured with the Brinkman haemoreflector (Brinkman & Zijlstra, 1949). The instrument was calibrated for each experiment by fully reducing and fully oxygenating samples of the animal's blood and obtaining an upper and lower calibration point. A straight line was then drawn between these two points. It is known, however, that the relationship between oxygen saturation and the intensity of reflected light in the band 600–700 nM. is not linear but is curvilinear at low values of saturation (below 40%). In the range of saturations encountered in these studies, i.e. above 50%, the assumption of a linear relationship does not introduce significant errors (Zijlstra, Mook, ten Hoor & Kruzinga, 1966). Duplicate measurements of saturation were carried out on each sample and the results discarded if these did not agree within 2%.

Haemoglobin and Packed Cell Volume

The haemoglobin concentration of arterial blood was measured for each flow determination by the cyanhaemoglobin method (Dacie & Lewis 1963) with spectrophotometric analysis at 540 mu. wavelength. Packed cell volume was also determined on each sample.

(e) The Calculation of Cerebral Oxygen Uptake

The cerebral oxygen uptake was calculated by multiplying the measured cerebral cortical blood flow by the arteriovenous oxygen difference. These determinations therefore included the errors associated with the flow determination, the haemoglobin estimation and the saturation measurements. There was therefore a relatively wide scatter of values for oxygen uptake and it was necessary to make multiple determinations in order to detect significant changes.

The calculation of cerebral oxygen uptake in this way depends on two assumptions (1) that the venous blood sampled from the superior sagittal sinus has drained from the cerebral cortex and (2) that blood flow in the area monitored is the same as blood flow over the rest of the cortical surface from which venous blood drains into the sagittal sinus. Evidence has been presented above that both these criteria were fulfilled.

The measurements are therefore valid values for the oxygen uptake of the cerebral cortex of the dog under the particular conditions of this study. These conditions were that the dog was anaesthetised with a "sleep" dose of thiopentone and thereafter ventilated with nitrous oxide and oxygen. There is a great deal of evidence (already stated) that barbiturate anaesthesia reduces the oxygen uptake of the cerebral cortex. For this reason no measurements of flow or oxygen uptake were made in these studies for at least 2 hours after the last dose of thiopentone had been given. This time scale was based on considerations and investigations of barbiturate activity in the dog which have already been described. Nonetheless it was felt that a comparison of blood flow and oxygen uptake of the cerebral cortex should be made between animals in which anaesthesia was

induced with barbiturates and animals in which a non-barbiturate induction of anaesthesia was performed.

Study

Method

In 4 dogs anaesthesia was induced without barbiturates using volatile agents only; after induction and surgical preparation anaesthesia was maintained with unsupplemented nitrous oxide and oxygen. Measurements of cerebral cortical blood flow and oxygen uptake were made and compared with measurements made in another group of animals during nitrous oxide-oxygen anaesthesia but after induction with thiopentone.

In the non-barbiturate group anaesthesia was induced by placing the dog in a large perspex box through which nitrous oxide and oxygen were blown at 15 litres/minute. Halothane was introduced into this mixture up to a concentration of 8%. Provided the dog was competently handled and was given time to become accustomed to the box before induction was commenced, anaesthesia could be accomplished in this way without causing the animal any distress. As soon as unconsciousness supervened, the dog was quickly intubated and ventilated with nitrous oxide and oxygen and 0.5-1% halothane while the surgical preparations were performed. The halothane was then discontinued and no flow measurements were made until the last evidence of halothane had been absent from the E.E.G. for at least one hour. The average period of halothane administration during surgical preparation was 42 minutes and the average time allowed for washout before the first measurements was 2 hours 15 minutes. The time between induction of anaesthesia and measurement of flow was therefore the same as in the group induced with thiopentone, i.e. 3 - 4 hours.

The anaesthetic technique for the animals induced with thiopentone

	BLOOD FLOW	OXYGEN UPTAKE	Pa_{co_2}	B.P.
$N_2O + O_2$ After Thiopentone	0.88 ±0.19	0.066 ±0.014	40.7 ±5.2	141 ±14
$N_2O + O_2$ No Thiopentone	1.17*** ±0.22	0.070 ±0.004	42.0 ±4.5	153** ±22

Table 5. Comparisons of blood flow and oxygen uptake of the cerebral cortex together with Pa_{co_2} and blood pressure values between animals in which anaesthesia had been induced with thiopentone and those in which thiopentone had not been used. All measurements made during nitrous oxide-oxygen anaesthesia.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Blood flow and oxygen uptake in ml./G./min; B.P. and $Paco_2$ in mm.Hg. Mean values for blood flow are based on 84 measurements in 24 dogs in the thiopentone group and 14 measurements in 4 dogs in the non-barbiturate group. Mean values for oxygen uptake are based on 52 measurements in 15 dogs in the thiopentone group and 8 measurements in 3 dogs in the non-barbiturate

has already been described.

Results

All the results for blood flow and oxygen uptake of the cerebral cortex obtained in the four animals studied without thiopentone administration are given in Table App. I together with the levels of blood pressure and of $Paco_2$ existing at the time of the flow determinations. In Table 5 the mean results are presented and compared with the group of dogs in which anaesthesia was induced with thiopentone: these latter results were obtained from a subsequent series of experiments, the detailed results of which will be found in Tables App. 2, App. 3, App. 4 and App. 9.

The mean value for cerebral cortical flow under nitrous oxide anaesthesia without thiopentone induction (1.17 ± 0.22 mls./G./min.) was 33% greater than the value for flow under nitrous oxide following thiopentone induction (0.88 ± 0.19 mls./G./min.). This difference is highly significant ($p < .001$).

The mean value for oxygen uptake of the cerebral cortex was slightly higher in the group that had not received thiopentone (0.070 ± 0.004 mls./G./min, compared with 0.066 ± 0.014 mls./G./min.) but this difference was not statistically significant.

The mean blood pressure during nitrous oxide anaesthesia without thiopentone was significantly higher than in the group which had been induced with thiopentone (153 ± 22 mm.Hg. and 141 ± 14 mm.Hg. respectively). The $Paco_2$ values were not significantly different between the two groups.

Comment

Both cerebral cortical flow and mean blood pressure were significantly higher in the group which had not received thiopentone. The higher cerebral cortical flow probably reflects a higher oxygen requirement, on

the basis of the theory of regulation of cerebral flow to metabolic requirement to be discussed more fully subsequently. The failure to detect an increased oxygen uptake in this study was not surprising in view of the small number of animals and the wide scatter of oxygen uptake in the non-barbiturate group results. The higher blood pressure supports the contention that the level of anaesthesia was lighter in the group which did not have thiopentone. This is not to say that barbiturate itself was responsible for lowering flow and oxygen uptake so long after its administration but merely to postulate that the nitrous oxide anaesthesia was being potentiated by low levels of circulating barbiturate. It should be noted therefore throughout this thesis that the control values for cerebral cortical flow and oxygen uptake are probably slightly lower than would occur with nitrous oxide-oxygen anaesthesia alone in the dog.

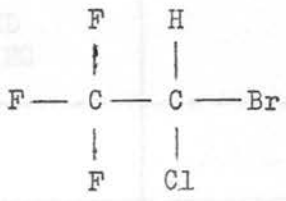
CHAPTER 3

The Influence of Halothane on the Blood Flow and Oxygen Uptake of the Cerebral Cortex

(a) Introduction

Halothane is the first drug to be considered in this thesis because it is a very widely used volatile anaesthetic which is frequently recommended for neurosurgical anaesthesia (Gilbert, Millar & Brindle, 1960).

The chemical formula of halothane is:-



It has a blood:gas partition coefficient of 2.3 and a brain:blood coefficient of 2.6. Halothane therefore is more blood soluble than nitrous oxide but less soluble than either trichloroethylene or chloroform. The rate of increase in arterial concentration is therefore more rapid than with the latter two drugs.

In clinical practice, halothane is commonly employed as a supplement to nitrous oxide-oxygen in concentrations of 0.5 to 2.0% and this therefore was the range of concentrations which was particularly studied in the following experiments, though a few measurements were made during deep anaesthesia with 4% halothane.

INDICATED DIAL READING	ACTUAL HALOTHANE OUTPUT
0.5%	0.46%
2.0%	1.98%
4.0%	4.12%

Table 6. Concentrations of halothane obtained with the vaporiser used in these studies at different settings of the control dial.

(b) Methodology

The methodology was as described in the main methodology section (see above). After making several measurements under unsupplemented nitrous oxide-oxygen anaesthesia, halothane in concentrations of 0.5%, 2% or 4% was added to the anaesthetic mixture. The drug was vaporised from an accurate, temperature compensated vaporiser (Fluctec II), the calibration of which had been checked by refractometry (see Table 6). Further measurements of cerebral cortical flow and cerebral cortical oxygen uptake were then made.

In order to gain more information about the effects of 0.5% halothane during the first 20 minutes of administration, a slightly different protocol was followed in some of the later experiments. A measurement of flow was first made during unsupplemented nitrous oxide-oxygen anaesthesia; following this, 0.5% halothane was added for a period of 10-15 minutes when a further measurement was carried out. The halothane was then discontinued and after a time for washout, which was always in excess of the duration of administration, a second control measurement under nitrous oxide anaesthesia was made. In this way several short periods of halothane administration were possible during each experiment.

	$N_2O + O_2$	0.5% Halothane All Measurements	$N_2O + O_2$	0.5% Halothane 1st 20 minutes	$N_2O + O_2$	0.5% Halothane over 60 minutes
Blood Flow	0.88 ±0.19	0.94 ±0.27	0.88 ±0.19	1.02** ±0.25	0.96 ±0.18	0.84 ±0.27
Mean B.P.	141 ±14	126*** ±17	142 ±14	132** ±17	143 ±11	123*** ±16
Pa_{CO_2}	38.9 ±4.2	39.9 ±4.0	39.0 ±4.4	40.0 ±5.1	38.2 ±2.3	39.0 ±3.4

Table 7. The effect of 0.5% halothane on blood flow through the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(The blood flow results (mls./G./min.) are mean values based on 84 measurements under nitrous oxide-oxygen and 87 measurements during 0.5% halothane administration in 24 dogs. B.P. and $Paco_2$ in mm.Hg.)

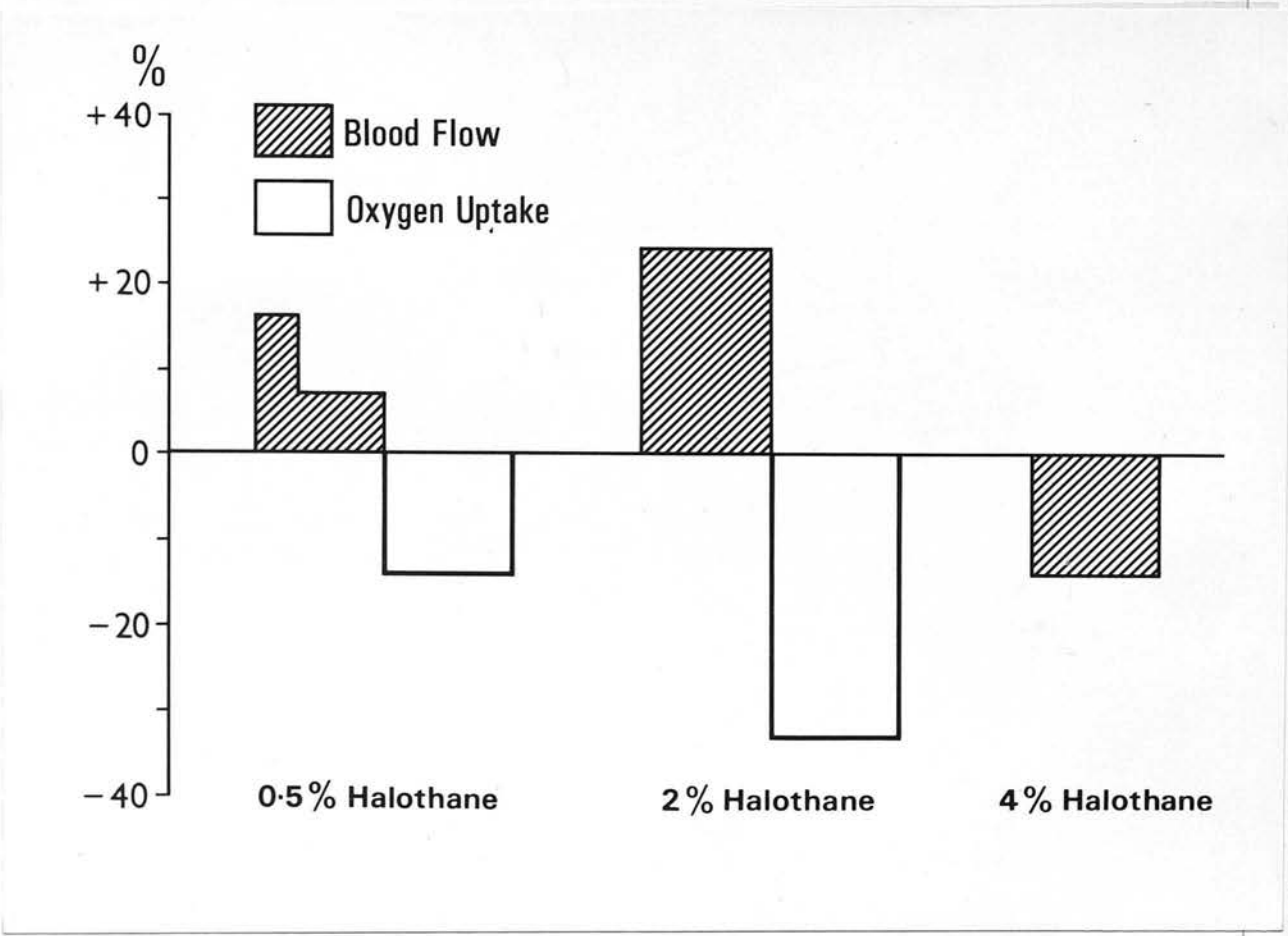


Figure 4 The effect of 0.5%, 2% and 4% halothane on the blood flow and oxygen uptake of the cerebral cortex. The figure illustrates changes in flow and oxygen uptake produced by halothane as compared with the values under unsupplemented nitrous oxide-oxygen anaesthesia.

	0-20 minutes 0.5% Halothane	Over 60 minutes 0.5% Halothane	% Change
Blood Flow	1.02 ±0.25	0.84 ±0.27	-18%**
Mean B.P.	132.0 ±16.9	123.1 ±15.6	-7%**
Pa_{co_2}	40.0 ±5.1	39.0 ±3.4	-2%

Table 8. Comparison of cerebral cortical blood flow during the first 20 minutes of 0.5% halothane administration with flow following more than 60 minutes of 0.5% halothane.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Blood flow in mls./G./min; B.P. and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	0.5% Halothane All Measurements	$N_2O + O_2$	0.5% Halothane 1st 20 minutes
C.V.R.	1.67 ±0.37	1.45*** ±0.47	1.68 ±0.37	1.36*** ±0.36
Mean B.P.	141 ±14	126*** ±17	142 ±14	132** ±17

Table 9. The effect of 0.5% halothane on cerebrovascular resistance and on blood pressure.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Cerebrovascular resistance (C.V.R.) in arbitory units and B.P. in mm.Hg.)

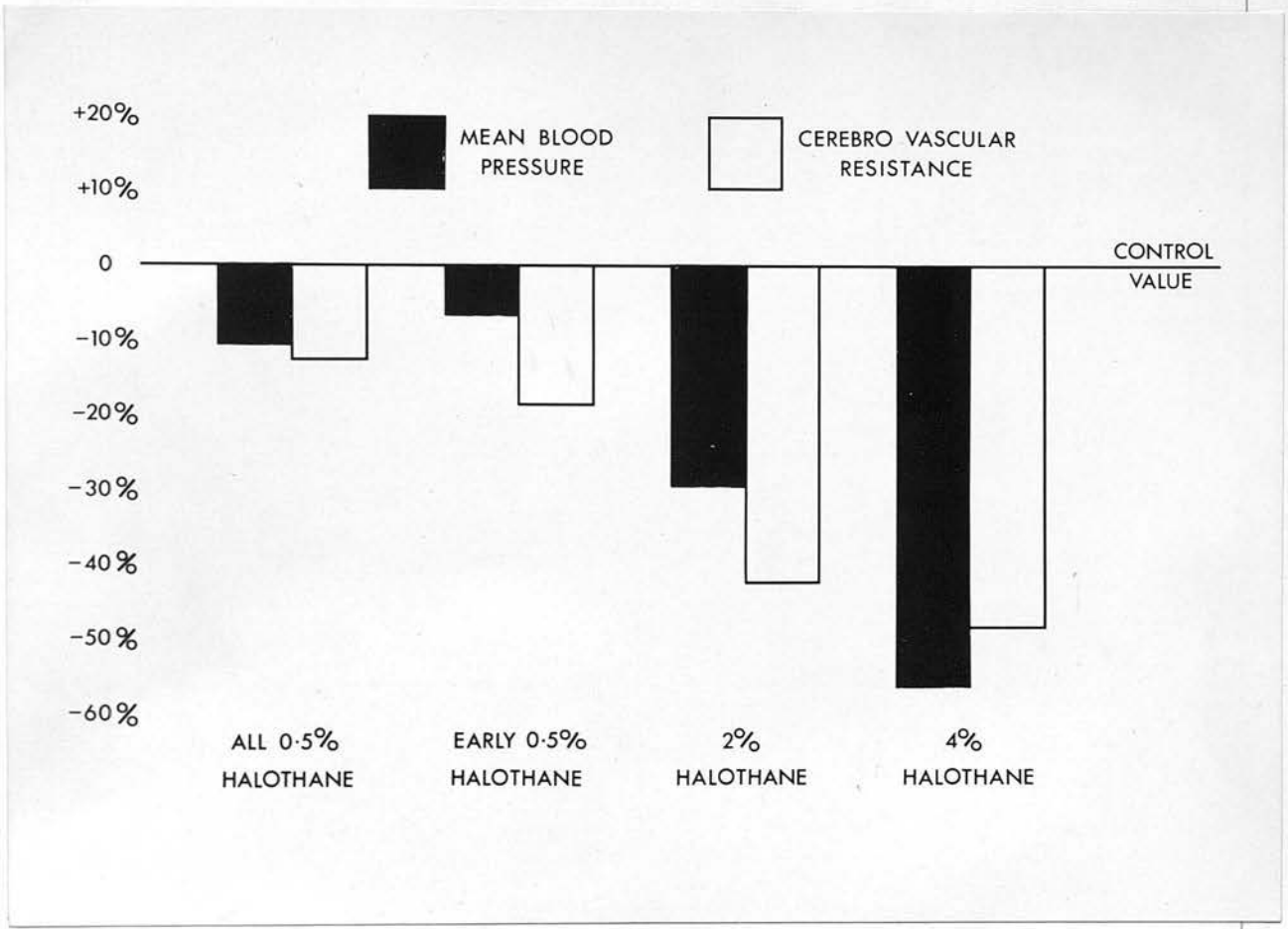


Figure 5 The effect of different concentrations of halothane on blood pressure and cerebrovascular resistance. With early 0.5% halothane and with 2% halothane the reduction in cerebrovascular resistance was greater than would be accounted for by the reduction in blood pressure.

(c) Results

Effect of Halothane on Blood Flow through the Cerebral Cortex

0.5% Halothane

17 dogs were studied using the continuous administration method and a further 7 using the repeated short administration technique. In all, there were 84 measurements during nitrous oxide-oxygen anaesthesia and 87 measurements during 0.5% halothane administration. The individual flow results are given in Tables App. 2 and App. 3.

The mean values derived from these results are given in Table 7 and illustrated in Figure 4. From Table 7 it will be seen that the mean value for cortical flow during the administration of 0.5% halothane was not significantly different from that under unsupplemented nitrous oxide-oxygen anaesthesia. These comparisons were made at virtually the same arterial Pco_2 but the mean blood pressure fell by 11%. If, however, one considers only the first 20 minutes of 0.5% halothane, then there was a significant increase of 16% in cortical blood flow, at unchanged $Paco_2$ and with a 6% fall in mean blood pressure. The flows measured during the more prolonged halothane administration (i.e. over 60 minutes) were not significantly different from the nitrous oxide controls but were significantly lower than the early (i.e. up to 20 minutes) halothane flows as shown in Table 8. Cerebrovascular resistance was markedly reduced by 0.5% halothane (see Table 9 and Fig. 5), the reduction being greater in the first 20 minutes of administration.

0.5% halothane in nitrous oxide-oxygen therefore caused an increase in cerebral cortical flow which was not maintained since flow returned to the previous control level after about 20 minutes of administration.

The other measurements made, i.e. arterial oxygen saturation, (Ao_2)

	$N_2O + O_2$	0.5% Halothane
A_{O_2}	97.3 ±2.9	95.5 ±3.0
Art. pH	7.30 ±0.06	7.28 ±0.06
Pa_{CO_2}	38.9 ±4.2	39.9 ±4.0

Table 10. Mean values for arterial oxygen saturation, arterial pH and Pa_{CO_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 0.5% halothane. (Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	2% Halothane All Measurements	$N_2O + O_2$	2% Halothane with B.P. greater than 90 mm.Hg.
Blood Flow	0.79 ±0.19	0.98* ±0.36	0.79 ±0.20	1.07** ±0.36
Mean B.P.	138 ±19	97*** ±21	139 ±18	110*** ±17
Pa_{co_2}	39.2 ±3.4	39.3 ±3.6	39.5 ±3.3	40.1 ±3.2

Table 11. The effect of 2% halothane on blood flow through the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Blood flow results (mls./G./min.) are mean values based on 34 nitrous oxide measurements and 26 halothane measurements in 9 dogs. In the group with blood pressures above 90 mm.Hg. there were 30 nitrous oxide measurements and 14 halothane measurements in 7 dogs. B.P. and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	2% Halothane	$N_2O + O_2$	4% Halothane
C.V.R.	1.84 ±0.52	1.05*** ±0.32	1.56 ±0.37	0.80*** ±0.34
Mean B.P.	138 ±19	97*** ±21	143 ±19	62*** ±20

Table 12. The effect of 2% and 4% halothane on cerebrovascular resistance and mean blood pressure.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Mean values based in the 2% halothane group on 34 nitrous oxide measurements and 26 halothane measurements in 9 dogs and in the 4% halothane group on 19 nitrous oxide and 10 halothane measurements in 5 dogs.)

	$N_2O + O_2$	2% Halothane
A_{O_2}	98.3 ±1.7	98.0 ±2.4
Art. pH	7.30 ±0.03	7.29 ±0.04
Pa_{co_2}	39.2 ±3.4	39.3 ±3.6

Table 13. Arterial oxygen saturation, arterial pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 2% halothane.

(Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	4% Halothane
Blood Flow	0.95 ±0.16	0.82 ±0.22
Mean B.P.	143 ±19	62*** ±20
Pa_{CO_2}	39.3 ±2.5	39.1 ±3.8

Table 14. The effect of 4% halothane on blood flow through the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Blood flow results (mls./G./min.) are mean values based on 19 nitrous oxide and 10 halothane measurements in 5 dogs. B.P. and $Paco_2$ in mm.Hg.)

arterial pH and arterial Pco_2, are displayed for each flow measurement in Table App. 4 with mean values in Table 10. There were no significant differences in these parameters between the nitrous oxide-oxygen measurements and the halothane measurements.

2% Halothane

The effects of 2% halothane on cortical flow is shown in Table 11, Table App. 5 and Fig. 4 . 34 control (nitrous oxide-oxygen) and 26 halothane measurements were made in 9 dogs. Cerebral cortical flow increased by 24% during the administration of 2% halothane despite a fall of 30% in mean blood pressure. If one considers only those flows which were measured when the mean blood pressure was above 90 mm.Hg. then the increase in cerebral cortical flow with 2% halothane was 36%. The cerebrovascular resistance fell by 45% (Table 12 and Fig. 5).

Other measurements are displayed in Table 13 and Table App. 6; there was no significant difference between the mean values for Ao_2, pH or $Paco_2$ between the two groups.

4% Halothane

The results obtained with 4% halothane will be found in Table App. 7 and Table 14. There were 19 control and 10 halothane measurements in 5 dogs. Flow during the administration of 4% halothane was not significantly different from that under unsupplemented nitrous oxide-oxygen anaesthesia. However 4% halothane reduced the mean blood pressure from 143 ± 19 mm.Hg. under nitrous oxide-oxygen anaesthesia to 62 ± 20 mm.Hg. The cerebrovascular resistance fell from 1.56 ± 0.37 units to 0.80 ± 0.34 units, a highly significant decrease (Table 12 and Fig. 5).

Arterial oxygen saturation and arterial pH and Po_2 did not alter between

	$N_2O + O_2$	4% HALOTHANE
Ao_2	96.0 ±3.4	93.1 ±3.4
Art. pH	7.26 ±0.04	7.23 ±0.45
Pa_{co_2}	39.5 ±2.5	39.1 ±3.8

Table 15 Arterial oxygen saturation, arterial pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 4% halothane.

(Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

	BLOOD FLOW	BLOOD PRESSURE	C.V.R.	Pa_{CO_2}
$N_2O + O_2$	0.79	157	2.01	40
4% Hal.	0.63	75	1.19	37
4% Hal. + Hypertensin	0.99	118	1.18	43

Table 16. Cerebral cortical blood flow and cerebrovascular resistance in one animal (23/11/64) during anaesthesia with nitrous oxide-oxygen, then with 4% halothane and finally with 4% halothane together with hypertensin.

(Blood flow in mls./G./min; B.P. and $Paco_2$ in mm.Hg.)

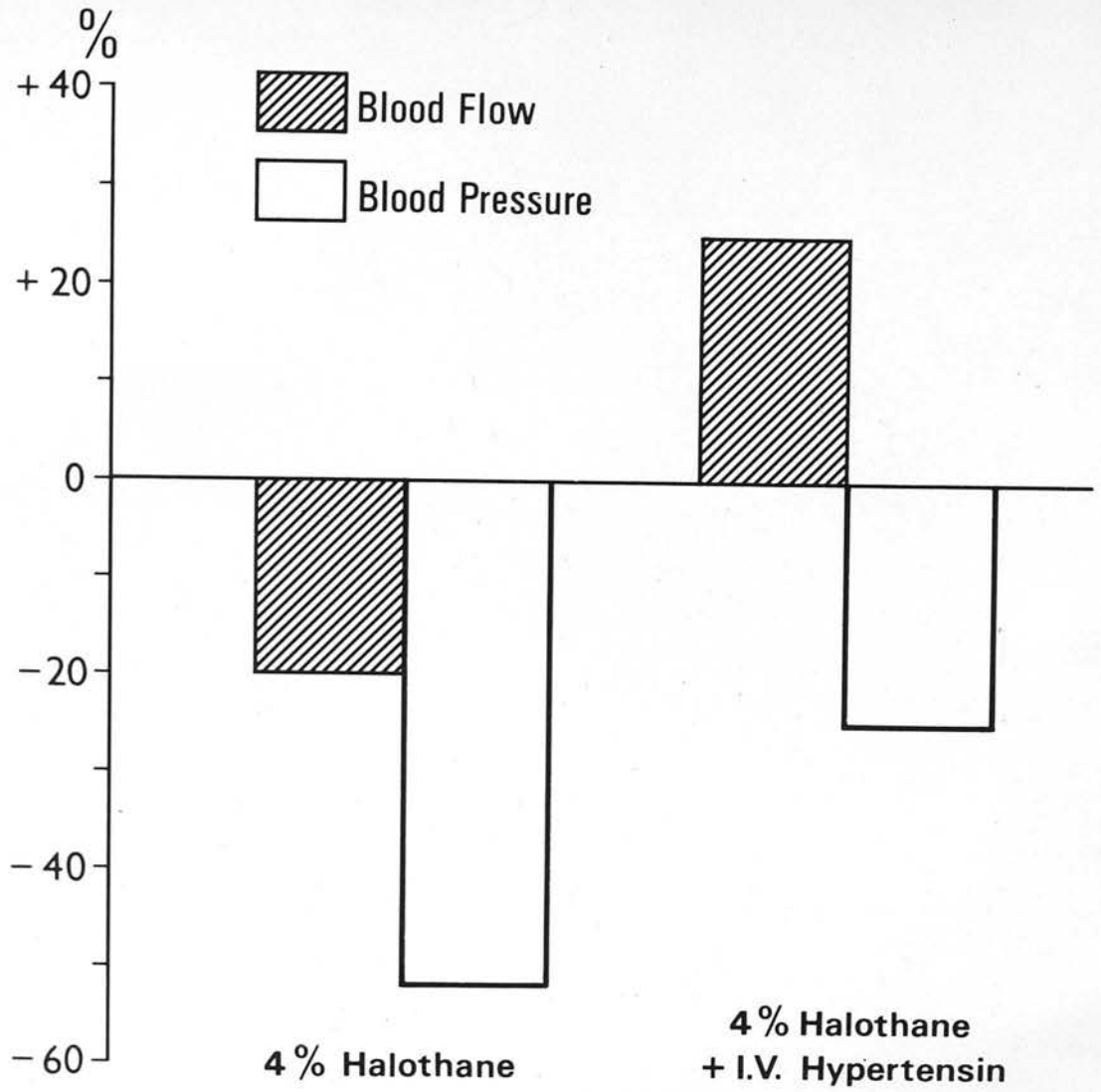


Figure 6 The effect of 4% halothane on blood flow prior to and during intravenous infusion of hypertensin. In this animal blood flow during 4% halothane administration was 20% below the value pertaining during unsupplemented nitrous oxide-oxygen anaesthesia while mean blood pressure was reduced by 50%. When the systemic hypotension was partially corrected by intravenous hypertensin infusion blood flow during 4% halothane administration was 25% above control values.

DATE	HALOTHANE CONCENTRATION	FRONTAL CORTEX	PARIETAL CORTEX	OCCIPITAL CORTEX
6/8/64	0.5% 0.5%	0.80 0.99	1.00 0.99	0.95 0.87
9/8/64	0.5% 0.5% 2% 2% 2%	0.74 0.85 0.93 1.20 1.09	0.83 0.78 0.93 0.93 1.13	
14/8/64	0.5% 0.5% 0.5% 0.5%	1.36 1.36 1.46 1.06	1.36 1.46 1.46 0.91	
Means		1.08 $\pm$ 0.24	1.07 $\pm$ 0.25	

Table 17. Blood flow through different areas of cerebral cortex during halothane anaesthesia.

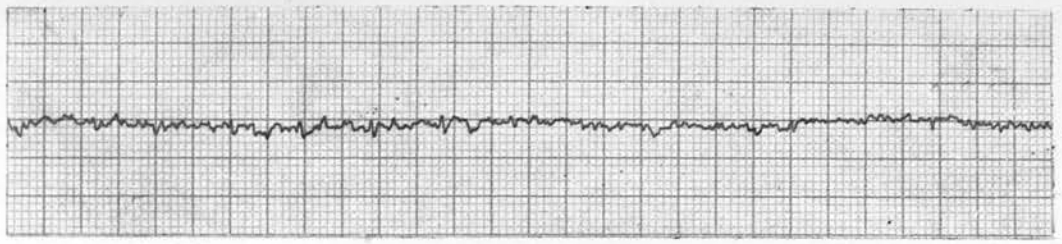
(Blood flow in mls./G./min.)

control and 4% halothane measurements (Table 15 and Table App. 8).

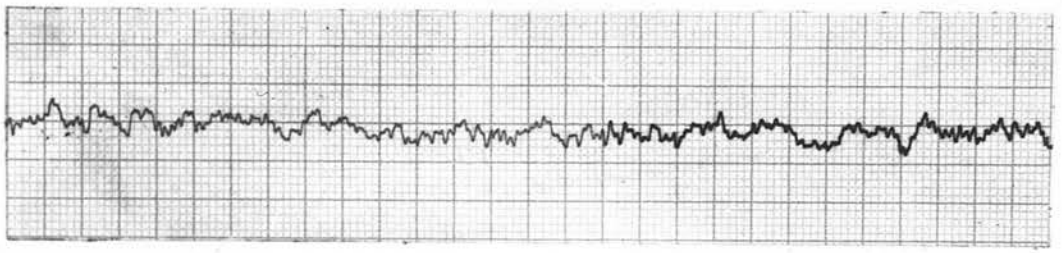
In one animal during 4% halothane anaesthesia the vasopressor agent, hypertensin, was infused intravenously at a rate sufficient to raise the mean blood pressure above 100 mm.Hg. When this was done blood flow through the cerebral cortex was 25% above the control value (Table 16 & Fig. 6) Furthermore the infusion of hypertensin in this animal, although it raised the arterial blood pressure did not alter the cerebrovascular resistance which remained at only 60% of the control value.

Blood Flow in Different Cortical Areas during Halothane Anaesthesia

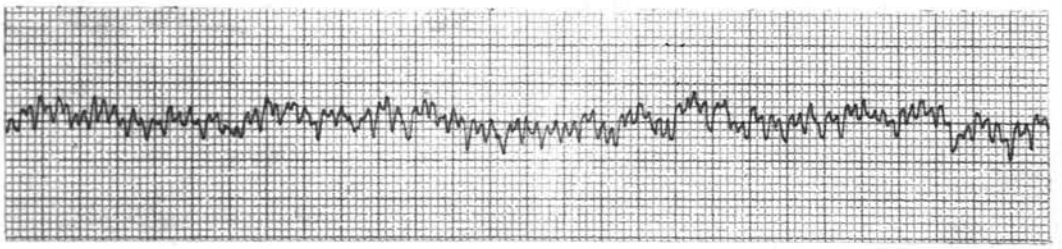
A study of the relationship between flows in different areas of cortex during anaesthesia with halothane was carried out. Measurements during 0.5% halothane administration were made in 3 dogs and during 2% halothane in one animal. The results are given in Table 17 ~~and Fig. xx~~ from which it can be seen that there was a close correlation between flows in different cortical areas. This table provides evidence that flow is fairly uniform over the cortical surface during halothane anaesthesia.



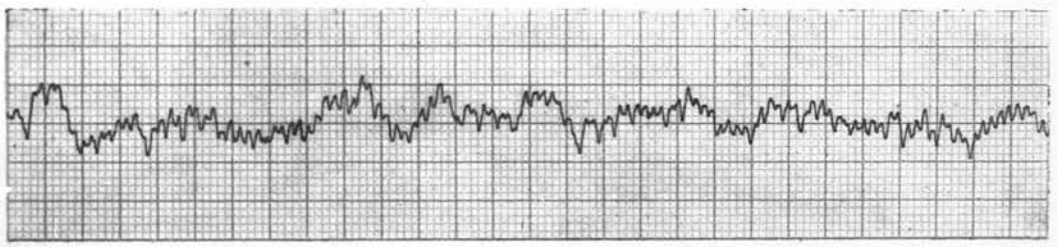
$N_2O + O_2$



14 mins. 0·5% HALOTHANE



9 mins. 2% HALOTHANE



13 mins. 2% HALOTHANE

Figure 7 The E.E.G. of the dog during anaesthesia with 0.5% halothane and with 2% halothane.

(d) Results

Effect of Halothane on the E.E.G., Oxygen Uptake, Cerebral Venous Oxygenation and Cerebral Arterio-venous Differences

All the preceding studies have dealt with cerebral cortical blood flow. However, as noted in the methodology section, cerebral venous blood was obtained in some of the experiments from the superior sagittal sinus. Using this blood, it was possible to determine the arterio-venous oxygen difference across the cerebral cortex and, knowing the cerebral cortical blood flow, to calculate the oxygen uptake of the cerebral cortex. This has been done during anaesthesia with 0.5% halothane and with 2% halothane and the results compared with the values existing under unsupplemented nitrous oxide-oxygen anaesthesia. The units of oxygen uptake used throughout were mls. of oxygen/G. of cerebral cortex/minute.

The E.E.G. activity present during anaesthesia with these two concentrations of halothane is shown in Figure 7. During 0.5% halothane theta waves appeared in the E.E.G. and on these was superimposed the fast activity seen during unsupplemented nitrous oxide-oxygen anaesthesia. This pattern resembles Level II of Gain & Paletz' (1957) classification of E.E.G. changes with halothane. 2% halothane produced a characteristic picture of high amplitude fast beta activity. This pattern was not recorded in man by Gain & Paletz (1957). With more prolonged administration of 2% halothane underlying delta waves appeared as in Level IV of Gain & Paletz' classification but the high amplitude beta persisted.

0.5% Halothane

There were 52 determinations of oxygen uptake under nitrous oxide-oxygen anaesthesia and 44 during anaesthesia with 0.5% halothane in nitrous

	$N_2O + O_2$	0.5% Halothane
Oxygen Uptake	0.066 ±0.014	0.057** ±0.016
Pharyngeal Temperature	38.4 ±0.6	38.2 ±0.9

Table 18. The effect of 0.5% halothane on the oxygen uptake of the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Oxygen uptake results (mls./G./min.) are mean values based on 52 measurements under nitrous oxide-oxygen and 44 measurements during anaesthesia with 0.5% halothane in 15 dogs. Pharyngeal temperature in °C.)

	CEREBRAL VENOUS OXYGEN SATURATION	
	$N_2O + O_2$	Halothane
0.5% Halothane All Measurements	58.3% $\pm$9.1%	62.2%* $\pm$9.1%
0.5% Halothane First 20 minutes	58.7% $\pm$9.1%	64.6%* $\pm$9.2%
2% Halothane	58.1% $\pm$7.4%	75.0%*** $\pm$3.0%

Table 19. Values for oxygen saturation of cerebral venous blood during nitrous oxide-oxygen anaesthesia and during anaesthesia with 0.5% and 2% halothane.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

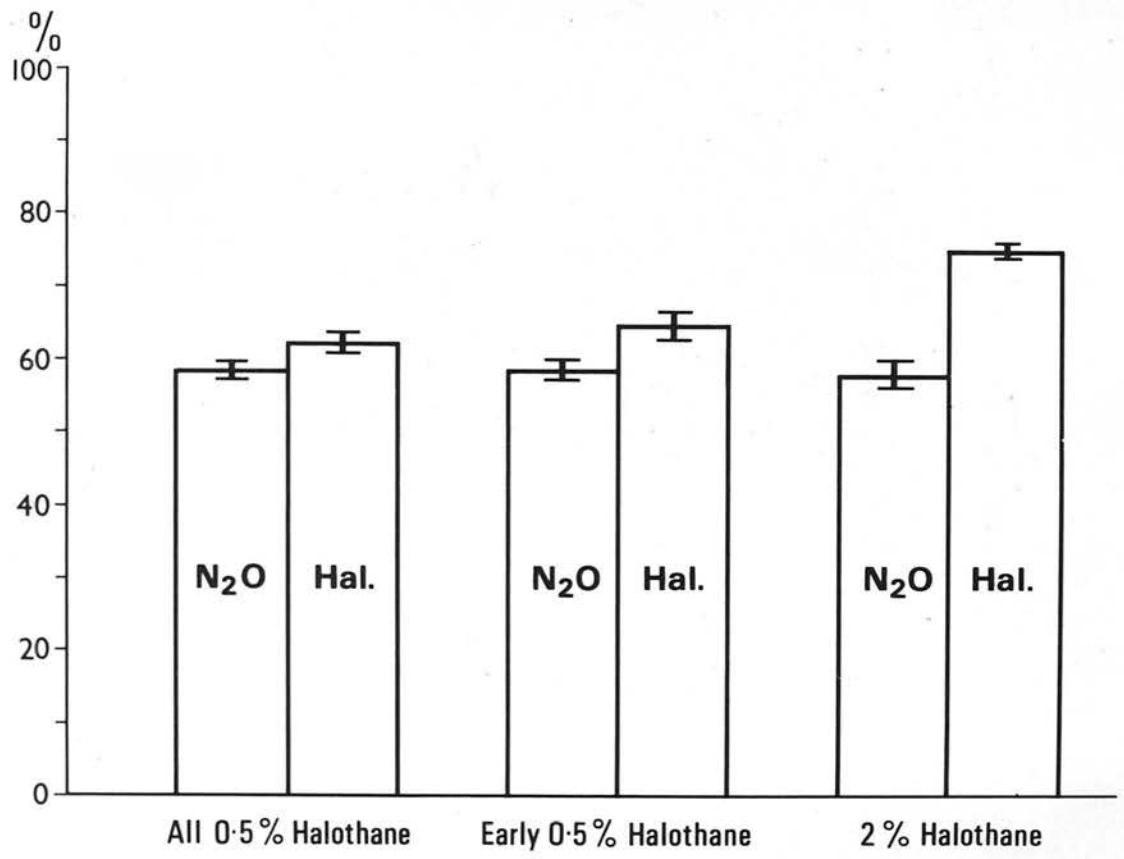


Figure 8 The effect of halothane on the oxygen saturation of cerebral venous blood as sampled from the superior sagittal sinus. Also indicated are the standard errors of the mean values.

Concentration of Halothane	A-V O_2 SATURATION DIFFERENCE		A-V Pco_2 DIFFERENCE		A-V pH DIFFERENCE	
	$N_2O + O_2$	Halothane	$N_2O + O_2$	Halothane	$N_2O + O_2$	Halothane
0.5%	39.0 ±9.1	34.0** ±8.7	13.2 ±3.8	10.8* ±4.3	0.062 ±0.023	0.045** 0.027
2%	40.7 ±7.6	23.2*** ±3.9	13.6 ±4.3	8.9** ±4.1	0.063 ±0.035	0.045 ±0.029

Table 20. Arterio-venous differences across the cerebral cortex for oxygen, Pco_2 and pH.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Saturation differences in percentage; Pco_2 differences in mm.Hg.)

	$N_2O + O_2$	2% Halothane
Oxygen Uptake	0.060 ±0.015	0.040*** ±0.011
Pharyngeal Temperature	38.4 ±0.6	38.3 ±0.5

Table 21. The effect of 2% halothane on the oxygen uptake of the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Oxygen uptake results (mls./G./min.) are mean values based on 17 measurements under nitrous oxide-oxygen and 12 measurements during anaesthesia with 2% halothane in 6 dogs. Pharyngeal temperature in °C.)

oxide-oxygen in 15 dogs after thiopentone induction of anaesthesia. The results are shown in Table 18, Table App. 9 and Fig. 4.

0.5% halothane reduced the oxygen uptake of the cerebral cortex by 14% compared with the value under unsupplemented nitrous oxide-oxygen anaesthesia ($.01 > p > .001$).

The results for cerebral venous oxygen saturation, cerebral arterio-venous oxygen saturation difference, arterial and cerebral venous Pco_2 and cerebral arterio-venous Pco_2 difference, arterial and cerebral venous pH and arterio-venous pH difference are displayed in Tables 19 and 20 and in Table App. 10A and B. 0.5% halothane produced a significant increase in the oxygen saturation of the cerebral venous blood from $58.3 \pm 9.1\%$ to $62.2 \pm 9.1\%$ (see Table 19 and Fig. 8). During the first 20 minutes of 0.5% halothane administration the increase in cerebral venous saturation was greater, from $58.7 \pm 9.1.\%$ to $64.6 \pm 9.2\%$. Since arterial oxygen saturation remained constant these increases in cerebral venous oxygen saturation led to narrowing of the cerebral arterio-venous oxygen saturation difference, as shown in Table 20.

The arterio-venous difference for Pco_2 was 13.2 ± 3.8 mm.Hg. under nitrous oxide-oxygen anaesthesia; this narrowed to 10.8 ± 4.3 mm.Hg. during 0.5% halothane. Similarly the arteriovenous pH difference fell significantly from 0.062 ± 0.023 to 0.045 ± 0.027 pH units during 0.5% halothane (Table 20).

2% Halothane

17 control measurements and 12 measurements of oxygen uptake under 2% halothane were made in 6 animals, the results being given in Table 21, Table App. 11 and Fig. 4.

2% halothane produced a highly significant fall in the oxygen uptake of the cerebral cortex, averaging 33%, when compared with the value under unsupplemented nitrous oxide-oxygen anaesthesia.

The individual values for cerebral arterio-venous differences are shown in Table App. 12A and B and the mean values in Tables 19 and 20. There was a highly significant increase in the oxygen saturation of the cerebral venous blood from 58.1±7.4% to 75.0±3.0% during 2% halothane anaesthesia (see also Fig 8). A corresponding fall in the arterio-venous oxygen saturation difference occurred. The arterio-venous difference for Pco_2 was 13.6±4.3 mm.Hg. under nitrous oxide anaesthesia and 8.9±4.1 mm.Hg. under 2% halothane, a highly significant fall. The arterio-venous pH difference fell from 0.063±0.035 to 0.045±0.029 pH units but this difference did not reach statistical significance.

(e) Discussion

1. The Influence of Halothane on Cerebral Cortical Blood Flow

These studies have shown that certain concentrations of halothane increase the blood flow through the cerebral cortex of the dog. Since in these experiments there was no rise in blood pressure, but in fact a fall, this increase in flow must indicate that halothane acts as a vasodilator of the cerebral cortical circulation.

With 0.5% halothane the increase was relatively small and of short duration but with a higher concentration (2%) the blood flow increase was considerable and sustained, except that flow began to fall as the blood pressure fell below 90 mm.Hg. With 4% halothane, however, cerebral cortical perfusion was not increased above control values/presumably because the mean blood pressure fell by more than 50%. In the experiment in which a vasopressor drug was administered during anaesthesia with 4% halothane (Table 16 and Fig. 6), blood flow rose above control values indicating vasodilatation by 4% halothane in the presence of an adequate perfusion pressure. The vasopressor employed, hypertensin, has been shown not by itself to have any direct action on the cerebral vessels (Bohr, Goulet & Taquini, 1961;/Agnoli, Ballistini, Bozzao & Fieschi, 1965). This spectrum of alterations in cerebral cortical flow with increasing concentration of halothane has been illustrated in Figure 4 which shows mean values for cerebral cortical blood flow during administration of 0.5%, 2% and 4% halothane. The greater increase in flow in the first 20 minutes of 0.5% administration is also shown in this figure.

At each concentration of halothane there was a highly significant fall in cerebrovascular resistance. However halothane also reduced the

mean blood pressure and it is well established that the cerebral circulation compensates for reductions in perfusion pressure by lowering its vascular resistance (Forbes, Nason, Wortman, 1937; Fog, 1938; McCall, 1953; Carlyle & Grayson, 1955; Rapela, Machowicz & Freeman, 1963; Haggendal & Johansson, 1965; Harper, 1966). It is not therefore justifiable to consider that these falls in cerebrovascular resistance provide independent evidence of cerebral vasodilatation by halothane. It is the flow increases with 0.5% and 2% halothane which indicate that the falls in cerebrovascular resistance produced by halothane were in excess of those required to compensate for the changes in perfusion pressure. The mean blood pressure was reduced by 4% halothane to 62 mm.Hg., and at this level of hypotension the cerebral circulation in the dog is known to have exceeded its maximum range of compensation. Flow at these low levels of perfusion pressure is pressure dependant (Harper, 1966) and therefore with 4% halothane flow was at or rather below control values. However when the blood pressure was raised by means of a vasopressor, the underlying cerebral vasodilatatory action of 4% halothane was revealed. Indeed the fact that cerebrovascular resistance did not increase when the blood pressure was raised from 75 to 118 mm.Hg. suggests that 4% halothane was itself producing near maximal vasodilatation.

The conclusion that halothane is a cerebral vasodilator has also been reached by others, though this relationship between concentration of halothane and flow has not previously been demonstrated.

Galindo and Baldwin (1963) measured flow in the internal carotid artery of the dog with an electromagnetic flowmeter, after clamping the external carotid during the administration of unknown concentrations of halothane (they were using an uncalibrated vaporiser). They found that

carotid blood flow increased at first and then fell with falling blood pressure, flow becoming equal to the control value when the mean blood pressure was 40.7% below the control level.

There are however two criticisms of this study. Firstly, measurement of flow in the internal carotid artery of the dog is not a valid measure of cerebral blood flow because of the extensive anastomoses which exist between the internal and external carotid systems so that an unknown proportion of the blood in the internal carotid artery is destined for extracranial structures. De La Torre, Netsky & Meschan (1959) have not only demonstrated anatomically the existence of these astomoses but, by dye injection studies, have proved their functional importance in the dog. Galindo and Baldwin attempted to avoid this difficulty by clamping the external carotid artery but De La Torre and co-workers (1959) had previously demonstrated that this procedure considerably increased the proportion of extracerebral blood carried by the internal carotid artery.

Galindo and Baldwin justify the acceptance of their carotid flow measurements as indicators of cerebral blood flow on three grounds (1) that the carotid artery is one of the three main vessels to the dog's brain, (2) that the c.s.f. pressure moved in the same direction as the flow measurements and (3) that the administration of CO_2 increased carotid blood flow. Argument (1) for the reasons given above is hardly conclusive. The fact that when the carotid blood flow increased the pressure of the cerebrospinal fluid also rose, in the absence of changes in central venous pressure, is a more weighty argument. However from the results given the mean c.s.f. pressure rose by an average of 79.2% on giving halothane yet this result was far from being statistically significant ($p < .3$). This naturally makes one wonder how many observations of c.s.f. pressure were

in fact made (no tables of the individual results are given in this paper). The 3rd argument was that administration of CO_2 always led to an increase in carotid flow. Since CO_2 dilates the cerebral vessels and constricts muscle vessels, the inference is that carotid flow can be accepted as a measure of cerebral flow. However CO_2 is a very potent dilator of cerebral vessels and therefore the net effect of an increase in C.B.F. and a decrease in extracranial flow may be to increase carotid flow during CO_2 administration; halothane is on the other hand a potent dilator of skin and subcutaneous vessels (Black & McArdle, 1962; Lindgren, Westermark & Wahlin, 1964) and the resultant increase in non-cerebral blood flow in the carotid artery might dictate an increase in total blood flow in the carotid artery whatever was happening to the cerebral vessels.

The second criticism of this study, is that the reported increase in carotid blood flow did not in fact reach statistical significance. Consequently these authors had to rely heavily on their demonstration of a large fall in carotid vascular resistance with halothane, a result which was statistically highly significant. The reasons for discounting changes in cerebrovascular resistance as evidence of direct vasodilatation by halothane have been cited above. Galindo and Baldwin themselves point out "it was difficult to differentiate between the effects of hypotension or halothane itself on the internal carotid vascular resistance".

Williams (1964) also concluded that halothane in unknown concentrations was a cerebral vasodilator. He perfused one common carotid artery in the dog by means of a pump oxygenator after cross clamping both vertebral and the opposite common carotid artery during a study of the increase in carotid vascular resistance produced when cold blood is infused into the carotid artery. He reported that if halothane was administered during

the infusion of cold blood carotid flow was increased by 37% though he did not state what the "anaesthetic gases" were for the control measurements. As these experiments were performed in dogs, the objections to the use of carotid flow measurement as an indicator of cerebral flow are the same as those discussed above in relation to the work of Galindo and Baldwin. Indeed the author ascribes the absence of an increase in carotid flow during CO_2 administration to vasoconstriction produced by CO_2 in the muscle bed perfused by carotid blood. Consequently the increase in flow with halothane could equally be ascribed to halothane induced vasodilatation in the skin and subcutaneous tissues.

Schmahl (1965) has measured the effect of halothane on the blood flow through the thalamus and hypothalamus using the thermoelectric heat clearance technique of flow measurement. This is a non-quantitative technique of measurement. He found that 1.9% halothane markedly elevated blood flow despite a 30 mm.Hg. reduction in mean blood pressure. However Schmahl made his measurements in spontaneously breathing cats during the administration of 1.9% halothane. This concentration must have produced severe respiratory depression since Beaton (1959) has shown that 2.5% halothane actually causes respiratory arrest in cats. The consequent hypercapnia in Schmahl's study must have contributed to and may even have accounted for the rise in cerebral blood flow found.

Wollman, Alexander, Cohen, Chase, Melman & Behar (1964) have employed the technique of Lassen and Munck (1955) to measure cerebral blood flow in man during halothane anaesthesia. This technique is a modification of the Kety-Schmidt (1948) method and uses radioactive krypton as the inert gas in place of the original nitrous oxide. It therefore, like the Kety-Schmidt technique, measures total cerebral blood flow. Wollman and

co-workers anaesthetised healthy volunteers with 1.2% halothane in oxygen and controlled ventilation, usually after obtaining muscular paralysis with tubocurarine. Measurements of cerebral blood flow were made after at least 90 minutes of anaesthesia with 1.2% halothane and the results were assessed by comparison with the values obtained in the same laboratory by the same technique in another group of conscious healthy volunteers. Assessed in this way, this concentration of halothane caused a 15% increase in total cerebral blood flow despite a fall in mean perfusion pressure to 56 mm.Hg. The authors state that this increase in flow was statistically significant but their criteria for significance appear to be different from the conventional limits since the p value given was $< .1$. The only other reservation that one might have about this carefully conducted study is some misgiving about the use of control values from a different group of subjects not studied at the same time, especially since there was in this study as in most others a considerable variation between individuals in cerebral blood flow under identical conditions. In the present thesis the influence of variation between the individual animals has been minimised by always comparing observations in the same animal.

The results of Wollman et al. appear to be very much in line with the results of the present study, i.e. they obtained an increase in flow of 15% with 1.2% halothane while in the present study flow increased 24% with 2% halothane. However the similarity cannot be pressed too closely for 4 reasons (1) possible species differences, (2) Wollman et al. measured total cerebral flow while the present study was concerned only with cerebral cortical flow, (3) in the study of Wollman et al. the mean arterial Pco_2 was 4 mm.Hg. lower in the halothane group as compared with the conscious group, and (4) their control values were of flow during consciousness while

in this study the control values were obtained under light anaesthesia with nitrous oxide.

An almost identical study was subsequently published by McHenry, Slocum, Bivens, Mayes & Hayes (1965). These workers found that 1.0% halothane in nitrous oxide-oxygen was associated with a value for total C.B.F. as determined by the technique of Lassen and Munck which was 55% greater than that in a group of conscious subjects studied concomitantly. This rise is very much greater than one would expect from the finding in the present study of a rise of 24% with 2% halothane. The fact that McHenry et al. were measuring total cerebral flow while only cerebral cortical flow was measured in the present studies would seem unlikely to account for the difference since it is difficult to believe that the non-cortical components, which are largely white matter with only a fifth of grey matter flow, could increase their perfusion enough to produce so great a total rise. This 55% increase was also greatly in excess of the 15% rise obtained by Wollman et al. with an almost identical concentration of halothane. The fact that McHenry et al. used nitrous oxide as the carrier for the halothane while Wollman et al. (1964) used oxygen cannot explain the discrepancy since it has been demonstrated (Wollman et al., 1965) that nitrous oxide anaesthesia does not alter cerebral perfusion from the conscious level. McHenry et al. explain the discrepancy by pointing out that the mean blood pressure in their series was higher than that in the group studied by Wollman et al. (76 mm.Hg. compared with 56 mm.Hg.) and also that the methods of calculating the C.B.F. differed somewhat. The difference in blood pressure between the two groups would certainly account for part of the discrepancy but the difference in calculating the flows would have just the opposite effect to that claimed by the authors. These

workers used, without later mathematical correction, an equilibration period of krypton inhalation of only 10 minutes although it has been clearly established by Lassen and Munck (1955) that even at 14 minutes equilibration between blood and brain for krypton is not complete. There is in fact good evidence of incomplete equilibration of the brain in the paper itself for in the two "typical" clearance curves illustrated, the arterial radioactivity at the start of washout was higher than the jugular venous activity. The error introduced by failure to reach equilibration between blood and brain concentration of krypton will be greater the lower the C.B.F. The control value for flow will therefore be higher than the true control value, as pointed out by the authors. However, given that halothane increases flow, the error will be less during halothane administration and therefore the halothane and control values will be closer than the true relationship, not the reverse as suggested in the paper.

A more likely explanation of the greater increase in flow is the fact that the mean arterial Pco_2 in the anaesthetised patients was 47 mm.Hg. while the control flows during consciousness were presumably measured at Pco_2 values within or below the normal range. Fortunately, however, a graph is given in the original paper relating flow under halothane anaesthesia to arterial Pco_2. From this one can calculate that at a $Paco_2$ of 40 mmHg. cerebral blood flow would have been about 71 ccs./100 G./min. under halothane anaesthesia, a rise of 25%. This order of flow increase would certainly be in keeping with the results presented in the studies reported here.

On the other hand, there are two studies reporting decreases in cerebral blood flow with halothane. In the first recorded study of the effects of

halothane on cerebral blood flow which came from this laboratory (McDowall, Harper & Jacobson, 1963), a fall in both the blood flow and the oxygen uptake of the cerebral cortex was observed with this anaesthetic drug. In those experiments however very low concentrations of halothane were used (less than 0.5%) and the drug was vaporised in air or oxygen. Consequently the level of anaesthesia was very light and the situation was not comparable with the present studies in which clinical concentrations of halothane in nitrous oxide have been employed. That earlier study did however demonstrate that very low concentrations of halothane in air produce reductions in blood flow in certain cortical areas. The reasons for believing that the flow reduction was regional is that if the measured flow is multiplied by the whole cortex arterio-venous oxygen difference the figure obtained for oxygen uptake is half that existing under nitrous oxide anaesthesia. Since, as we have seen, 2% halothane only reduced oxygen uptake by 33% it is almost inconceivable that less than 0.5% should cause a fall of 50%. The error in this calculation must therefore be that the localised flow measured was not representative of the rest of the cortex during anaesthesia with less than 0.5% halothane. This conclusion appears obvious now but was not so before the present studies on cerebral metabolism under different concentrations of halothane were performed. In the present work it has been shown that with 0.5% and 2% halothane flow over the cortical surface is fairly uniform and therefore valid calculations of oxygen uptake can be made from the localised flow determinations. There are several other factors which may have been active in producing the decrease in flow with halothane observed in this study. Firstly, this was a very early study and technical experience in making the surgical preparation was limited. Consequently it is likely that the exposed area of brain had been subjected

to more trauma than in later studies. It has been pointed out that after such brain trauma cerebral blood flow become dependent on perfusion pressure, i.e. autoregulation is lost (Harper 1965). Since halothane administration in these experiments lowered the blood pressure, the observed fall in flow may have been partly due to this.

Secondly, because the surgical preparation was slower in these early studies, the total dose of thiopentone administered was greater than in later work. Consequently although time was allowed for the E.E.G. to recover from thiopentone depression, the plasma levels of barbiturate must have been higher than in later studies. Under such circumstances Betz, Oehmig and Wunnerberg (1965) have shown that halothane reduces rather than increases cerebral blood flow.

Several factors were therefore at work in leading to this first result that halothane was a cerebral vasoconstrictor. Unfortunately their influence could not have been foreseen on the basis of the information available at that time.

Christensen, Hoedt-Rasmussen & Lassen (1965) used a radioactive gas clearance technique with external counting to measure cerebral blood flow (Hoedt-Rasmussen, 1965) during anaesthesia with 1% halothane in oxygen in man. They reported that halothane reduced the cerebral blood flow by 21% compared with the value obtained in the same four patients during consciousness. Both groups of observations were made at a $Paco_2$ of 40 mm.Hg. It is very difficult to see why this study yielded this result which is contrary to the studies reported above and contrary to the work of Wollman et al. (1964) and of McHenry et al. (1965). The mean blood pressure in these patients certainly dropped dramatically during halothane anaesthesia (mean = 60 mm.Hg.) but no more than in the study of

Wollman et al. (mean = 56 mm.Hg.). Induction of anaesthesia in both studies was with halothane in unpremedicated patients, in both studies the drug was administered in 100% oxygen and in both studies muscular paralysis was achieved with tubocurarine. The only apparent difference is that Christensen et al. were studying patients of a chronic mental institution while Wollman et al. made their measurements on healthy volunteers. At present nothing is known of the possible variability of the cerebral circulatory response to halothane in mental disease.

In summary, the experiments reported here indicate that halothane is a cerebral vasodilator, the effect being small and short lived with 0.5% halothane but well marked with higher concentrations. With very high concentrations the fall in cerebral perfusion pressure prevents any rise in flow despite markedly decreased cerebrovascular resistance.

DATE	OXYGEN UPTAKE WITH 0.5% HAL. AS % OF CONTROL
28/1/64	92% 98% 81% 95% 78% 73%
29/1/64	100% 90% 101%
26/2/64	95% 88% 106%
11/11/64	92% 96% 109% 115%
23/11/64	94% 68%
23/12/64	83% 57%
24/12/64	79% 67% 48% 62% 62%
MEANS	

DATE	OXYGEN UPTAKE WITH 0.5% HAL. AS % OF CONTROL
15/3/65	90% 87% 83%
17/3/65	116% 86% 94%
24/5/65	76% 80% 89% 95%
4/6/65	83% 98% 90%
7/6/65	100% 94%
9/7/65	66%
12/7/65	120% 76%
2/8/65	111%
	87.8% ±16.0%

Table 22A Oxygen uptake of the cerebral cortex during anaesthesia with 0.5% halothane expressed as percentages of the oxygen uptake during nitrous oxide anaesthesia in the same animal.

DATE	Oxygen Uptake with 2% Halothane as % of Control
7/6/65	77%
9/7/65	59% 61% 83%
12/7/65	96%
23/7/65	67%
26/7/65	51% 73% 67%
2/8/65	73% 65% 65%

Table 22B Oxygen uptakes of the cerebral cortex during anaesthesia with 2% halothane expressed as percentages of the oxygen uptake during nitrous oxide-oxygen anaesthesia in the same animal.

(e) Discussion

2. Effect of Halothane on the Oxygen Uptake of the Cerebral Cortex

The validity of the above measurements of cerebral cortical oxygen uptake rests on two assumptions: (1) that flow in the monitored area is representative of all areas of cortex draining into the sagittal sinus anterior at the point of sampling and (2) that the venous blood in the sinus has drained mainly from the cerebral cortex. Assumption (1) has been verified by the demonstration that blood flow over the cerebral cortex is fairly uniform during halothane anaesthesia (Table 17). The evidence for accepting assumption (2) has been given in the main methodology section.

These studies have demonstrated that halothane reduced the oxygen uptake of the cerebral cortex below the level existing under light nitrous oxide-oxygen anaesthesia. The reduction in oxygen uptake appears to be dependent on the concentration of halothane administered, 0.5% producing a fall of 14%, 2% halothane reducing uptake by 33%. To test whether this reduction with 2% halothane was significantly different from that with 0.5% the individual results were recalculated as percentage changes on the control value in the same animal and the statistical significance of the differences between these two groups of percentage changes calculated (see Table 22A and B). In this way the statistical effect of the variability of the control value for oxygen uptake under nitrous oxide-oxygen anaesthesia between individual animals was reduced. These calculations showed that 0.5% halothane reduced the oxygen uptake of the cerebral cortex to 88% of the value existing under nitrous oxide-oxygen while 2% halothane caused a fall to 70% of the nitrous oxide-oxygen value; the difference between these two results being highly significant ($p < .001$). Increasing concentrations of

halothane therefore cause progressively greater depression of the metabolic activity of the cerebral cortex during general anaesthesia. The E.E.G. patterns which were associated with these two levels of depressed cerebral oxygen uptake have been shown in Figure 7.

There have been no other studies of the oxygen uptake of the cerebral cortex with which to compare the above results. Wollman et al. (1964) measured the oxygen uptake of the whole brain during anaesthesia with 1.2% halothane in oxygen. They reported that during halothane anaesthesia the oxygen uptake was 15% below that of conscious man. However the oesophageal temperature of their anaesthetised subjects was 36°C and they concluded that "most of the 15% depression of C.M.R.o_2 seen in this study results from the lowered body temperature of the subject. A small reduction of C.M.R.o_2 by the anaesthetic agent itself cannot be ruled out".

In the study by McHenry et al. in which 1% halothane in nitrous oxide-oxygen was used, a fall of 27% in cerebral metabolic rate below conscious values was found. This result with 1% halothane in nitrous oxide is compatible with the present finding of a 14% reduction with 0.5% halothane and a 33% fall with 2% halothane in nitrous oxide. In McHenry et al.'s patients, as in the present study, induction of anaesthesia was with thiopentone. The correlation improves even further when one remembers that this 27% reduction is probably an overestimate of the true fall in cerebral metabolic rate because of the already mentioned methodological criticisms of their study. These criticisms imply that the control flow results and therefore the control values for C.M.R.o_2 were too high while the halothane results were less in error. It is very surprising to find these authors commenting that the depression in cerebral metabolic rate which they demonstrated with halothane "is similar to the depression noted with other

anaesthetic agents". Their reference for this statement is to Sokoloff (1959) who in reviewing the literature found no evidence as to the effect of volatile anaesthetic drugs other than an unpublished report by Kety that ether caused an unspecified depression of $C.M.R.o_2$. The barbiturates of course lower cerebral metabolic rate but there is not a priori reason for assuming that the volatile agents will do the same.

A general discussion of the relationship between flow and metabolic rate will be postponed until the actions of the other drugs studied has been considered.

(e) Discussion

3. Arterio-venous Differences for Oxygen, Hydrogen Ion Concentration and Carbon Dioxide Tension across the Cerebral Cortex under Halothane Anaesthesia

The observed narrowing of the arteriovenous differences for oxygen, pH and Pco_2 with the administration of 0.5% must be entirely ascribed to the fall in metabolic activity of the cortex since the mean blood flow did not change. The higher venous oxygen saturation in the first 20 minutes of halothane administration, however, was in part due to the increased flow noted at this time. With 2% halothane the elevation of cerebral cortical flow and the further depression of oxygen uptake together produced a very large rise in the saturation of the cerebral venous blood and a greater narrowing of the A-V differences.

One may also consider these results from the viewpoint of changes produced in cerebral tissue oxygenation during halothane anaesthesia. The mean venous oxygen saturation under nitrous oxide-oxygen was 58.3% and 58.7% in the two halothane studies (Table 19). From the dog's oxyhaemoglobin disassociation curve (Rossing & Cain, 1966) one can calculate venous Po_2 from these values and the simultaneously determined venous pH (7.23 and 7.25). The corresponding venous oxygen tensions are 40 mm.Hg. and 39 mm.Hg. The mean haemoglobin concentration for these animals was 16.1 ± 6.7gm./100 cc. blood and therefore the mean arterio-venous oxygen content difference can be calculated to have been 8.5cc./100cc. blood. If one assumes that oxygen is extracted from the blood as it moves along the brain capillaries at a constant rate and that pH falls uniformly then one can calculate that the mean capillary Po_2 under these circumstances would

have been 63mm.Hg. (using an 11 stage integration).

Kety (1957) has produced a mathematical derivation of mean tissue Po_2 from mean capillary Po_2 in the following form:-

$$\bar{p} = P_o - A\ (mR^2/4d)$$

where $\bar{p}$ is the mean tissue Po_2

p_o is the mean capillary Po_2

A is a factor relating to the geometry of the model; in this case a simple cylindrical capillary tissue model is assumed with capillary flow running parallel in the same direction. In calculating A, the radius of the capillary has been assumed to be 3.5 u and the radius of the tissue cylinder served by the capillary to be 30 u (Horstmann, 1960; Lierse & Horstmann, 1965; Lubbers D.W. - personal communication). This yields a value of 2.73 for A (Kety, 1957).

m is the oxygen consumption of the tissue which of course is known from the above results. The assumption is made that the specific gravity of cerebral cortex is unity.

R is the intercapillary distance. For the cerebral cortex this is known to be of the order of 30 u (Horstmann, 1960), i.e. half the usual capillary distance for the cerebral cortex (Lubbers - personal communication).

d is the diffusion coefficient of oxygen in tissue: Kety's value of 2.1×10^{-8} mls.O_2/cm.^{2}/min./mm.Hg. has been used.

In this way it can be calculated that the mean cerebral cortical tissue Po_2 under nitrous oxide anaesthesia was 44 mm.Hg.

When 0.5% halothane was administered the cerebral venous oxygen saturation rose to 62.2%. At the observed venous pH of 7.22 the calculated venous Po_2 was therefore 43 mm.Hg., the calculated mean

capillary Po_2 was 64 mm.Hg. and the calculated mean tissue Po_2 was 47 mm.Hg.

With 2% halothane the same calculations have been performed taking into account the change in oxygen consumption of the brain. The values are:

under 2% halothane, cerebral venous oxygen saturation = 75.0%

cerebral venous pH = 7.25

cerebral venous Po_2 = 52 mm.Hg.

mean capillary Po_2 = 76 mm.Hg.

and mean tissue Po_2 = 64 mm.Hg.

It is clear therefore that 0.5% halothane produces little alteration in cerebral tissue oxygenation but that higher concentrations produce marked increases.

There are no values in the literature for venous oxygen saturation of the superior sagittal sinus under halothane anaesthesia with which to compare the present findings. Wollman et al. (1964) measured a venous Po_2 of 53.7 mm.Hg. in blood drawn from the jugular bulb; this is equivalent at their observed venous pH to a saturation of 87%. However this result cannot be closely compared with the present findings because the arterial Po_2 was much higher (566 mm.Hg. compared with 120-150 mm.Hg. in this work) and because the drainage territory of the jugular bulb includes the whole brain while the superior sagittal sinus drains almost entirely from cortical grey matter.

It is a simple matter to calculate mean tissue Pco_2 for the cerebral cortex from the measured values of blood Pco_2 since Ponten and Siesjo (1966) have shown that:-

$$\text{mean tissue } Pco_2 = Pa_{co_2} + \left(\frac{Pvco_2 - Paco_2}{2}\right) + 0.5 \text{ mm.Hg.}$$

Using this formula it can readily be shown that mean cerebral cortical tissue Pco_2 fell by about 0.5 mm.Hg. during administration of 0.5% halothane. With 2% halothane, tissue Pco_2 fell from 45 to 44 mm.Hg. despite a small increase in arterial Pco_2 from 38 to 39 mm.Hg.

Similar calculations of tissue pH from mean cortical and cerebral venous pH values are not possible because active transport mechanisms are involved which tend to stabilise tissue pH and make it partially independent of blood pH (De Bersaques & Leusen, 1954; Robin, Whaley, Crump, Bickelmann & Travis, 1958; Manfredi, 1962; Mitchell, Bainton, Severinghaus & Edelist, 1964; Severinghaus, 1965).

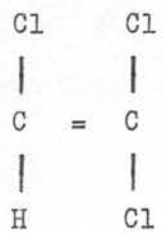
CHAPTER 4

The Influence of Trichloroethylene on the Blood Flow and Oxygen Uptake of the Cerebral Cortex

(a) Introduction

It was considered important to study trichloroethylene because it, like halothane, is commonly employed in neurosurgical anaesthesia in the belief that it has no adverse influence on surgical operating conditions (Ayre, 1944; Brittain, 1948; Hunter, 1948; Woringer, Brogly & Schneider, 1951; Ballantine & Jackson, 1954).

The chemical formula of trichloroethylene is:-



It has a blood : gas partition coefficient of 9.15 and so is approximately four times more soluble in blood than in halothane. The rate of increase of arterial concentration is therefore slower than that of halothane. In fact Mapleson (1963) has shown that, because trichloroethylene is metabolised, its arterial concentration never exceeds 20% of the inspired concentration and at 10 minutes is only 10% of the inspired. The rate of increase of arterial concentration is so slow between 10 minutes and 24 hours of administration that the anaesthetic depth remains virtually constant (Mapleson, 1963).

In clinical practice it is usually used as a supplement to nitrous oxide-

oxygen anaesthesia and is said to be administered in concentrations ranging from 0.5 to 2% (Wood-Smith & Stewart, 1964). In fact the administered concentrations are in the lower part of this concentration range because tachypnoea readily occurs with the higher concentrations (Lee & Atkinson, 1964) and because, with the usual system of administration (the Boyle bottle), concentrations over 1% are rarely obtained (Mapleson, 1957). The concentration range which was studied in the following experiments was therefore 0.3 - 0.9%.

(b) Methodology

This drug was studied in the same way as was halothane. After the control measurements of flow had been made under nitrous oxide-oxygen anaesthesia, trichloroethylene was added to the anaesthetic gases from a Fluotec II vaporiser. The vaporiser was set at the 1.0%, 1.5%, 3.0% or the 4.0% settings and at these settings, the vaporiser delivered 0.3, 0.5, 0.7 and 0.9% trichloroethylene respectively as was determined by refractometry. All the results to be cited therefore relate to trichloroethylene concentrations of less than 1%.

As with the halothane study, it was decided to make a special study of the first 20 minutes of trichloroethylene administration and this was done in a second group of experiments, designated Study IB. The methodology in this subgroup was the same as described for short halothane administrations.

Controlled ventilation under paralysis with suxamethonium chloride was employed in all experiments.

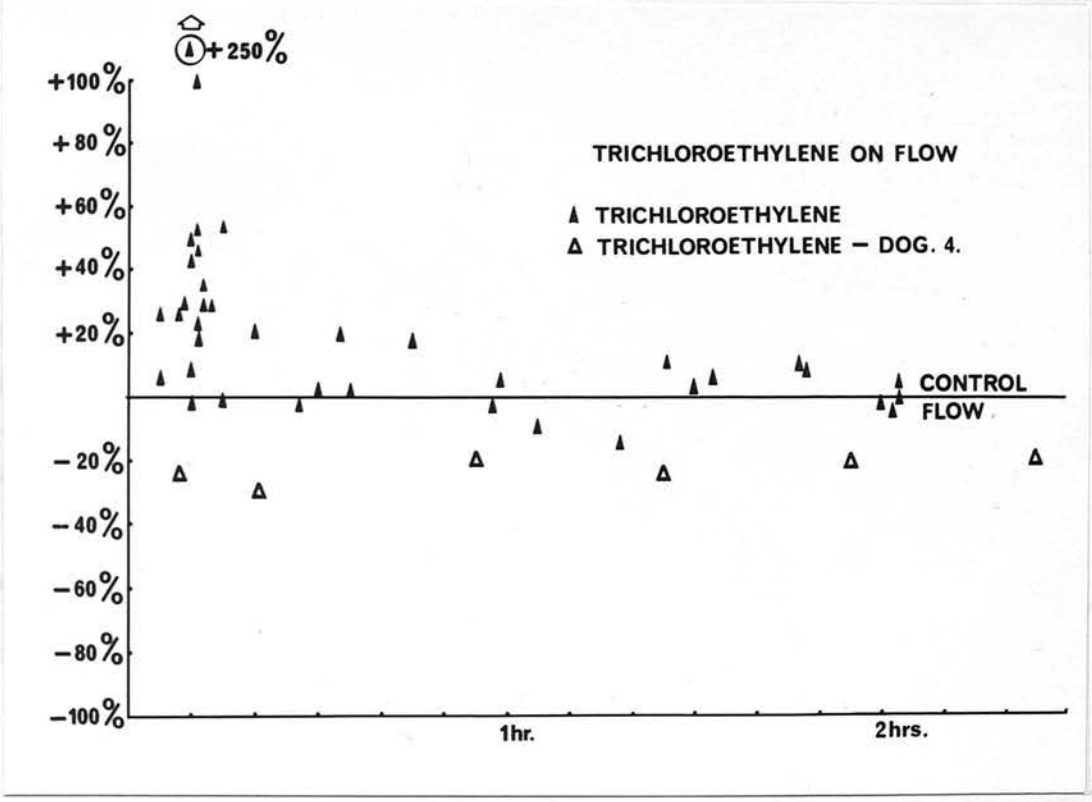


Figure 9 All individual values for cerebral cortical blood flow during trichloroethylene anaesthesia as compared with the control values during unsupplemented nitrous oxide oxygen anaesthesia. The vasodilatatory action of trichloroethylene during the first 20 minutes of its administration is clearly seen. Dog no. 4 of this series (20/6/63) behaved atypically, showing a decrease in flow throughout trichloroethylene administration.

	$N_2O + O_2$	TRICHLOROETHYLENE (PROLONGED ADMINISTRATION)	$N_2O + O_2$	TRICHLOROETHYLENE (1st 20 MINUTES)
Blood Flow	0.76 ±0.11	0.72 ±0.15	0.83 ±0.20	1.11*** ±0.37
Mean B.P.	151 ±27	147 ±22	155 ±24	157 ±20
Pa_{CO_2}	35.9 ±2.6	35.3 ±2.5	39.5 ±4.4	39.4 ±3.8

Table 23. The effect of trichloroethylene on blood flow through the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(The blood flow results (mls./G./min.) are mean values based, in the study of prolonged administration of trichloroethylene, on 18 nitrous oxide measurements and 31 trichloroethylene measurements in 6 dogs. In the study of the first 20 minutes of administration, there were 49 blood flow measurements under nitrous oxide-oxygen and 21 measurements during trichloroethylene administration in 11 dogs. B.P. and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	Prolonged Trichloroethylene	$N_2O + O_2$	Trichloroethylene 1st 20 minutes
C.V.R.	2.03 ±0.67	2.08 ±0.60	1.97 ±0.60	1.55** ±0.56
Mean B.P.	151 ±27	147 ±22	155 ±24	157 ±20

Table 24. The effect of trichloroethylene on cerebrovascular resistance and mean blood pressure.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(B.P. in mm.Hg.)

	$N_2O + O_2$	PROLONGED TRICHLOROETHYLENE
A_{O_2}	97.7% ±2.3%	98.4% ±1.6%
Art. pH	7.31 ±0.03	7.31 ±0.04
Pa_{CO_2}	35.9 ±2.6	35.3 ±2.5

Table 25 Mean values for arterial oxygen saturation, arterial pH and Pa_{CO_2} during nitrous oxide-oxygen anaesthesia and during prolonged anaesthesia with trichloroethylene (Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

(c) Effect of Trichloroethylene on Blood Flow through the Cerebral Cortex

Study 1A - Prolonged Administration of Trichloroethylene

Six experiments were performed in which trichloroethylene was administered for a prolonged period of time (up to 3 hours) and flow measurements made repeatedly. The individual results are in Table App. 13 and Figure 9 and the mean results are given in Table 23. It will be seen that mean cerebral cortical flow under trichloroethylene was not significantly different from mean flow under unsupplemented nitrous oxide-oxygen anaesthesia at the same carbon dioxide tension. One animal however showed an atypical decrease in flow of about 25% throughout trichloroethylene anaesthesia (indicated distinctively in Figure 9). All the mean results given include the measurements made in this animal but even if it is excluded the mean cerebral cortical flow under trichloroethylene in the other five experiments was still not significantly different from the mean nitrous oxide value.

The mean blood pressure during trichloroethylene anaesthesia was not significantly different from that during nitrous oxide anaesthesia nor was there any significant difference in the mean values for cerebrovascular resistance (Table 24).

No difference was detected between the mean values for arterial oxygen saturation, arterial pH, or arterial carbon dioxide tension between the two groups of observations (Table 25 and Table App. 14).

	$N_2O + O_2$	1st 20 MINUTES TRICHLOROETHYLENE
A_{O_2}	98.6 ±1.8	98.9 ±1.2
Art. pH	7.28 ±0.06	7.28 ±0.07
Pa_{co_2}	39.5 ±4.4	39.4 ±3.8

Table 26 Mean values for arterial oxygen saturation, arterial pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during the 1st 20 minutes of anaesthesia with trichloroethylene.

(Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

(c) Effect of Trichloroethylene on Blood Flow through the Cerebral Cortex

Study 1B - 1st 20 minutes of Trichloroethylene Administration

These results were obtained during short administration (up to 20 minutes) of trichloroethylene in concentrations of less than 1%. The results obtained in Study 1A during the first 20 minutes of administration have been also included in this section. There were 21 measurements of cerebral cortical flow in 11 animals during the first 20 minutes of trichloroethylene; individual results on Table App. 15 and Figure 9 and mean results are on Table 24.

During the first 20 minutes of trichloroethylene anaesthesia there was a pronounced and highly significant increase in cerebral cortical flow (+34%; $p < .001$). Since there was no change in mean blood pressure, the cerebrovascular resistance fell significantly (Table 24).

The values for arterial oxygen saturation, arterial pH and arterial Pco_2 were virtually identical between control and trichloroethylene groups (see Table 26 and Table App. 16).

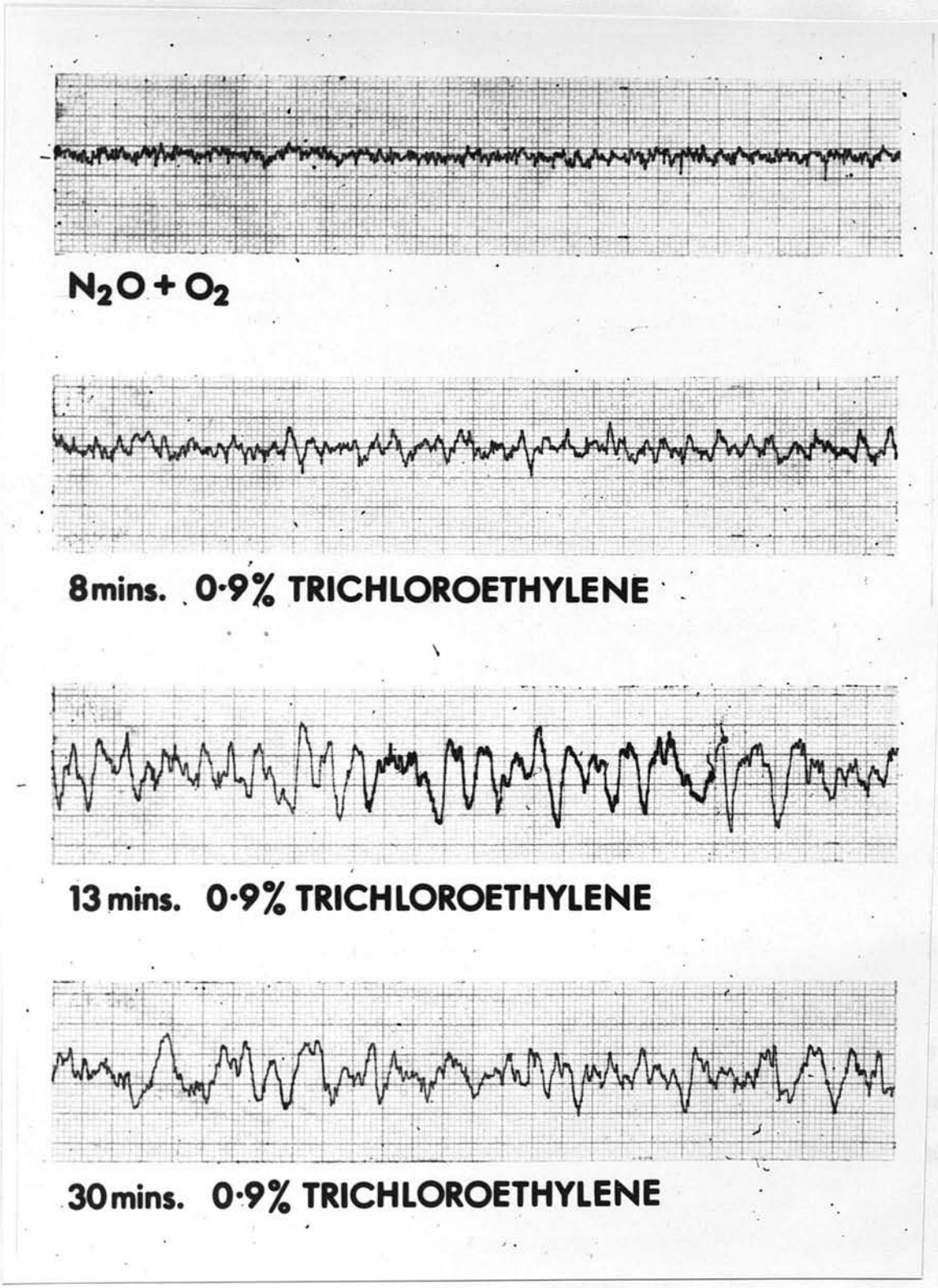


Figure 10 The E.E.G. of the dog during anaesthesia with 0.9% trichloroethylene.

	$N_2O + O_2$	TRICHLOROETHYLENE
Oxygen Uptake	0.061 ±0.018	0.053* ±0.019
Pharyngeal Temperature	38.3 ±0.6	37.8** ±0.8

Table 27 The effect of trichloroethylene on the oxygen uptake of the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Oxygen uptake results (mls./G./min.) are mean values based on 41 measurements under nitrous oxide-oxygen and 38 measurements during anaesthesia with trichloroethylene in 9 dogs. Pharyngeal temperature in °C.)

	CEREBRAL VENOUS OXYGEN SATURATION %	
	$N_2O + O_2$	TRICHLOROETHYLENE
Prolonged Trichloroethylene	54.5 ±4.2	61.0* ±7.7
1st 20 minutes Trichloroethylene	64.3 ±10.3	78.0*** ±11.1

Table 28 Values for oxygen saturation of cerebral venous blood during nitrous oxide anaesthesia and during trichloroethylene anaesthesia (both prolonged administration and administration for less than 20 minutes).

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

	A-VO_2 SATURATION DIFFERENCE		A-V Pco_2 DIFFERENCE		A-V pH DIFFERENCE	
	$N_2O + O_2$	TRICHLOROETHYLENE	$N_2O + O_2$	TRICHLOROETHYLENE	$N_2O + O_2$	TRICHLOROETHYLENE
Trichloroethylene (Prolonged)	43.3 ±4.9	37.4* ±7.7				
Trichloroethylene (1st 20 minutes)	34.4 ±10.2	20.9*** ±10.8	10.6 ±2.9	5.7*** ±1.9	0.043 ±0.015	0.030* ±0.017

Table 29. Arterio-venous differences across the cerebral cortex for oxygen, Pco_2 and pH. during nitrous oxide-oxygen anaesthesia compared with during trichloroethylene anaesthesia.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Saturation differences in percentage; Pco_2 differences in mm.Hg.)

(d) Effect of Trichloroethylene on E.E.G., Oxygen Uptake, Cerebral Venous Oxygenation and Cerebral Arterio-venous Differences

The effect of increasing duration of administration of 0.9% trichloroethylene on the E.E.G. in the dog is shown in Figure 10. It can be seen that despite the high blood solubility of the drug, obvious changes were produced in the electrical activity of the brain within 8 minutes of the commencement of trichloroethylene. These changes consisted of the appearance of theta waves on which was superimposed the same fast activity present before trichloroethylene. After 13 minutes the record was dominated by high amplitude delta waves together with some theta activity. There was no great change in the E.E.G. pattern between 13 and 30 minutes of administration which is in accord with Mapleson's prediction (1963) that arterial trichloroethylene concentration will remain virtually constant after the first 10 minutes of administration. These E.E.G. changes are similar to those found in man (Faulconer & Bickford, 1960).

The administration of trichloroethylene produced a significant reduction of 13% in the oxygen uptake of the cortex; individual results Table App. 17, mean values Table 27. The mean oesophageal temperature was 0.5°C lower in the trichloroethylene measurements.

The values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen difference, for arterial and cerebral-venous Pco_2 and cerebral arterio-venous Pco_2 difference and for arterial and cerebral venous pH and cerebral arterio-venous pH differences are given individually in Table App. 18A and B and the mean values are in Tables 28 and 29. The mean cerebral venous oxygen saturation was higher during prolonged trichloroethylene administration than during nitrous oxide

anaesthesia; 61.0% cf. 54.5%) and this result was statistically significant (Table 28). During the first 20 minutes of trichloroethylene administration the saturation of the cerebral venous blood was very greatly increased on the nitrous oxide value (78% cf. 64%); this result was highly significant ($p < .001$) (Table 28). Similarly, during this early period of trichloroethylene anaesthesia the cerebral arterio-venous difference for oxygen was lower (21% cf. 34%; $p < .001$). The arterio-venous Pco_2 difference was also significantly smaller (5.7 mm.Hg. cf. 10.6 mm.Hg.).(Table 29).

The lower cerebral venous oxygen saturation under nitrous oxide-oxygen anaesthesia in Study 1A as compared with the corresponding value under nitrous oxide-oxygen in Study 1B was due to the lower arterial Pco_2 in the former study (36 mm.Hg. cf. 40 mm.Hg.).

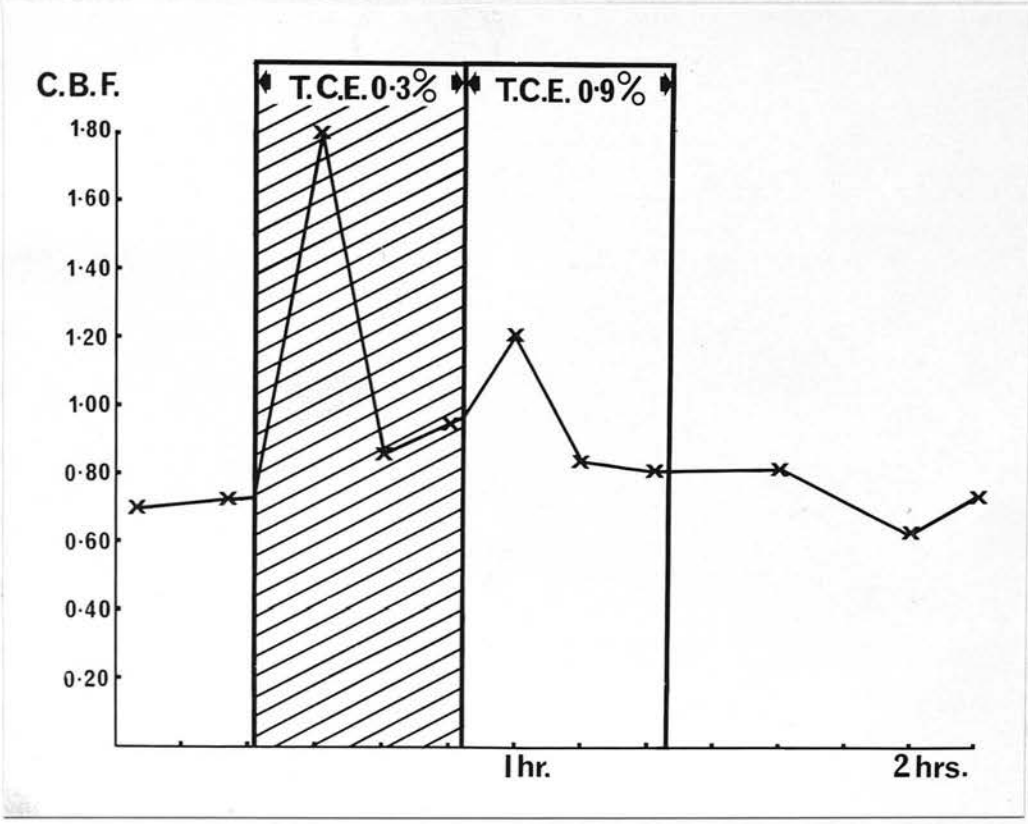


Figure 11 Changes in cerebral cortical blood flow with trichloroethylene in one animal. On administration of 0.3% trichloroethylene there was a marked increase in blood flow but this was not maintained with time. When the concentration of trichloroethylene was increased to 0.9%, there was a second short lived increase in blood flow.

(e) Discussion

1. The Influence of Trichloroethylene on Blood Flow through the Cerebral Cortex

These results demonstrate that trichloroethylene when added to nitrous oxide-oxygen in concentration of less than 1% produces a marked increase in cerebral cortical blood flow during the first 20 minutes of its administration. The cerebrovascular resistance falls considerably at this time and, since blood pressure is not affected, this must indicate cerebral vasodilatation. After this initial phase both flow and cerebrovascular resistance return to their previous control levels despite continuing trichloroethylene administration. These conclusions are reached on the basis of the statistically analysed mean data given above. To illustrate these changes each measurement of blood flow during trichloroethylene anaesthesia has been plotted against the duration of trichloroethylene administration in Figure 9. This figure demonstrates clearly the early but short-lived increase in cerebral blood flow which occurs with this drug. In Figure 11 the results from one animal have been plotted against time. When trichloroethylene was first administered to this animal, there was a large increase in cerebral cortical flow. This increase fell away quite rapidly so that after 20 minutes of administration the cortical flow was not different from the control value. At this point the trichloroethylene concentration was abruptly increased when there was another, though less marked, increase in flow but again this was not maintained. One may conclude then that when the cerebral cortical vessels are first exposed to trichloroethylene, they dilate but tachyphylaxis to this effect of trichloroethylene quickly develops and the vessels return to their previous diameter.

The only other reference to the effect of trichloroethylene on cerebral blood flow is a brief account in an article by Nowill, Stephen and Searles (1953) which states that trichloroethylene causes an increase in cerebral blood flow which is less than that which follows administration of 5% CO_2. This conclusion was based on measurements in rabbits and one monkey using the thermoelectric probe technique of flow measurement. Since these workers give no details of their measurement technique nor of their actual results it is impossible to assess the validity of their conclusions. They do not state the circumstances under which the control measurements were made, nor do they indicate the site of the brain in which flow was measured nor do they report the arterial carbon dioxide tension, the blood pressure or the body temperature of their experimental animals.

(e) Discussion

(2) Effect of Trichloroethylene on the Oxygen Uptake of the Cerebral Cortex

Trichloroethylene in concentrations of less than 1% reduced the oxygen uptake of the cerebral cortex by 13% below the level existing during unsupplemented nitrous oxide-oxygen anaesthesia. Unfortunately the mean oesophageal temperature during the trichloroethylene measurements was 0.5°C. lower than during the nitrous oxide measurements. It is well recognised that cerebral oxygen consumption is reduced when the body temperature falls. Rosomoff and Holaday (1954) have studied the relationship between temperature and cerebral oxygen uptake in the dog and found that oxygen uptake falls by 6-7% per °C. Using this data one can see that of the 13% fall in oxygen uptake of the cerebral cortex found during trichloroethylene anaesthesia approximately 3% was due to the 0.5°C. fall in temperature. It is clear therefore that trichloroethylene was itself responsible for the greater part of the observed reduction in oxygen uptake during its administration and that the fall in cerebral oxygen uptake during light trichloroethylene anaesthesia was similar to that during light halothane anaesthesia.

There is no other information in the literature on the oxygen uptake of the brain during trichloroethylene anaesthesia with which to compare this result.

The observed reduction in oxygen uptake together with the increase in flow during the first 20 minutes of trichloroethylene administration produced a marked increase in the oxygen saturation of the cerebral venous blood (Table 28). Substituting the measured values in Kety's equation,

which was fully discussed in the halothane section, one can calculate that during early trichloroethylene anaesthesia the mean cerebral tissue oxygen tension rose from 52 mm.Hg. to 65 mm.Hg.

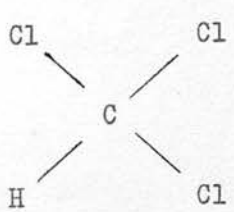
CHAPTER 5

The Influence of Chloroform on the Blood Flow and Oxygen Uptake of the Cerebral Cortex

(a) Introduction

Chloroform is a volatile anaesthetic drug which clinically resembles halothane in a number of respects but is probably slightly more potent (Mørch & Jobgen, 1959; Dobkin, Harland & Fedoruk, 1961; McReynolds, Thorogood & Morris, 1963). It has largely fallen into disuse because of alleged hepatotoxicity and because it is said to predispose to cardiac arrhythmias (Wood-Smith & Stewart, 1964). However attempts have recently been made to reawaken clinical interest in the drug since several authorities believe that its dangers have been seriously exaggerated (Waters, 1951; Griffiths & Ozguc, 1964; Davidson, 1965). It was decided to include chloroform in the present study because the drug differs chemically from the other two halogenated hydrocarbons studied in that it has only a single carbon atom. It was felt that a study of chloroform might determine whether a relationship between chemical structure and cerebrovascular effects existed.

The chemical formula for chloroform is:-



Its blood : gas partition coefficient is 8.4 and its brain : blood

coefficient is 1.0. The rate of rise of its arterial concentration therefore is greater than that of trichloroethylene but less than that of halothane.

The concentration of chloroform required for maintenance of anaesthesia is 0.5 - 1.5% (Wood-Smith & Stewart, 1964) and therefore in these studies the concentration administered was 1.0%.

(b) Methodology

After the control measurements had been made in the usual manner, during unsupplemented nitrous oxide-oxygen anaesthesia, chloroform was introduced from a Chlorotec vaporiser. The vaporiser was adjusted to the 1% setting, it having previously been ascertained, by refractometry, that at this setting the particular vaporiser used delivered 1.03% chloroform.

	$N_2O + O_2$	1% Chloroform
Blood Flow	0.79 ±0.19	0.94*** ±0.21
Mean B.P.	158 ±12	142*** ±15
Pa_{CO_2}	36.3 ±4.0	37.1 ±5.4

Table 30 The effect of 1% chloroform on blood flow through the cerebral cortex.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(The blood flow results (mls./G./min.) are mean values based on 35 measurements under nitrous oxide-oxygen and 32 measurements during 1% chloroform administration in 12 dogs. B.P. and $Paco_2$ in mm.Hg.)

	$N_2O + O_2$	1% Chloroform
C.V.R.	2.18 ±0.48	1.58*** ±0.34
Mean B.P.	158 ±12	142*** ±15

Table 31 The effect of 1% chloroform on cerebrovascular resistance and on blood pressure.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(B.P. in mm.Hg.)

	$N_2O + O_2$	1% Chloroform
Ao_2	96.8 ±2.7	96.1 ±3.1
Art. pH	7.328 ±0.039	7.285*** ±0.059
Pa_{co_2}	36.3 ±4.0	37.1 ±5.4

Table 32 Mean values for arterial oxygen saturation, arterial pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 1% chloroform.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(Arterial oxygen saturation (Ao_2) in percentage and $Paco_2$ in mm.Hg.)

(c) Results

Effect of Chloroform on Blood Flow through the Cerebral Cortex

32 measurements of cerebral cortical blood flow were made in 12 animals during anaesthesia with 1% chloroform in nitrous oxide-oxygen. The individual results are given in Table App. 19 and the mean results in Table 30.

1% chloroform caused a mean increase in cerebral cortical blood flow of 24% ($p < .001$). Of the 32 separate measurements flow increased on 25 occasions, stayed the same once and fell on 6 occasions. The range of individual flow measurements was from -19% to +62%. The longest period of administration studied was 1½ hours at which time there was no evidence of flow returning to the control value.

With this concentration of chloroform, the mean blood pressure fell from 158 to 142 mm.Hg. The cerebrovascular resistance fell very much more than could be accounted for by the observed drop in B.P. thus indicating cerebral vasodilatation by the chloroform (Table 31).

The values for arterial oxygen saturation, arterial carbon dioxide tension and arterial pH are given in Table 32 and Table App. 20. Arterial oxygen saturation and Pco_2 were virtually identical in the two groups of results but a metabolic acidosis, evidenced by a fall in arterial pH at constant arterial Pco_2, developed during chloroform anaesthesia in these dogs.

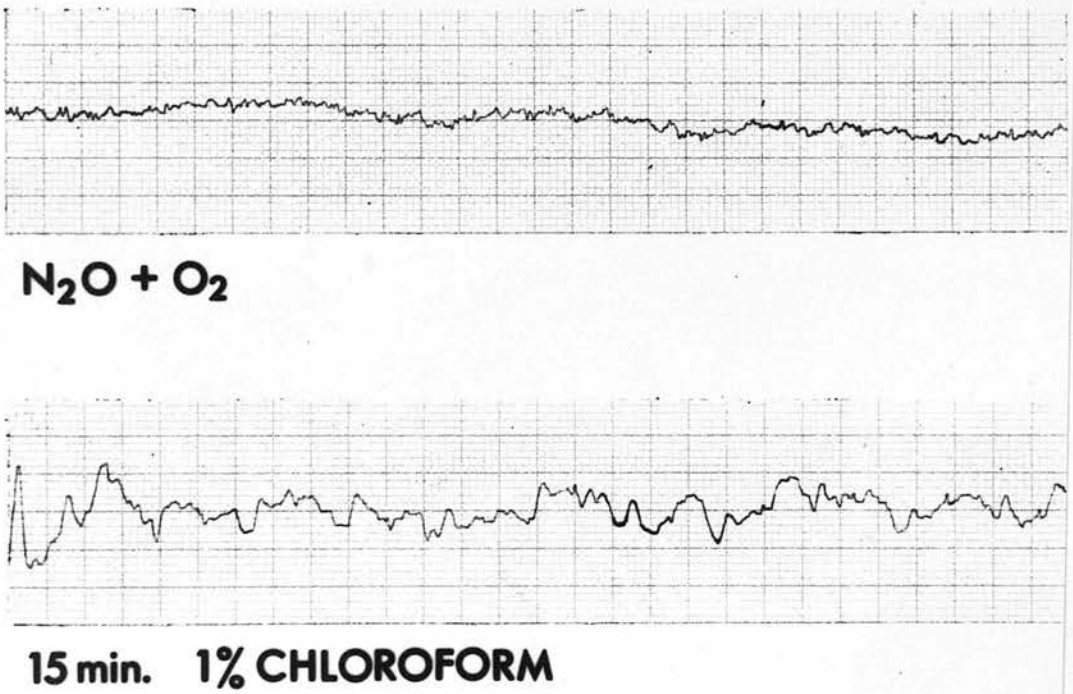


Figure 12 The E.E.G. of the dog during anaesthesia with 1% chloroform.

	$N_2O + O_2$	1% Chloroform
Oxygen Uptake	0.060 ±0.013	0.055 ±0.010
Pharyngeal Temperature	38.0 ±1.3	38.2 ±1.1

Table 33 The effect of 1% chloroform on the oxygen uptake of the cerebral cortex.

(Oxygen uptake results (mls./G./min.) are mean values based on 17 measurements under nitrous oxide-oxygen and 14 measurements during anaesthesia with 1% chloroform in 6 dogs. Pharyngeal temperature in $^{o}C.$)

	CEREBRAL VENOUS OXYGEN SATURATION %	A-V_{O_2} DIFFERENCE %
$N_2O + O_2$	61.1 ±5.4	35.5 ±6.4
1% Chloroform	71.7** ±4.4	25.0*** ±5.5

Table 34 The effect of 1% chloroform on cerebral venous oxygenation and cerebral arterio-venous oxygen saturation difference.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

(d) Results

The Effect of Chloroform on the E.E.G., Oxygen Uptake, Cerebral Venous Oxygenation and Cerebral Arterio-venous Differences

Figure 12 shows the changes in the E.E.G. produced by the administration of 1% chloroform. It will be seen that during 1% chloroform, the pattern was of delta activity with some superimposed faster theta waves. This pattern of electrical activity corresponds exactly with Level V of the classification of Pearcy, Knott, Pittinger & Keasling (1957) for the E.E.G. changes produced by chloroform in dogs. These workers considered that levels III and IV of their classification were indicative of full surgical anaesthesia and therefore the cerebral blood flow and oxygen uptake results reported in this thesis are those associated with a fairly deep plane of surgical anaesthesia.

14 measurements of cerebral oxygen uptake during chloroform administration were made in 6 animals (Table 33 and Table App. 21). The observed fall in oxygen uptake of 8% did not reach statistical significance. The mean cerebral venous oxygen saturation rose markedly from 61% to 72% during chloroform administration (Table 34 and Table App. 22). There was also a highly significant fall in the arterio-cerebral venous difference for oxygen (Table 34 and Table App. 22). Calculation of mean cerebral tissue oxygen tension is not possible in this group because at the time of these studies venous pH was not being measured.

(e) Discussion

These results show that chloroform is a dilator of the cerebral vasculature leading to marked increases in cerebral cortical blood flow despite small falls in blood pressure. There is one feature that renders these chloroform results different from the results with the other volatile anaesthetics studied and that is the metabolic acidosis which occurred during chloroform administration. The development of metabolic acidosis during chloroform anaesthesia in dogs has been noted before by Dobkin, Harland & Fedoruk (1961). This acidosis could not, however, have been responsible for the observed increase in cerebral blood flow since it has been shown that alterations in blood pH, other than those due to changes in $Paco_2$, do not affect cerebral blood flow (Harper & Bell, 1963).

Since chloroform has been in use as a general anaesthetic for well over a century one might expect to find a considerable volume of literature dealing with its action of cerebral haemodynamics and metabolism. In fact there appears to have been only one previous study of the subject. Finesinger & Cobb (1935) studied the action of drugs on the cerebral circulation by measuring changes produced in the diameter of the cerebral cortical vessels lying in the pia mater. They noted that the administration of chloroform to cats produced increases in pial artery diameter which ranged from 5 to 30%. They further observed that pial artery dilatation was greater in deeper chloroform anaesthesia. The evaluation of these findings is difficult because it is clear from their data that many of their animals were grossly hypotensive during chloroform administration, mean arterial pressures as low as 30 mm.Hg. being recorded. It was not until three years after this study that Fog (1938) showed that hypotension

itself produces increases in pial artery diameter. Fog interpreted these changes as evidence of an autoregulatory mechanism tending to maintain flow constant despite falling cerebral perfusion pressure - an interpretation which has been supported by much recent work (Noell & Schneider, 1944; Carlyle & Grayson, 1955; Rapela, Machowicz & Freeman, 1963; Schneider, 1963; Haggendal & Johansson, 1965; Harper, 1966). Therefore it is not possible to be confident that the changes in pial artery diameter noted by Finesinger and Cobb during chloroform anaesthesia were produced by the drug itself and not by the associated hypotension. Furthermore, the authors fail to state how many of their animals were studied under controlled ventilation, a vital point since chloroform is a potent respiratory depressant (Wood-Smith & Stewart, 1964) and leads to hypercapnia in the spontaneously ventilating animal or patient. Finally since the chloroform was vaporised in air, and during spontaneous ventilation in some of the animals, it is probable that respiratory depression and increased venous admixture produced significant hypoxaemia in some of their animals. When the arterial oxygen tension falls below 60 mm.Hg. increases in cerebral flow occur (McDowall, 1966 quoting unpublished work by Harper, McDowall & Jacobson) and therefore part of the observed cerebral vasodilatation may have been due to this factor.

	ΔPa_{CO_2}	Δ Blood Flow	Δ Blood Flow $N_2O + O_2$
HALOTHANE	39 → 30	- 30%	- 13%
TRICHLOROETHYLENE	36 → 22	- 24%	- 27%
CHLOROFORM	39 → 28	- 18%	- 15%

Table 35 Percentage reductions in blood flow through the cerebral cortex produced by hypocapnia during anaesthesia with halothane, trichloroethylene or chloroform. Also shown are the changes in blood flow which are known to occur when Pa_{CO_2} is lowered to the same degree under unsupplemented nitrous oxide-oxygen anaesthesia.

	ΔPa_{CO_2}	Δ Blood Flow	Δ Blood Flow $N_2O + O_2$
HALOTHANE	43 → 69	+ 69%	+ 41%
TRICHLOROETHYLENE	36 → 82	+ 150%	+ 102%
CHLOROFORM	40 → 63	+ 71%	+ 36%

Table 36 Percentage increases in blood flow through the cerebral cortex produced by hypercapnia during anaesthesia with halothane, trichloroethylene or chloroform. Also shown are the changes in blood flow which are known to occur when Pa_{CO_2} is raised to the same degree under unsupplemented nitrous oxide-oxygen anaesthesia.

CHAPTER 6

The Influence of Hypocapnia and of Hypercapnia on Blood Flow through the Cerebral Cortex during Anaesthesia with Halothane, Trichloroethylene and Chloroform

(a) Introduction

It was decided to test in several animals the responsiveness of the cerebral cortical vessels to changes in arterial Pco_2 during anaesthesia with these drugs in order to determine whether normal cerebrovascular control mechanisms are inactivated by these volatile anaesthetic agents.

(b) Methodology

In some animals after measuring flow during the administration of halothane, trichloroethylene or chloroform the arterial Pco_2 was altered and further measurements made. Hypocapnia was induced by increasing the tidal volume of the ventilator and hypercapnia by adding CO_2 to the inspired gases.

(c) Results

The individual results are shown in Tables App. 23, 24, 25, 26, 27 and 28. The mean results, expressed as percentage changes are given in Tables 35 and 36. Included in these tables are the percentage changes in blood flow through the cerebral cortex which would occur if $Paco_2$ were altered to the same extent under unsupplemented nitrous oxide-oxygen anaesthesia (these latter changes being calculated from the results of Harper and Glass, 1965). For example, from Table 35 it can be seen that when $Paco_2$ is lowered

from 36 to 22 mm.Hg. during trichloroethylene anaesthesia, blood flow through the cerebral cortex falls by 24% while the same change in $Paco_2$ during unsupplemented nitrous oxide-oxygen anaesthesia would reduce flow by 27%.

(d) Discussion

These results demonstrate that the cerebral blood vessels retain their responsiveness to changes in arterial Pco_2 during anaesthesia with these volatile anaesthetic drugs.

During anaesthesia with halothane or chloroform, the mean blood pressure was below the values existing under unsupplemented nitrous oxide-oxygen anaesthesia. Haggendal & Johansson (1965) and Harper & Glass (1965) have shown that the influence of changes in $Paco_2$ on cerebral cortical blood flow becomes less as the mean blood pressure is reduced until at a mean B.P. of 50 mm.Hg. no response to alterations in arterial Pco_2 occurs. In order to obtain the most meaningful comparisons of CO_2 effects during anaesthesia with halothane and chloroform, the percentage changes in flow observed have been compared with the changes which would have occurred under nitrous oxide-oxygen anaesthesia at the same reduced blood pressure. (No significant hypotension was present during the trichloroethylene measurements) The lowering of blood pressure during nitrous oxide-oxygen anaesthesia in the study of Harper and Glass (1965) was achieved by controlled haemorrhage while in the present studies hypotension was presumably the result of drug induced peripheral vasodilatation and reduced cardiac output. None the less, because the cerebral circulation appears to be unaffected by sympathetic vasoconstriction affecting other parts of the body (Lassen, 1959), it is reasonable to compare results obtained at the same perfusion pressure even

although the mechanism of hypotension is different in the two situations.

When the percentage changes in flow with alterations in $Paco_2$ during anaesthesia with these drugs are compared with the changes under unsupplemented nitrous oxide-oxygen anaesthesia at the same blood pressure it is clear that blood flow is at least as sensitive to changes in $Paco_2$ during halothane, trichloroethylene and chloroform anaesthesia. Similar cerebrovascular sensitivity to $Paco_2$ changes during halothane anaesthesia has been reported by Alexander, Wollman, Cohen, Chase & Behar (1964) and by McHenry et al (1965) but has not previously been described with either trichloroethylene or chloroform.

CHAPTER 7

General Discussion of the Results of Part I

This thesis compares the effects of three volatile anaesthetic drugs, halothane, trichloroethylene and chloroform on the cerebral circulation and metabolism. The E.E.G. records presented show that the concentrations of these drugs administered produced definite changes in the electrical activity of the brain indicative of depression of cerebral activity. In addition, there is evidence in the literature which allows a comparative assessment of the depth of anaesthesia associated with the concentrations of these drugs used.

Dobkin, Harland and Fedoruk (1962) have found that an inspired concentration of 1% trichloroethylene produces a depth of anaesthesia in dogs similar to that due to 2% halothane. Dobkin, Harland and Fedoruk (1961) and McReynolds et al. (1963) believe that chloroform is slightly more potent than halothane at the same inspired concentration though Mørch and Jobgen (1959) disagree. In this study therefore 1% chloroform can be considered to fall in anaesthetic potency between 0.5 and 2% halothane, being closer to the latter. The increase in cerebral cortical blood flow with 1% chloroform was in fact the same as that with 2% halothane. The lesser fall in oxygen uptake with chloroform was due to an anomalous increase in oxygen uptake found in one animal with this drug, to the somewhat lighter anaesthetic depth and to the greater blood solubility of chloroform. This last point is relevant because with the greater blood solubility the arterial concentration of chloroform rises more slowly and so anaesthesia deepens more gradually than is the case with halothane (see below).

Trichloroethylene in the concentrations administered in this study (0.3 to 0.9%) is equivalent to 0.6 to 1.8% halothane (or to slightly lower concentrations of chloroform). The depression of oxygen uptake produced by trichloroethylene was similar to that produced by 0.5% halothane since the majority of the trichloroethylene measurements were made with the lower concentrations of trichloroethylene.

In discussing the anaesthetic concentrations referred to in this thesis it is necessary to stress that these were inspired and not alveolar or arterial concentrations. On account of the high blood solubility of these drugs, the alveolar and arterial concentrations will have been much lower than the inspired concentrations in all these studies, the effect being greatest with trichloroethylene and least with halothane (Eger & Larson, 1964). In the case of halothane, Mapleson (1963) has shown that the arterial concentration equals 40% of the inspired after 10 minutes of administration and 60% of the inspired at 60 minutes. The great majority of the measurements reported here were obtained after between 10 and 60 minutes of halothane administration. The comparable figures for chloroform are that the arterial concentration equals 20% of the inspired at 10 minutes and 40% at 60 minutes. With trichloroethylene, the arterial concentration is about 10% of the inspired at 10 minutes and does not exceed 20% even after many hours of administration.(Mapleson, 1963). The reason for discussing the results in terms of inspired concentrations is to allow ready correlation with clinical practice and experience since it is invariably inspired concentrations which are used clinically.

Of course if the results presented in this thesis are to be correlated with clinical practice then it is necessary to know what the equivalent anaesthetic concentrations of these drugs are for man and for dog.

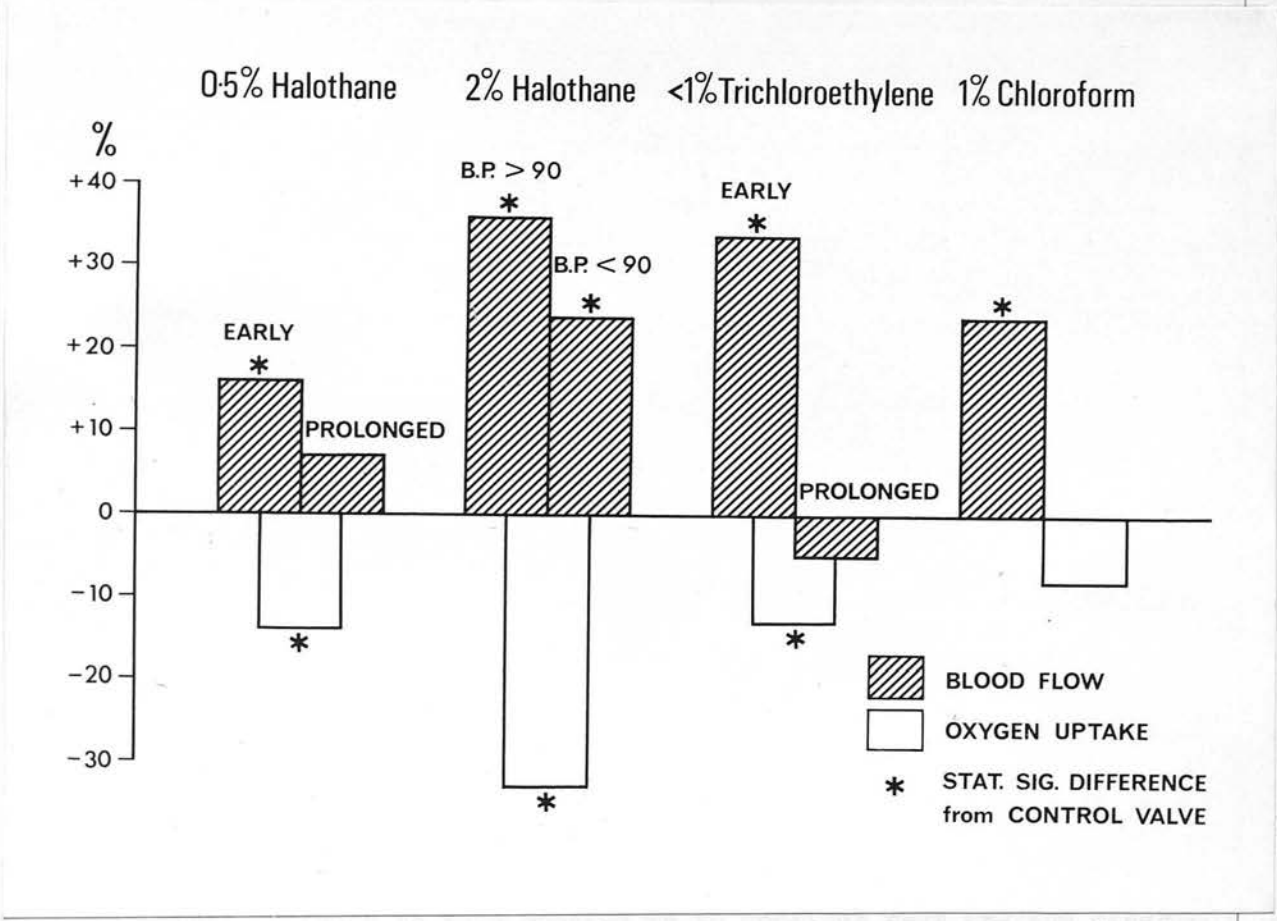


Figure 13 Changes in blood flow and oxygen uptake of the cerebral cortex during administration of halothane, chloroform and trichloroethylene. With halothane and trichloroethylene, blood flow changes during the first 20 minutes of administration are indicated by the first block and the overall changes by the second block of the respective blood flow columns.

Fortunately these equipotent concentrations are rather precisely known from the work of Eger, Brandstater, Saidman, Regan, Severinghaus and Munson (1965). These workers found that surgical anaesthesia in the dog required an alveolar concentration of 0.87% halothane while in man the figure was 0.74%. As the surgical stimulus used to test anaesthesia was rather less severe in man, these workers concluded that equipotent anaesthetic concentrations of halothane for man and dog are virtually identical. Eger et al. did not study either trichloroethylene or chloroform but it seems probable from their work that species differences between man and dog in sensitivity to the volatile anaesthetics do not exist.

To turn now to the blood flow results, it is clear from these studies that halothane, trichloroethylene and chloroform when administered in clinical concentrations act as vasodilators of the cerebral vasculature (see Figure 13). Detailed study of the action of different concentrations of halothane has further shown that the degree of cerebral vasodilatation is related to the concentration of the drug administered. The question which therefore arises is why should these drugs which vary considerably in chemical structure all act in the same way on the cerebral vasculature.

The first approach to this problem is to consider what are the other pharmacological actions of these drugs which they share in common. Most obvious of these is the fact that all are general anaesthetics. However the present imperfect understanding of the mechanism of drug action in the production of general anaesthesia limits the value of this approach. In the studies reported here it has been established that general anaesthesia with these drugs is associated with a reduction in the oxygen uptake of the cerebral cortex; in other words aerobic cellular metabolism is depressed. Is therefore the observed cerebral vasodilatation produced linked in some

way to the metabolic depression of the brain produced by these anaesthetics?

There is a considerable body of evidence against this suggestion. It has been shown that in many different situations depression of cerebral metabolic rate is associated with a reduction in cerebral blood flow. For example general anaesthesia produced by the barbiturate group of drugs results in a fall in both cerebral blood flow and in cerebral metabolic rate (Himwich et al., 1947; Pierce et al., 1962). Furthermore, Gleichman et al. (1962) found that the reduction in cerebral cortical blood flow under barbiturate anaesthesia was proportional to the associated depression of cerebral metabolic rate. Similar proportionate reductions in cerebral metabolic rate and cerebral blood flow have also been demonstrated in hypothermia (Rosomoff & Holaday, 1954; Bering, Taren, McMurrey & Bernhard, 1956). This evidence has led to the formulation of the hypothesis that, in the brain, blood flow is regulated to meet metabolic requirements. The concept is that flow is controlled by the local tissue tension of carbon dioxide so that if metabolism decreases, tissue Pco_2 tends to fall and this produces an increase in local cerebrovascular resistance and a consequent fall in cerebral blood flow. The net result is that tissue Pco_2 is maintained constant over a range of metabolic rates by adjustment of cerebral perfusion. A recent slight modification to this hypothesis has been the suggestion that the controlling mechanism is not tissue Pco_2 itself but tissue pH, which is of course partly dependent on tissue Pco_2 (Betz & Kozak, 1967; Lassen, 1966).

As has been pointed out, the present results show that the volatile anaesthetic drugs, halothane and trichloroethylene depress cerebral metabolic rate (the depression of C.M.R.o_2 with chloroform just failed to reach statistical significance). In the terms of the above hypothesis

	CEREBRAL VENOUS OXYGEN SATURATION		
	BEFORE	DURING	CHANGE
0.5% Halothane All results.	58.3% ±9.1%	62.2% ±9.1%	+3.9%*
0.5% Halothane 1st 20 mins.	58.7% ±9.1%	64.6% ±9.2%	+5.9%*
2% Halothane	58.1% ±7.4%	75.0% ±3.0%	+16.9%***
< 1% Trichloroethylene 1st 20 mins.	64.3% ±10.3%	78.0% ±11.1%	+13.7%***
<1% Trichloroethylene Prolonged Administration	54.5% ±4.2%	61.0% ±7.7%	+6.5%*
1% Chloroform	61.1% ±5.4%	71.7% ±4.4%	+10.6%**

Table 37 Comparison of the changes in cerebral venous oxygen saturation produced by the various volatile anaesthetics studied.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

flow therefore should fall. However the converse was the case; flow increased while metabolic rate fell and the higher the concentration of drug the wider became the discrepancy. Cerebral blood flow during anaesthesia with these drugs was therefore "inappropriate" to the level of metabolic demand. As a result the oxygen saturation of cerebral venous blood rose (results summarised in Table 37) and cerebral venous Pco_2 fell, indicating changes in the same directions of tissue Po_2 and tissue Pco_2.

Do the "inappropriate" increases in cerebral blood flow with these drugs imply that the normal controlling mechanisms have been either inactivated or depressed? This cannot be the case since flow responsiveness to alterations in $Paco_2$ has been shown to be unimpaired during anaesthesia with these volatile drugs.

One must conclude then that the changes in cerebral blood flow produced are in the opposite direction to those predicted by the hypothesis of flow regulation to metabolic demand despite the fact that the mechanism of metabolic control of flow via tissue Pco_2 appears to be functioning normally.

What other pharmacological actions are common to these three drugs? The mean blood pressure fell with halothane and chloroform but this could hardly account for an INCREASE in flow. Similarly any depression in cardiac output which they caused would if anything affect cerebral perfusion in the opposite direction.

Chloroform produces a sympathomimetic response marked by elevation of plasma catechol amine levels (Richardson, Woods & Richardson, 1957) while halothane reduces sympathetic nervous activity (Price, Linde & Morse, 1963). The common cerebral vasodilatation produced by these two drugs cannot therefore be ascribed to changes in sympathetic activity. In any case the

cerebral circulation is peculiarly unresponsive to changes in autonomic tone (Harmel, Hafkenschiel, Austin, Crumpton & Kety, 1949; Sokoloff, 1959). Cerebral vasoconstriction however has been shown to accompany intravenous infusions of catechol amines in normotensive dogs maintained at constant blood pressure (Haggendal, 1965). The cerebral vasodilatation seen with chloroform therefore occurred despite and not because of the elevation in plasma catechol amines.

In the absence of any correlation with the known common pharmacological actions of these drugs, it becomes necessary to postulate that each of them produces vasodilatation "directly" that is by relaxing the tone of the smooth muscle of the cerebral arterioles. In this connection the observations of Smith and Vane (1966) may be relevant. These workers studied the effect on vascular smooth muscle of perfusing isolated strips of artery with perfusion fluids of different oxygen tensions. They showed that the higher the Po_2 of the perfusate the greater was the smooth muscle tone, i.e. that high oxygen tensions caused "direct" vasoconstriction. From these observations they postulated that the tone of vascular smooth muscle is dependent upon the enzymatic supply of energy and that this enzymatic reaction is oxygen limited so that if the rate of oxygen supply is increased then more energy is produced and smooth muscle tone thereby increases. The observations reported in this thesis could readily be explained if the volatile anaesthetics studied depressed the enzymatic reaction from which the energy for smooth muscle contraction is derived. Unfortunately no studies have been reported in the literature on the responses of isolated vessels to exposure to volatile anaesthetic drugs. Burns and Epstein (1959) were able to show that when one dog's hind limb is perfused with blood from another animal receiving halothane vasodilatation occurs in the cross-

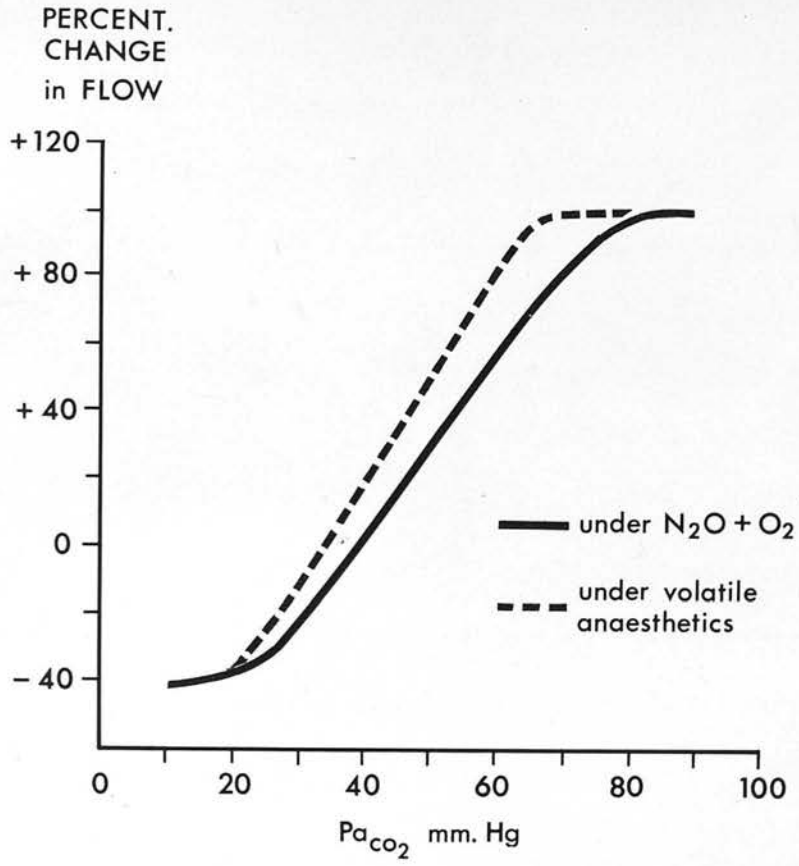


Figure 14 Schematic representation of the "shift to the left" in the blood flow - Paco2 curve produced by administration of the volatile anaesthetics studied (the blood flow - Paco2 relationship under nitrous oxide-oxygen anaesthesia is from the work of Harper & Glass, 1965).

perfused limb, suggesting a direct action of halothane on the vessel wall. This direct response of peripheral vessels to halothane cannot however be translated to the cerebral vessels since these latter are known to respond differently to humoral and chemical agents even when directly applied (Bohr, Goulet and Taquini, 1961).

It does seem at least possible that drugs which act as depressants of cellular metabolism might well depress the rate of the reaction responsible for smooth muscle tone and that such depression would be common to all these volatile anaesthetics. The fact that the barbiturates which also depress cerebral metabolism do not produce cerebral vasodilatation could readily be ascribed to failure of such drugs to penetrate the arteriolar wall.

The observation that the responsiveness of cerebral blood flow to changes in Pco_2 is not reduced by these drugs means that, although the "resting tone" of the cerebral vessels may be lowered, the normal mechanisms of control are still active. Figure 14 is a diagrammatic representation of this concept. The flow-$Paco_2$ curve produced by Harper & Glass (1965) is shown as a continuous line while the dotted line indicates the shift to the left produced by the vasodilatatory action of these anaesthetic drugs. It will be seen that the flow-Pco_2 curves are separated only in the middle range of Pco_2 values for at very high and at very low Pco_2 values it is likely that maximum vasodilatation or constriction will have been effected by the CO_2 level and that the influence of the anaesthetic will be small.

Besides this interaction between the influence of Pco_2 and of volatile anaesthetics, there is a relationship between drug effect and mean arterial blood pressure. Under nitrous oxide-oxygen anaesthesia in the dog it has been demonstrated by Harper (1966) that reducing the mean blood pressure from 150 mm.Hg. to about 80 mm.Hg. has little effect on cerebral blood flow but

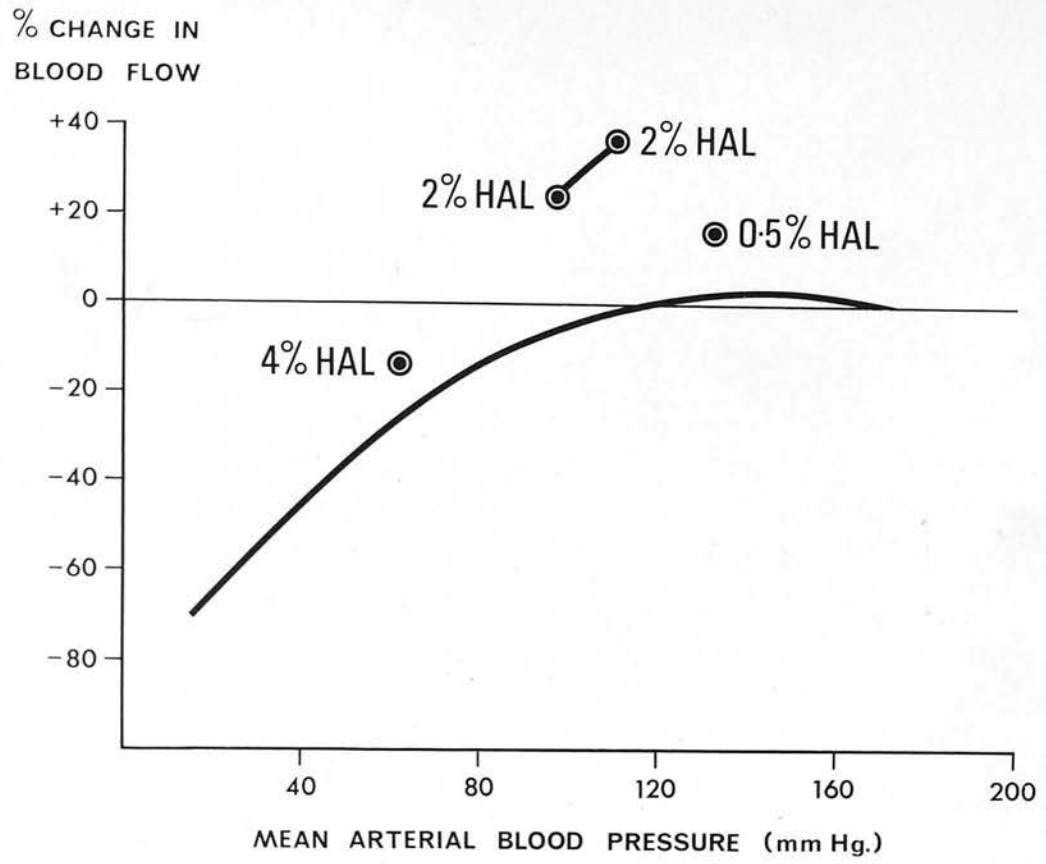


Figure 15 The effects of 0.5%, 2% and 4% halothane on blood flow as compared with the blood flow present at similar levels of hypotension during nitrous oxide-oxygen anaesthesia (the nitrous oxide-oxygen results were obtained from the work of Harper (1966)).

that with reductions below 80 mm.Hg. flow falls proportionately with mean perfusion pressure. In addition Harper & Glass (1965) have shown that raising the arterial Pco_2 has more effect on flow at normal and at high blood pressures than it has at low pressures. Indeed at a mean pressure of 50 mm.Hg. these workers found that arterial Pco_2 had no influence on cerebral blood flow. The same is likely to be true of these anaesthetic drugs and it has been shown in this thesis that 2% halothane is a more potent cerebral vasodilator when the mean blood pressure is above 90 mm.Hg. In Figure 15 therefore the halothane findings have been superimposed on the flow pressure diagram of Harper (1966). This figure illustrates the important point that at any blood pressure above that at which flow becomes entirely pressure dependent, the administration of halothane increases flow above the level which would exist during unsupplemented nitrous oxide-oxygen anaesthesia at the same reduced blood pressure.

From the results presented and the literature reviewed it is now possible to describe a composite picture of cerebral haemodynamics and metabolism during the course of clinical anaesthesia. Induction of anaesthesia in clinical practice in this country is normally accomplished with a small dose of barbiturate (0.2 - 0.5 G. in the adult) sufficient only to produce light unconsciousness. Light anaesthesia with barbiturates reduces the cerebral oxygen uptake by 36% (Wechsler, Dripps & Kety, 1951) and therefore the depression produced by the smaller doses used for induction of anaesthesia will be less than this. Concomitantly with the fall in oxygen uptake a proportionate fall in cerebral blood flow will occur (Gleichmann et al., 1962). Anaesthesia is then often continued with nitrous oxide-oxygen together with either halothane or trichloroethylene. From the work presented here, it can be stated that the introduction of either of these

agents into the anaesthetic mixture will produce a wave of cerebral vasodilatation and a further reduction in cerebral metabolic rate so that the brain will appear more vascular and the colour of the blood in the cerebral veins will become lighter as the cerebral venous oxygen saturation rises. Any further increase in the concentration of the volatile drug will produce a further increase in flow and a deeper fall in cerebral metabolic rate. What happens to arterial Pco_2 depends on whether ventilation is spontaneous or controlled. If spontaneous, then respiratory depression will lead to a rise in arterial Pco_2 and to a further increase in cerebral blood flow. If ventilation is controlled and the patient is hyperventilated then the influence of the volatile drug on flow will become less as the arterial Pco_2 falls. The volatile agent will however still produce appreciable cerebral metabolic depression so that the saturation of the cerebral venous blood and therefore the local tissue Po_2 will be higher during hypocapnia than would otherwise be the case.

A similar relationship exists for cerebral perfusion pressure. If the anaesthetic technique is associated with hypotension then the influence of the volatile drug on flow will become progressively less as the mean B.P. falls until a level is reached at which flow has become entirely dependent on perfusion pressure and will be uninfluenced by the anaesthetic. None the less, the volatile anaesthetic will still produce a depression of cerebral metabolic rate, so that cerebral tissue oxygen tension will be higher during hypotension than if no volatile agent were administered.

Clinical Significance of the Results of Part 1

There would appear to be two main clinical implications of the findings of this Part of the thesis. These are:-

(1) the possibility that the cerebral vasodilatation seen during the administration of these drugs might seriously elevate intracranial pressure

and (2) the possibility that the increased cerebral blood flow and reduced cerebral oxygen requirements which accompany administration of these drugs might increase the tolerance of the brain to periods of circulatory insufficiency.

The first of these two possibilities forms the basis of Part II of this thesis and so need not be considered further here.

In considering cerebral protection against ischaemia, the anaesthetist thinks in terms of four main groups of patients. Firstly there are those patients who are presented for surgery with pre-existing cerebral arteriosclerosis. The concern in this group is that anaesthesia may, by lowering cerebral perfusion pressure, lead to acute regional ischaemia within the supply area of the atheromatous vessel. Secondly there are those patients whose perfusion pressure is to be deliberately lowered by drug induced hypotension in order to improve surgical operating conditions. The third group consists of neurosurgical cases in whom, for surgical reasons, it is necessary to temporarily occlude one of the vessels of supply to the brain, e.g. the internal carotid artery during carotid disobliteration. Finally there is the group of patients who are to undergo elective total circulatory arrest in order to allow the performance of cardiac or neurosurgical operative procedures.

From the physiological point of view there are three ways in which protection of the brain might be afforded to such patients:-

(1) the collateral blood supply to an ischaemic area might be improved

(2) the quantity of oxygen stored in the brain prior to circulatory arrest might be increased

and (3) the rate of oxygen consumption by the brain might be reduced.

As regards the collateral blood supply to an ischaemic area, it might be held that, because halothane, early trichloroethylene and chloroform increase cerebral blood flow, more blood might reach ischaemic areas during anaesthesia with these agents. Such an increase of blood flow would be of value to patients with pre-existing cerebral arteriosclerosis and to patients undergoing procedures requiring regional interruption of the cerebral circulation. Of course a more potent cerebral vasodilator than the volatile anaesthetics is carbon dioxide and indeed hypercapnia has been used as a means of protecting the brain during internal carotid occlusion by Homi, Humphries, Young, Beven and Smart (1966) who claimed that this procedure reduced the incidence of postsurgical neurological deficit. However, Wylie (1966) in discussing this paper by Homi et al. pointed out that only a few patients fail to tolerate temporary unilateral carotid occlusion and that if one was careful to select only these "at risk" cases it could be shown that hypercapnia offered no protection against ischaemic neurological damage during carotid occlusion. There are also sound theoretical grounds for doubting whether vasodilator drugs could be of any possible benefit in this clinical situation because the cerebral vessels in an area of ischaemia are already dilated by tissue hypoxia. Administration of a cerebral vasodilator under these circumstances may merely divert blood away from the ischaemic area because of the consequent reduction in cerebro-vascular resistance in non-ischaemic areas.

It should be noted in this connection that measurement of the oxygen content of cerebral venous blood in order to determine the adequacy of regional cerebral oxygenation, as has been done during anaesthesia by several groups of workers (Lyons, Clark, McDowell, H. & McArthur, 1964; Viancos,

Sechzer, Keats & DeBakey, 1966) may be fallacious because an increase in cerebral venous oxygen content may only indicate diversion of blood by the vasodilator away from the ischaemic area. After all, the highest cerebral venous oxygenation will occur when the ischaemic area is not perfused at all.

It is therefore most unlikely that cerebral vasodilatation produced by volatile anaesthetics will be of any clinical value in improving the perfusion of an area of regional ischaemia in the brain. Indeed the converse may occur.

The possibility of increased cerebral oxygen storage during administration of volatile anaesthetic drugs may be quickly dismissed. It is true that this thesis has shown that these drugs do elevate mean cerebral tissue Po_2 but the amount of the increase is small, being of the order of only 20 mm.Hg. This together with the low solubility of oxygen in tissue establishes the point that the consequent increase in cerebral oxygen storage could have only a marginal effect on the safe duration of cerebral circulatory arrest. However the combined use of hyperbaric oxygen and volatile anaesthetic drugs may elevate mean tissue Po_2 sufficiently to significantly affect cerebral oxygen storage (McDowall, Jennett, Bloor & Ledingham, 1966).

The finding which has the greatest likelihood of being clinically important is the observed reduction in cerebral oxygen consumption with halothane and trichloroethylene. The fall in oxygen consumption has been shown to be related to the concentration of halothane administered and therefore to the depth of anaesthesia. The possibility arises therefore that this reduced oxygen requirement of the brain, particularly during deep anaesthesia, may prolong the period of cerebral circulatory arrest compatible with full neurological recovery.

Unfortunately there has been no controlled experimental study on this

point but since hypothermia also reduces cerebral oxygen requirements (Field, Fuhrman & Martin, 1944; Rosomoff & Holaday, 1954; Adams, Elliot, Sutherland, Wylie & Dunbar, 1956; Bering, Taren, McMurrey & Bernhard, 1956) it is relevant to point out that hypothermia certainly prolongs the period of cerebral ischaemia or hypoxia compatible with neuronal survival (Loughheed & Kahn, 1955; Owens, Sawyers & Ward, 1956; Rosomoff, 1956; Jacobson & Lawson, 1963; Campkin, 1965). It may be therefore that anaesthesia with these volatile anaesthetics will confer a degree of protection to the brain during ischaemia and hypoxia in the same way and for the same reason as does hypothermia. Indeed some quantitative predictions may be made on the basis of the data presented in this thesis and the equivalent data from the literature on hyopthermia. General body hypothermia to 28-30°C. appears to reduce cerebral oxygen uptake by 50% (Rosomoff & Holaday, 1954; Adams et al., 1956) while 2% halothane reduces oxygen uptake by 33%. Since hypothermia to 28°C. increases the safe duration of circulatory arrest in dogs by a factor of 3 (Smith, Ledingham, Norman, Douglas, Bates & Lee, 1963) it may be that 2% halothane will approximately double the duration of safe circulatory arrest at normothermia. Since it has been shown that the degree of depression of cerebral oxygen uptake is a function of halothane concentration it is likely that 4% halothane will provide even greater protection.

Although throughout the above discussion, the protection afforded to brain by halothane on account of depressed cerebral oxygen consumption has been considered in terms of total circulatory arrest, similar protection would be expected also in patients with regional ischaemia due to surgical interruption of the cerebral circulation or to pre-existing cerebral arteriosclerosis. In the case of deliberate drug induced hypotension, it

is known that the great majority of patients tolerate the reduction in cerebral perfusion pressure without neuronal damage because of the efficiency of cerebral autoregulation (Enderby, 1961; Eckenhoff, Enderby, Larson, Davies & Judevine, 1963). However tragedies occasionally occur and it is likely that anaesthesia with halothane would provide an extra margin of safety.

During the time that the work for this thesis has been in progress, two reports have appeared in which it has been suggested that general anaesthesia with volatile anaesthetic drugs protects the brain from regional ischaemia during elective temporary occlusion of the internal carotid artery (Wells, Keats & Cooley, 1963; Lyons et al., 1964). After the presentation of the second of these papers, Spencer (1964) commented "I would seriously doubt that the oxygen metabolism of the brain is changed (by general anaesthesia) and have not seen any data to prove this concept". The present thesis provides the necessary evidence to substantiate this clinical approach to the problem of temporary cerebral ischaemia.

AUTHOR'S WORK

PART II

Studies of the Influence of Volatile Anaesthetic Drugs on Cerebrospinal and Cerebral Venous Pressures

CHAPTER 1

Introduction to Part II of Thesis

In Part I, it was shown that halothane, trichloroethylene (during the first 20 minutes of its administration) and chloroform increase cerebral cortical blood flow and it was suggested that one clinically relevant consequence of this blood flow increase might be that cerebrospinal fluid pressure would be elevated. A search of the literature at the time of starting these investigations revealed that it was generally believed that anaesthetic agents did not appreciably affect cerebrospinal fluid pressure (Bozza, Maspes & Rossanda, 1961) though some authorities excluded ether from this generalisation (~~xxxxxxxxxxxxx~~ Woringer, Brogly & Dorgler, 1954; Lundberg, Kjallquist & Bien, 1959).

As regards the anaesthetic agents which are to be examined in this thesis, trichloroethylene was generally thought to be without effect on c.s.f. pressure (Woringer, Brogly & Schneider, 1951; Sondergard, 1961) though Hunter (1964) disagreed with this view. There was some evidence, fully reviewed subsequently, that halothane increased c.s.f. pressure though the amount of the increase and its mechanism were disputed. From the clinical point of view, Brindle, Gilbert & Millar (1957) had advocated the use of halothane in neurosurgery because of its "freedom from increases in cerebrovenous and cerebrospinal fluid pressures". One of the surprising features of all the previous literature was the absence of any attempt to differentiate between the effects of these drugs in patients with intracranial tumours from the effects in patients without intracranial pathology.

Some of the studies did indeed study patients of both groups but the results were not separately considered. Finally with respect to chloroform, there had been no recent study of the influence of this drug on c.s.f. pressure and most of the older evidence was difficult to interpret because of the hypotension, hypercapnia and hypoxia which accompanied the administration of this drug in air to spontaneously breathing animals.

The investigations of this Part of the thesis fall into three parts:-

(1) an initial study on the effects of halothane and chloroform in dogs

(2) an investigation of the influence of halothane and trichloroethylene on c.s.f. pressure in patients without intracranial pathology

and (3) a study of halothane on intracranial pressure in patients with intracranial tumours.

CHAPTER 2

The Influence of Halothane and Chloroform on Cerebrospinal Fluid, Cerebral Venous and Central Venous Pressures in Dogs

(a) Methodology

Eight unpremedicated, mongrel dogs were studied; in 3 of these the study was abandoned for technical reasons (see Table App. 29). Anaesthesia was induced with a sleep dose of thiopentone and maintained with 70% nitrous oxide and 30% oxygen. Orotrachael intubation was performed and ventilation was controlled using an automatic ventilator. To allow control of ventilation, muscular paralysis was produced with suxamethonium chloride administered as required intravenously diluted in saline to a concentration of 1 mg./cc.

A catheter was inserted into one femoral artery and advanced until its tip lay in the abdominal aorta; this catheter was employed for the measurement of mean arterial blood pressure with a damped mercury manometer and for the sampling of arterial blood.

A flexible plastic catheter was placed in the cisterna magna. This catheter was of the type which consists of a central metal needle and an outer plastic cannula ("Branula"). The dog's head was fully flexed, a short incision was made in the skin at the back of the neck and the combined needle and cannula inserted into the cisterna magna through the atlanto occipital membrane. The central needle was then withdrawn leaving only the flexible catheter in the cisterna magna. Slowly the dog's neck was extended to return the head to its normal position.

In 2 animals (dogs nos. 8 & 9) after reflection of skin and muscle, a midline trephine hole was made in the skull overlying the superior sagittal sinus near its midpoint. A metal cannula was inserted into the sagittal sinus to allow measurement of the venous pressure within this vessel; this pressure will hereafter be referred to as the cerebral venous pressure.

In experiments 2, 5 and 8 central venous pressure was measured via a catheter passed via one external jugular vein into the great veins of the thorax.

In experiments 1, 2 and 5 measurement of c.s.f. and central venous pressures was accomplished with simple narrow bore saline manometers. In experiments 8 and 9, c.s.f., cerebral venous and central venous pressures were measured with pressure transducers (Statham gauges) connected to suitable amplifiers (Devices) and thence to an ultraviolet recorder (SE Laboratories Ltd.). Calibration of the pressure records was performed at the beginning and at intervals of half an hour during the experiment by reference to a water manometer. Subsequently the UV record was plotted onto arithmetical graph paper and it is these plots which are shown in the accompanying illustrative figures.

Once the surgical preparations had been completed no measurements were made until a time of 3 hours had elapsed since the induction dose of thiopentone. During this time ventilation was adjusted to produce an arterial Pco_2 of near 40 mm.Hg., as measured by the technique of Andersen et al. (1960). The environmental temperature of the animal was adjusted so that the pharyngeal temperature of the dog was close to 38°C.

Control measurements of all parameters (i.e. during nitrous oxide-oxygen anaesthesia, suxamethonium paralysis and controlled ventilation) were made. Then either halothane (Experiments 2, 5, 8 & 9) or chloroform (Experiments

1 and 2) was introduced into the anaesthetic gases from the same calibrated vaporisers as those used in the blood flow studies. The subsequent changes in c.s.f., cerebral venous and central venous pressures were followed and recorded. Halothane or chloroform administration was then discontinued and further pressure measurements made. The exact protocol differed from experiment to experiment and will be described as each experiment is discussed.

(b) Detailed Description of Methodology

Much of the methodology of these experiments was the same as that used for the cerebral blood flow experiments and so has already been discussed in detail. The additional features of these pressure studies were the use of sagittal sinus pressure measurements as an index of cerebral venous pressure, the measurement of c.s.f. pressure in the cisterna magna and the measurement of central venous pressure.

The insertion of a cannula in the sagittal sinus might have altered the venous pressure by producing partial obstruction to the blood flow within the sinus. Although narrow cannulae were employed it cannot be denied that the presence of the cannula in the relatively rigid sinus must have to a degree impeded flow. However the elevation in venous pressure produced must have been small because in experiment 9, c.s.f. pressure was measured prior to and subsequent to placement of the sagittal sinus cannula and no detectable alteration in c.s.f. pressure occurred. Since elevating cerebral venous pressure increases c.s.f. pressure (Becht, 1920) this lack of change in c.s.f. pressure indicates negligible change in cerebral venous pressure as a result of the placement of the sagittal sinus cannula. Bedford (1935) agrees that a cannula in the superior sagittal sinus of the dog is unlikely to produce significant venous obstruction.

The bone overlying the sagittal sinus was removed to allow exposure of the sinus. It is very unlikely that this altered the venous pressure within the sinus or the intracranial pressure because the diameter of the trephine used was only 1 cm. and because the superior wall of the sinus in the dog is so fibrous and non-elastic. To exclude this possibility, however, in dog 9 the skull defect over the sagittal sinus was closed with

dental cement.

The cannula in the cisterna magna would not be expected to alter intracranial dynamics unless c.s.f. escaped around or through the cannula or unless the cannula produced bleeding into the c.s.f. Leakage of c.s.f. was considered to be likely if the cannula, having once been in the cisterna magna became dislodged and hence one experiment was abandoned (dog.No. 4) when the cannula came out of the sinus during manipulation of the animal's head. Great care was taken at the time of connecting the c.s.f. cannula to the pressure measuring circuit that c.s.f. was not lost from the skull. This was done by filling the dead space of all catheters and taps with saline prior to connection to the cisterna magna catheter. At the end of each experiment, 1 cc. of c.s.f. was aspirated to determine whether bleeding had occurred into the c.s.f.; this was not found in any of these experiments.

The measurement of central venous pressure via a catheter passed into the great veins of the thorax is of course a well established technique.

EXPT. NO.	C.S.F. PRESSURE				Pa_{CO_2}
	CONTROL ($N_2O + O_2$)	DURING 0.5% HALOTHANE	AFTER 0.5% HALOTHANE	INCREASE WITH 0.5% HALOTHANE	
2	139	212	141	+ 73	37
5	183	264	71	+ 81	43
5	83	194	106	+ 111	48
8	170	210	160	+ 40	43
8	140	199	-	+ 59	44
9	146	251	118	+ 105	38
MEANS	144 ±35	222 ±29	119 ±34	+ 78 ± 27	42.2 ±4.1

Table 38 The effect of 0.5% halothane on c.s.f. pressure (mm. H_2O) during normocapnia in dogs.

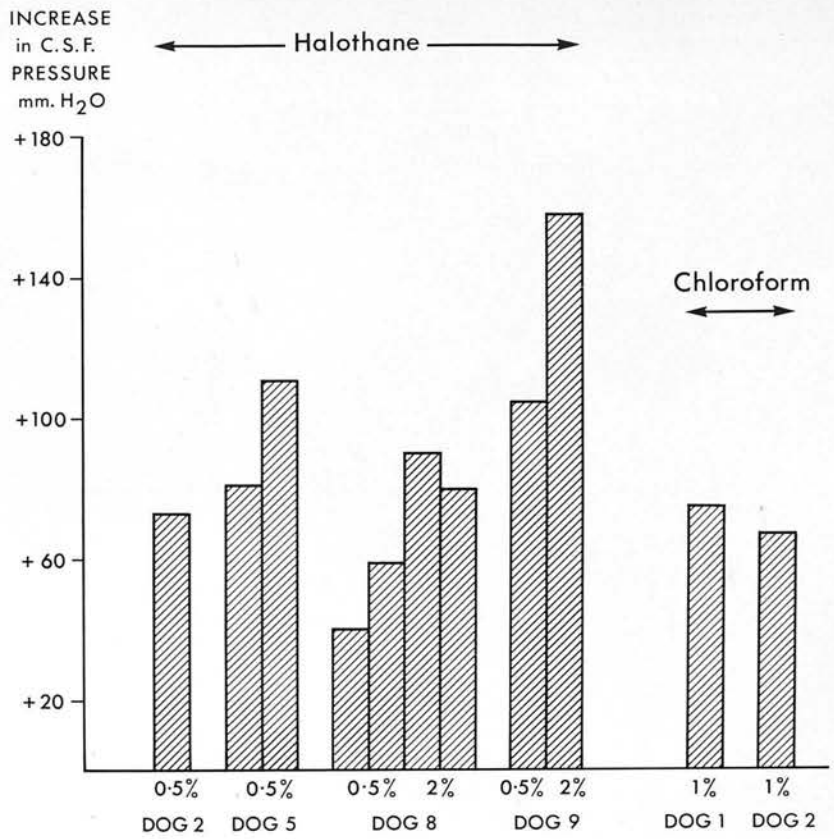


Figure 16 The increases in c.s.f. pressure produced by 0.5% and 2% halothane and by 1% chloroform in dogs. 2% halothane caused a greater rise in c.s.f. pressure than did 0.5% in the 2 animals in which both concentrations were administered.

EXPT. NO.	% HALOTHANE	INCREASE IN C.S.F. PRESSURE	INCREASE IN CEREBRAL VENOUS PRESSURE
8	0.5%	+ 40	-
8	2.0%	+ 90	+ 120
8	0.5%	+ 59	+ 60
8	2.0%	+ 80	+ 80
9	0.5%	+ 105	-
9	2.0%	+ 158	+ 140

Table 39 The effects of 0.5% and 2.0% halothane on c.s.f. and cerebral venous pressures (mm. H_2O) in dogs.

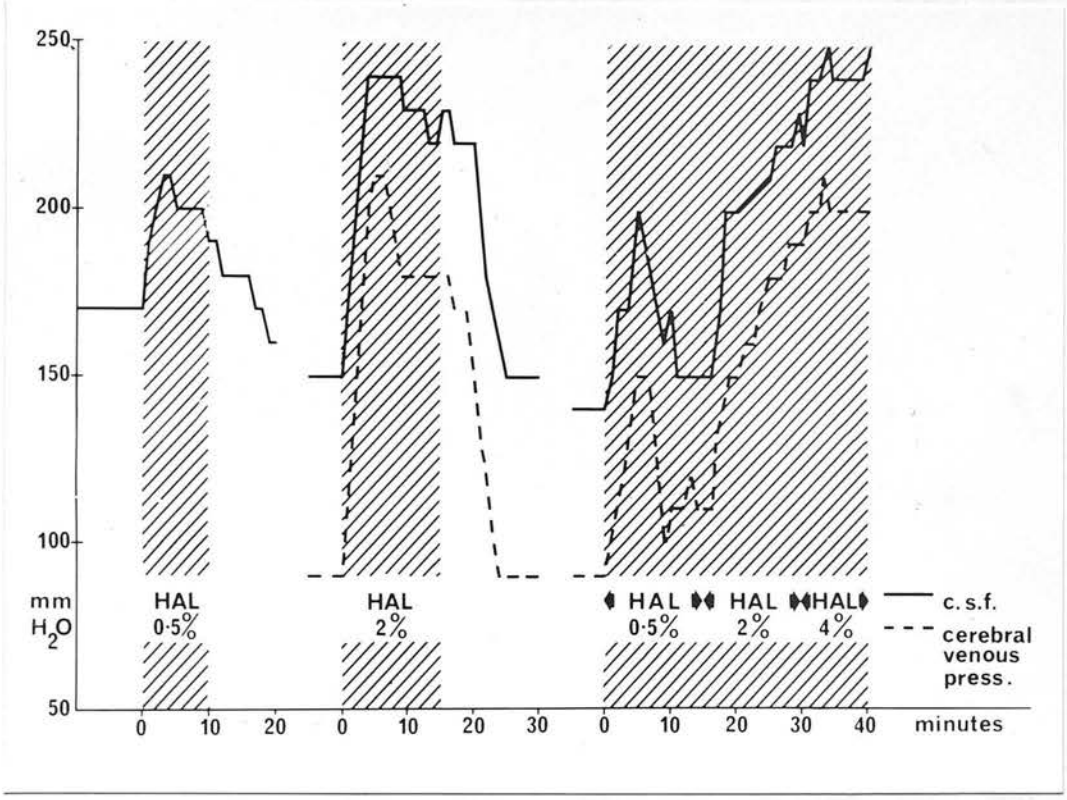


Figure 17 c.s.f. and cerebral venous pressure records from Dog 8. Both 0.5% and 2% halothane increased c.s.f. and cerebral venous pressures but the increases were greater with the higher halothane concentration. The halothane induced changes in these pressures were not well maintained with time.

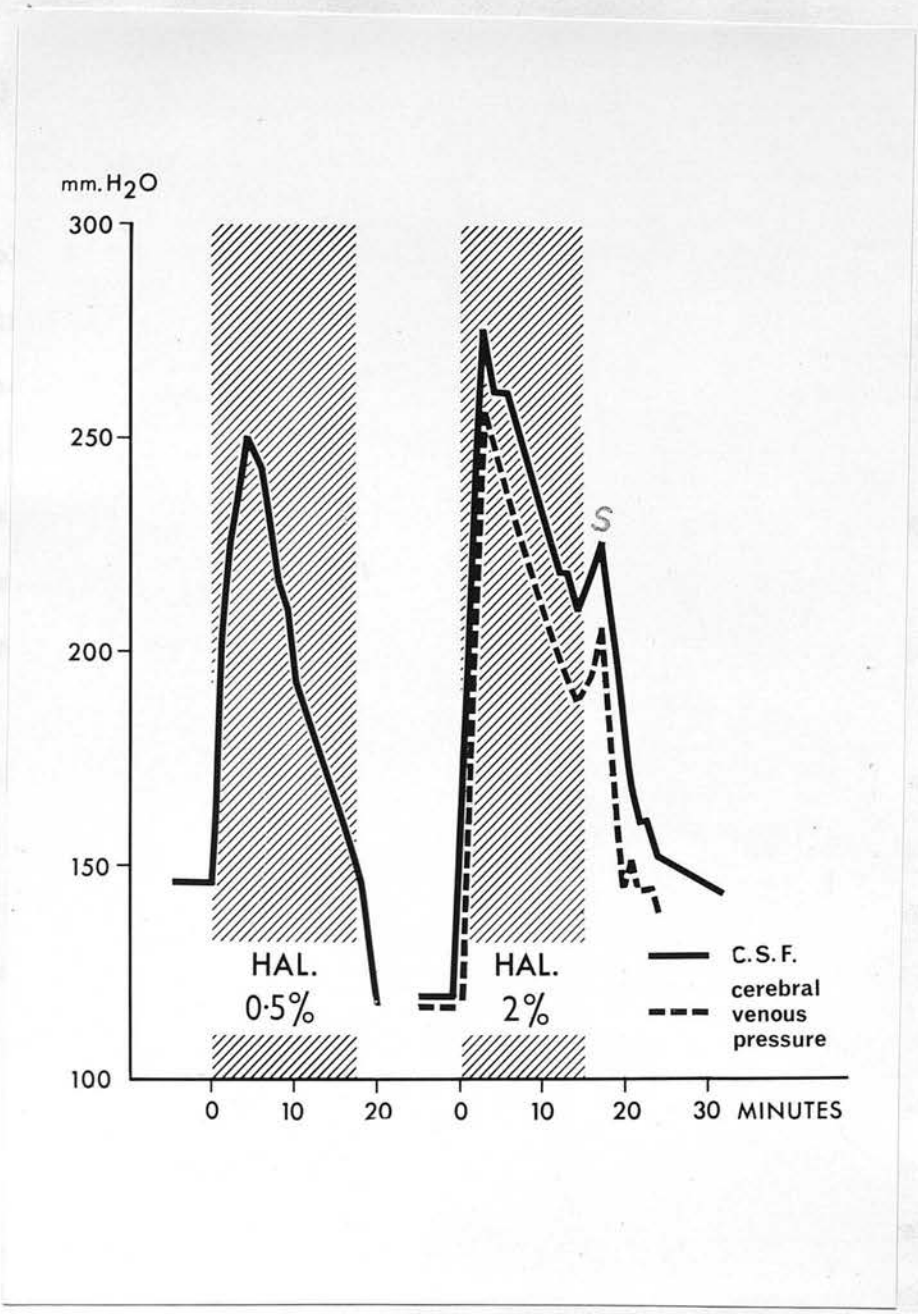


Figure 18 c.s.f. and cerebral venous pressure records from Dog 9. Halothane administration produced relatively short lived increases in these pressures. The small increase in both c.s.f. and cerebral venous pressures marked (S) corresponded to the intravenous injection of suxamethonium chloride.

(c) Results

(1) The Effect of Halothane on c.s.f., Cerebral Venous and Central Venous Pressures

Table 38 gives the values for c.s.f. pressure before, during and after administration of 0.5% halothane. It will be seen that in each experiment there was an increase in c.s.f. pressure during halothane administration (see also Figure 16) and that the pressure fell again on stopping the drug. The mean control value for c.s.f. pressure was 144 $\pm$ 35 mms.H20 and the mean increase with 0.5% halothane was of 78 $\pm$ 27 mms.H20.

These results were obtained at arterial Pco_2 values within the normal range. However in dog 2, $Paco_2$ was subsequently lowered from 37 mm.Hg. to 27 mm.Hg. by hyperventilation. With the reduction in $Paco_2$, c.s.f. pressure during nitrous oxide-oxygen anaesthesia fell from a mean of 139 mm.H20 to a mean of 76 mm.H20. When 0.5% halothane was administered under these circumstances, c.s.f. pressure rose by only 18 mm.H20 as compared with a rise of 73 mm.H20 during normocapnia.

In dogs 8 and 9, the effects of 0.5% and 2% halothane on c.s.f. and cerebral venous pressure were measured and compared. The results are presented in Table 39. It will be seen that both c.s.f. and cerebral venous pressure rose when halothane was administered and that the rise of both pressures was greater with the higher concentration of the drug (see also Figs. 17 & 18). From Table 39 it can also be clearly seen that the increases in c.s.f. pressure were very similar in magnitude to the increases in cerebral venous pressure during halothane administration.

Individual records of these two experiments are shown in Figures 17 and 18 and close scrutiny of these records reveals the interesting point

EXPT. NO.	% HALOTHANE	DURATION OF HALOTHANE	TIME TO 1st PRESSURE CHANGE	TIME TO PEAK PRESSURE	PRESSURE CHANGE AFTER PEAK
2	0.5%	16 mins.	1 min.	13 mins.	PRESSURE RISE MAINTAINED 13–16 mins.
5	0.5%	1 hr. 40 mins.	1 min.	9 mins.	PRESSURE DECLINED AFTER PEAK
5	0.5%	6 mins.	1 min.	4 mins.	INSUFFICIENT TIME FOR OBSERVATION
8	0.5%	10 mins.	1 min.	3 mins.	PRESSURE DECLINED AFTER PEAK
8	2%	15 mins.	1 min.	4 mins.	PRESSURE DECLINED AFTER PEAK
9	0.5%	17 mins.	1 min.	4 mins.	PRESSURE DECLINED AFTER PEAK
9	2%	15 mins.	1 min.	3 mins.	PRESSURE DECLINED AFTER PEAK

Table 40 Time relationships of c.s.f. pressure changes during halothane administration in dogs.

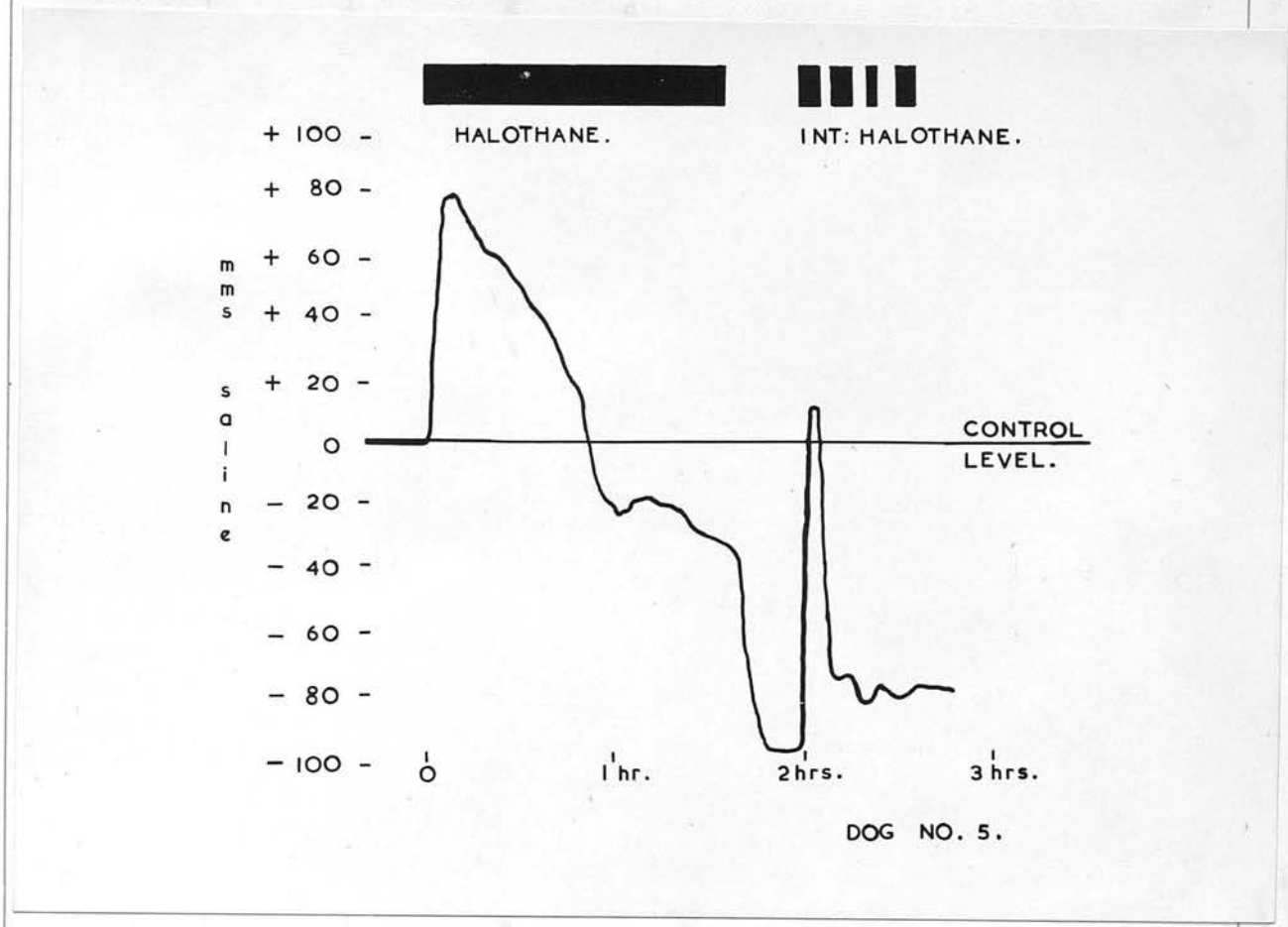


Figure 19 c.s.f. pressure changes with prolonged 0.5% halothane administration in Dog 5. The increase in c.s.f. pressure produced by halothane was not maintained since c.s.f. pressure returned to control values after 52 minutes of halothane administration. Withdrawal of halothane produced a marked fall in c.s.f. pressure to below the initial control values.

EXPERIMENT NO.	CONTROL ($N_2O + O_2$)	DURING 1% CHLOROFORM	AFTER 1% CHLOROFORM	INCREASE WITH 1% CHLOROFORM	Pa_{CO_2}
1	*	*	*	+ 75	38
2	141	208	109	+ 67	37

Table 41 The effect of 1% chloroform on c.s.f. pressure (mm. H_2O during normocapnia in dogs.

(Arbitory zero reference used in the first experiment)

that the increases in c.s.f. and in cerebral venous pressures were not well maintained. With both pressures, the peak increase occurred at between 3 and 5 minutes and was followed by a gradual fall towards baseline values. With 2% halothane[a] similar tendency for c.s.f. and cerebral venous pressures to rise to a peak and then to fall despite continuing halothane administration can be discerned. In Table 40 the time relationships of the c.s.f. pressure changes with halothane are given for each experiment; it will be seen that with only one exception, the halothane induced rise in c.s.f. pressure was not maintained beyond 3 - 9 minutes after the commencement of halothane.

This point was further studied in dog 5 in which 0.5% halothane was administered for 1 hour and 40 minutes (see Figure 19). The peak pressure in this animal was attained after 9 minutes of halothane; thereafter a slow fall in c.s.f. pressure occurred so that the pressure had returned to control values after 52 minutes of halothane administration. Withdrawal of halothane caused an abrupt fall in c.s.f. pressure even although at this time pressure was back to control values.

In the two dogs in which central venous pressure was measured (dogs 2 and 5) no significant change occurred with administration of 0.5% halothane.

(2) The Effect of Chloroform on c.s.f. and Central Venous Pressures

In experiments 1 and 2, the administration of 1% chloroform elevated c.s.f. pressure (see Table 41 and Fig. 16). Central venous pressure in experiment 2 rose by 7 mm.H2O during chloroform anaesthesia but at this time the increase in c.s.f. pressure was 67 mm.H2O.

CHAPTER 3

The Influence of Halothane, Trichloroethylene and Chloroform on Cerebral and Central Venous Pressure in Dogs with Open Dura

(a) Methodology

In addition to the above experiments in which a specific study was made of the relationship between c.s.f. and cerebral venous pressure, a number of animals in the blood flow series of experiments also had cerebral venous pressure measured. It should be emphasised that in these animals the dura had been opened. Consequently, due to the escape of c.s.f., both c.s.f. and cerebral venous pressures were reduced below their normal values. Furthermore since any rise in cerebral venous pressure would tend to be cushioned by displacement of c.s.f. out through the open dura these measurements, unlike those just described above, can only be considered to indicate in a qualitative fashion the direction of change in cerebral venous pressure during anaesthesia with the drugs under study.

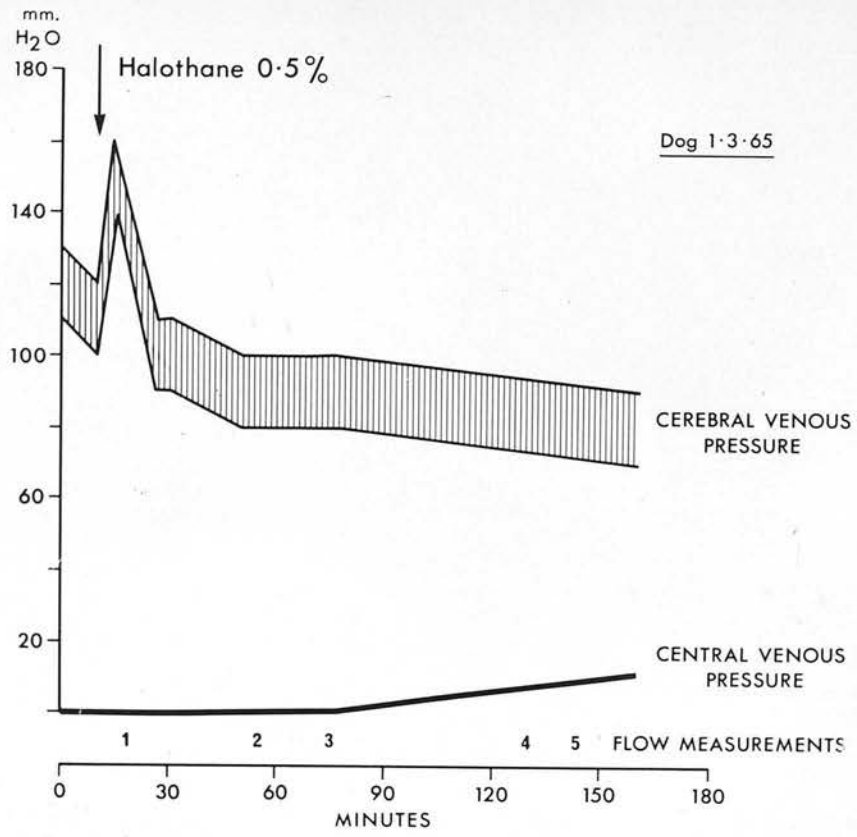


Figure 20 0.5% halothane administration in this dog produced a brief rise in cerebral venous pressure. Cerebral cortical blood flow was measured when the venous pressure increase was subsiding and was found to be not different from control values. (The figures at the foot of the record indicate the times of measurement of cerebral cortical blood flow).

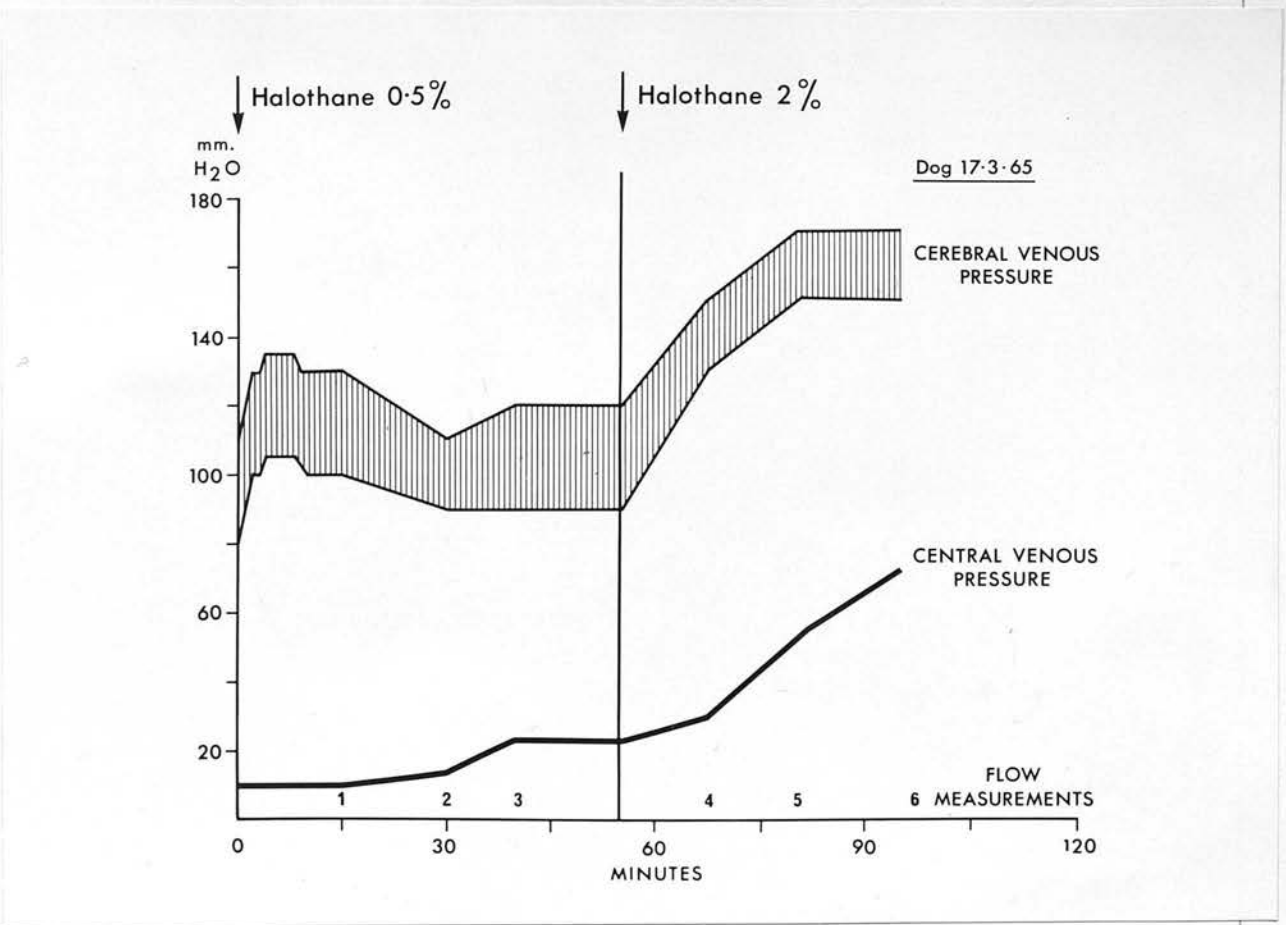


Figure 21 The rise in cerebral venous pressure with 0.5% halothane in this animal was accompanied by a marked increase in cerebral cortical blood flow. 2% halothane increased cerebral venous pressure further but this was probably related to the concomitant increase in central venous pressure since there was no further alteration in cerebral blood flow. (The figures at the foot of the record indicate the times of measurement of cerebral cortical blood flow).

(b) Results in Animals with Open Dura

Halothane

Measurements of cerebral venous and central venous pressures were made in two animals (1/3/65 and 17/3/65) prior to and during halothane administration. The results are shown in Figures 20 and 21.

In the first of these (Figure 20) there was a short-lived increase in cerebral venous pressure with the introduction of 0.5% halothane into the anaesthetic mixture at a time when there was no alteration in central venous pressure. The first measurement of cerebral cortical blood flow under halothane in this animal was not made until 6 minutes after the commencement of halothane administration by which time cerebral venous pressure was already falling from its peak value and in fact this flow measurement showed no significant change on control values

In the other animal (Fig. 21) there was also a quick increase in cerebral venous pressure with halothane and a concomitant flow measurement showed that flow was above control values. When 2% halothane was administered cerebral blood flow did not increase further in this particular animal but cerebral venous pressure increased again. However measurement of central venous pressure showed that it also had risen and in fact the increase in central venous pressure (+50 mm.H20) almost certainly accounted for the change in cerebral venous pressure (+57 mm.H20) in this animal.

Trichloroethylene

Cerebral venous pressure was measured in 5 animals during cerebral blood flow studies. The results of these measurements are given in Table

DATE	$N_2O + O_2$		TRICHLOROETHYLENE	
	BLOOD FLOW	CEREBRAL VENOUS PRESSURE	BLOOD FLOW	CEREBRAL VENOUS PRESSURE
7/5/63	0.74 0.79 0.67	7.0 4.0 4.0	1.11 0.87 0.71 0.61 0.80 0.79 0.76	12.0 10.0 7.0 5.0 4.0 6.0 5.5
9/5/63	0.73 0.80 0.79	5.5 4.0 5.0	0.96 0.90 0.81 0.76	7.0 8.0 7.0 8.0
13/5/63	0.71 0.82 0.80	10.0 10.0 8.0	0.77 0.79 0.70 0.80 0.76	8.0 7.0 7.0 8.0 7.0
20/6/63	0.84 0.76 0.72	4.0 3.0 3.0	0.58 0.54 0.61 0.58 0.60 0.61 0.60 0.62	4.0 3.0 4.0 5.0 6.0 5.0 5.0 6.0
27/6/63	0.53 0.57 0.58	4.0 5.0 5.0	0.59 0.54 0.58 0.61 0.53	5.0 6.0 6.0 6.0 6.0
MEANS	0.72 ±0.10	5.4 ±2.3	0.71 ±0.14	6.3 ±1.9

Table 42 Cerebral cortical blood flow (mls./G/min.) and cerebral venous pressure (cm. H_2O) during nitrous oxide-oxygen anaesthesia and during anaesthesia with trichloroethylene in nitrous oxide-oxygen in dogs.

EXPERIMENT DATE	$N_2O + O_2$		1% CHLOROFORM	
	BLOOD FLOW	CEREBRAL VENOUS PRESSURE	BLOOD FLOW	CEREBRAL VENOUS PRESSURE
11/10/63	0.64 0.61	6.0 5.0	1.00 0.86 0.82	9.0 16.0 16.0
18/10/63	0.54 0.54 0.56	5.0 5.0 7.0	0.64 0.69	11.0 14.0
26/10/63	0.70 0.59 0.67 0.68	14.0 8.0 7.0 9.0	0.95	17.0
19/8/64	0.83 0.83 0.86	8.0 8.0 8.0	1.23 1.36 1.36 1.15	- 13.0 13.5 18.0
MEANS	0.67 $\pm$0.11	7.5 $\pm$2.5	1.01*** $\pm$0.26	14.2*** $\pm$2.9

Table 43 Cerebral cortical blood flow (mls./G/min.) and cerebral venous pressure (cms. H_2O) during nitrous oxide-oxygen anaesthesia and during anaesthesia with 1% chloroform in nitrous oxide-oxygen in dogs.

(* = $p < .05$; ** = $p < .01$; *** = $p < .001$)

42 from which it can be seen that marked increases in cerebral venous pressure occurred in the 2 animals which exhibited the greatest flow increases in the early period of trichloroethylene administration (7/5/63 and 9/5/63). However the mean cerebral venous pressure during trichloroethylene anaesthesia (6.3 $\pm$ 1.9 cms.H20) was not significantly different from the mean cerebral venous pressure during nitrous oxide-oxygen anaesthesia (5.4 $\pm$ 2.3 cms.H20). There was no significant change in cerebral cortical blood flow in this group of animals either (Table 42).

Chloroform

Measurements of cerebral venous pressure during the administration of 1% chloroform were made in 4 animals. In every case the administration of chloroform produced a marked rise in cerebral venous pressure which paralleled the increases in cerebral blood flow simultaneously measured (see Table 43). The mean cerebral venous pressure during chloroform anaesthesia was 14.2 $\pm$ 2.9 cms.H20, while the mean control value was 7.5 $\pm$ 2.5 cms.H20; this increase with chloroform was highly significant ($p < .001$).

CHAPTER 4

Summary of Main Findings of Studies of Cerebrospinal Fluid, Cerebral Venous and Central Venous Pressures in Dogs

Discussion of these animal results will be deferred so that they may be considered along with the investigations in man to be described below. At this point the findings will only be summarised thus:-

(1) halothane and chloroform elevate c.s.f. pressure in anaesthetised dogs at constant $Paco_2$

(2) in the case of halothane the increase in c.s.f. pressure has been shown to be dependent upon the concentration of halothane administered and the existing arterial Pco_2.

(3) halothane, chloroform and early trichloroethylene elevate cerebral venous pressure and the changes appear normally to be related to changes in measured blood flow through the cerebral cortex. However in one instance the increase in cerebral venous pressure during 2% halothane was due to a rise in central venous pressure.

(4) with halothane it has been shown that the elevations in c.s.f. and in cerebral venous pressure produced by halothane are very similar in magnitude.

(5) the increases in c.s.f. and cerebral venous pressures with halothane are not maintained with time but tend to return to their control values despite continuing halothane administration.

CHAPTER 5

The Influence of Halothane and Trichloroethylene on Cerebrospinal Fluid Pressure in Patients without Intracranial Pathology

(a) Methodology

The effect of halothane (0.5% or 1%) or of trichloroethylene (0.9%) on lumbar c.s.f. pressure and on central venous pressure was studied in 35 patients anaesthetised for surgical treatment of lumbar disc lesions. All patients studied had given their free consent to the investigation. Of these 35 patients, the records from 11 patients were discarded for the reasons stated in Table App. 30. Details of the remaining 24 patients as regards age, sex and investigation performed are given in Table App. 31.

The patients were premedicated with 100 mgs. of pethidine and 0.6 mg. of atropine one hour before operation. Induction of anaesthesia was performed with a dose of thiopentone just sufficient to produce sleep. Suxamethonium chloride was administered and, under the resultant muscular paralysis, orotracheal intubation with a flexometalic cuffed tube was performed. A thermocouple lead was passed into the oesophagus for the measurement of mid oesophageal temperature. Ventilation was controlled using an automatic ventilator ("Barnet") and anaesthesia maintained with 70% nitrous oxide and 30% oxygen. When recovery of muscle tone from the effects of suxamethonium was seen, a dose of tubocurarine between 35 and 55 mgs. according to the size of the patient was administered to produce prolonged muscular paralysis. A plastic catheter was inserted into an antecubital vein and advanced until its tip was within the subclavian vein

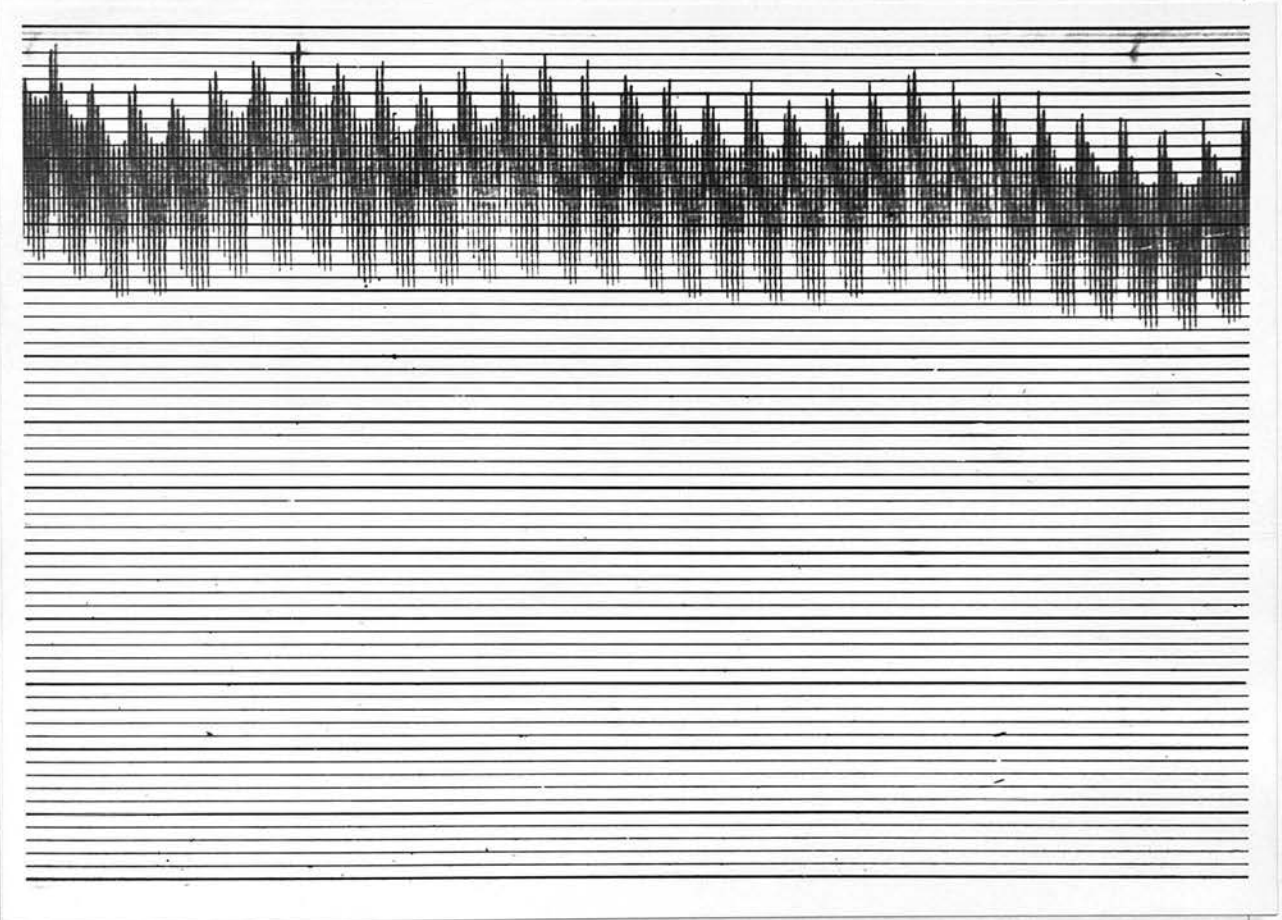


Figure 22 Photograph of record of c.s.f. pressure as obtained with Statham pressure transducer and ultraviolet recorder.

as judged by measurement and by examination of the venous pressure record. This site was chosen as the most distal likely to give a true measurement of central venous pressure.

The patient was then turned into the lateral position and, under full aseptic precautions, a lumbar puncture needle was inserted into the lumbar subarachnoid space, great care being taken to avoid loss of more than a few drops of c.s.f. All measurements were made with the patient in the lateral position.

The minute volume of ventilation was adjusted according to an estimate of the patients weight and on most occasions a $Paco_2$ of between 35 and 45 mm.Hg. was attained. Time limitations prevented subsequent alterations in minute volume. However in some of the later investigations an infra red analyser allowed measurement of end tidal Pco_2 and so facilitated the correct setting of minute volume. An electric blanket was placed over the patient to reduce the fall in body temperature which tended to occur under anaesthesia.

C.s.f. and central venous pressures were measured in the early studies with simple saline manometers but latterly with electronic pressure transducers, amplifiers and recorders. Those results based on measurements with saline manometers are marked distinctively in the detailed Appendix Tables. The zero reference for all pressure measurements was taken as the midline of the back with the patient in the lateral position. The records of c.s.f. pressure showed pulsations at the same rate as the heart beat and also slower variations in time with the respiratory phases of the ventilator. An example of the record obtained from the ultraviolet recorder is shown in Figure 22. When analysing these results c.s.f. pressures at both systole and diastole were plotted during the expiratory

pause of the ventilator. Mean c.s.f. pressure was calculated as being equal to the diastolic c.s.f. pressure plus one third of the pulse pressure of the c.s.f.

Capillary blood samples were taken from the finger tip before and after the 10 minute period of administration of the volatile anaesthetic and were measured for pH and Pco_2 by the technique of Andersen et al.(1960). The results were corrected for the difference in temperature between the patient and the pH electrode by application of Rosenthal's (1948) factor. The mean oesophageal temperature during the period of pressure measurement was 35.7 $\pm$ 0.8°C (range 34.2 - 37.3°C). Systolic blood pressure was measured intermittently by upper arm sphgmomamometry.

Measurements of c.s.f., central venous and systolic blood pressure were made during unsupplemented nitrous oxide-oxygen anaesthesia. The volatile agent under study, either halothane or trichloroethylene, was then introduced from a calibrated vapouriser (Fluotec Mk II) and the changes in these pressures followed, for 10 minutes. The volatile drug was then discontinued and the pressures recorded for a further 5- 10 minutes.

PATIENT	MEAN C.S.F. PRESSURE				Pa_{CO_2}
	CONTROL $N_2O + O_2$	DURING 0.5% HALOTHANE	AFTER 0.5% HALOTHANE	INCREASE WITH 0.5% HALOTHANE	
6	214	257	205	+ 43	39
14	21	73	29	+ 52	43
16	125	172	-	+ 47	45
17	88	214	80	+126	40
32	129	204	-	+ 75	39
38	190	270	207	+ 80	37
40	100	139	83	+ 39	39
43	114	161	136	+ 47	46
MEANS	123 ±60	186 ±64	123 ±72	64 ±29	41.0 ±3.3

Table 44 The effect of 0.5% halothane on mean c.s.f. pressure (mm. H_2O) in patients during normocapnia.

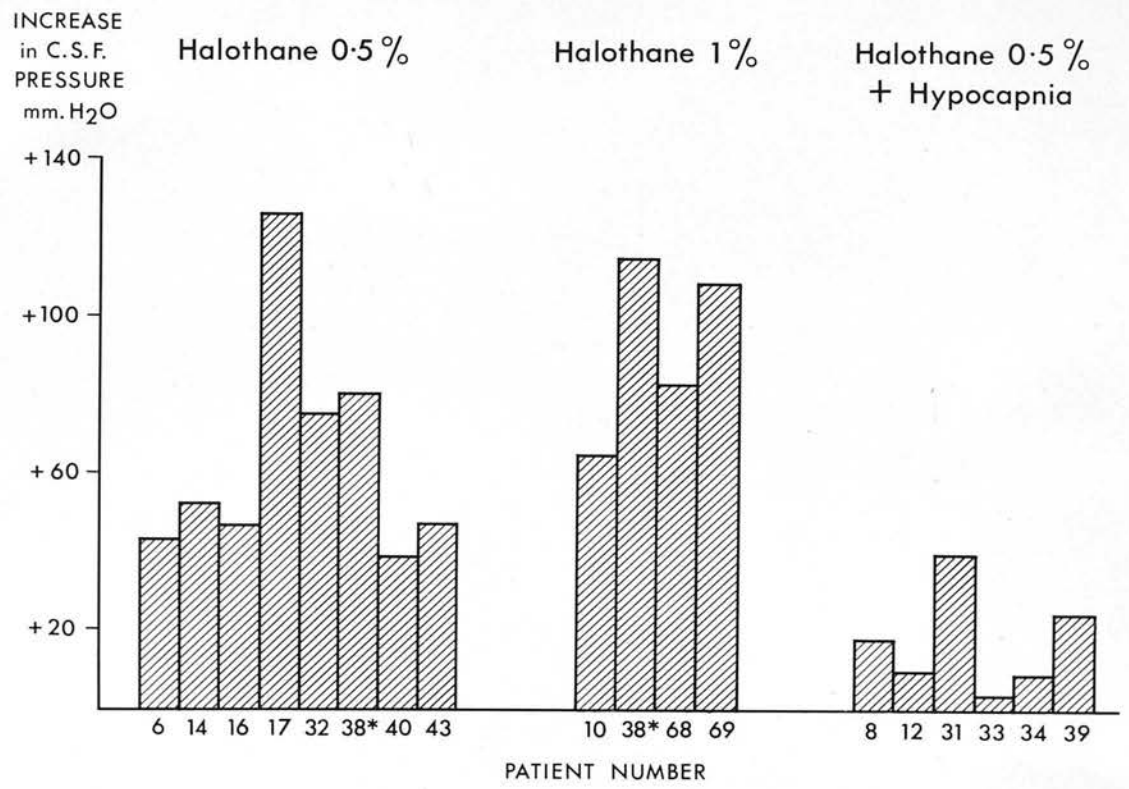


Figure 23 The increases in lumbar c.s.f. pressure produced by halothane in patients. In the one patient to whom both concentrations of halothane were administered, 1% halothane caused a greater rise than 0.5%. The administration of halothane during hypocapnia produced only small increases in c.s.f. pressure.

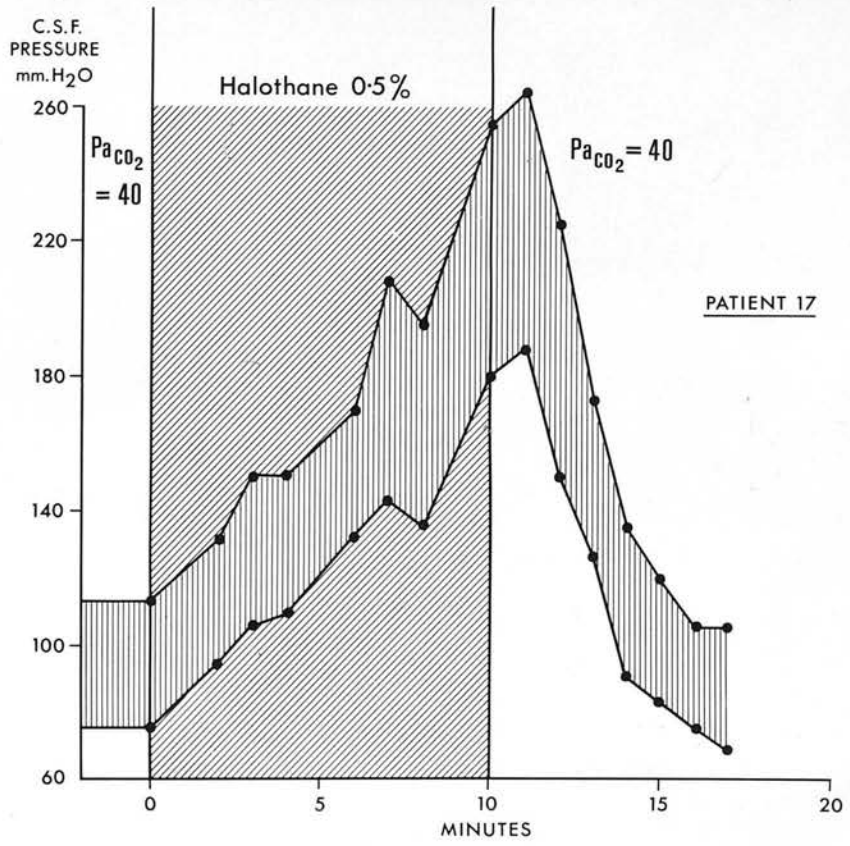


Figure 24 A typical plot from one patient of the c.s.f. pressure changes produced by 0.5% halothane administration at constant Paco2.

(b) Results

The Influence of Halothane on c.s.f. Pressure in Man

(1) 0.5% Halothane during Normocapnia

The influence of 0.5% halothane during normocapnia on c.s.f. pressure was studied in 8 patients and, in 4, central venous pressure was also measured. The detailed results of all measurements are given in Table App. 32. The arterial Pco_2 in these patients ranged from 37 to 46 mm.Hg. with a mean value of 41.0 ± 3.3 mm.Hg. The mean c.s.f. pressure before, during and after 0.5% halothane administration for each patient is given in Table 44, from which it will be seen that the administration of 0.5% halothane increased lumbar c.s.f. pressure in every patient studied (see also Figure 23). The mean control c.s.f. pressure in this group was 123 ± 60 mm.H20 with a range from 21 to 214 mm.H20. During administration of 0.5% halothane the mean c.s.f. pressure was 186 ± 64 mm.H20 with a range from 73 to 270 mm.H20. 0.5% halothane therefore caused a mean increase of 64 ± 29 mm.H20 (range + 39 + 126 mm.H20). In 6 of these 8 cases c.s.f. pressure was also measured after stopping halothane and there was a fall to near control values in every case. A typical graph of the c.s.f. pressure changes with 0.5% halothane is shown in Figure 24.

The increase in c.s.f. pressure occurred very quickly after introducing the halothane into the anaesthetic gases - within one minute in 5 cases and within 2 minutes in the other 3. The time to reach peak pressure was very variable (from 3 to 16 minutes) while the return to the baseline occurred within 3 to 10 minutes of discontinuing the halothane.

In an attempt to assess whether the halothane induced rise in c.s.f. pressure was maintained with time, 4 patients were studied for longer

PATIENT	PULSATIONS OF C.S.F.		
	BEFORE	0.5% HAL.	AFTER
14	4	16	6
17	38	77	37
32	53	74	-
38	90	90	80
40	25	42	25
43	64	92	86

Table 45 Amplitude of pulsations of c.s.f. pressure (mm. H_2O) before, during and after the administration of 0.5% halothane in patients.

than 10 minutes (maximum 20 minutes)(Nos. 6, 14/40 and 43). In 2 of these patients c.s.f. pressure reached a peak value and then began to fall despite continuing halothane administration. In the other 2, the halothane induced rise was maintained throughout the 15 and 20 minutes respectively of halothane administration.

As was pointed out in the methodology section, the c.s.f. pressure showed fluctuations at the same rate as the pulse. The magnitude of these fluctuations was measured during unsupplemented nitrous oxide-oxygen anaesthesia and during 0.5% halothane administration; the results are given in Table 45. Patients whose c.s.f. pressure was measured with saline manometers have been excluded from this Table because the heavy damping of this system made the results meaningless except for assessing mean pressure. In addition one patient whose c.s.f. pressure was measured electronically had a "damped" record, probably due to an undetected air bubble in the connecting catheter. Of the remaining 6 patients, the size of the arterial pulsations of the c.s.f. increased with halothane administration in 5; in the 6th there was no change.

Of the 4 patients receiving 0.5% halothane whose central venous pressure was also measured, no change in this pressure occurred in 3. In the 4th central venous pressure rose by 8 mm.H2O at a time when c.s.f. pressure had increased by 80 mm.H2O.

(2) 1% Halothane during Normocapnia

The effect of 1% halothane on c.s.f. pressure was determined in 4 patients and in 3 central venous pressure was also measured. $Paco_2$ was in the range 38 to 45 mm.Hg. Detailed results are presented in Table App. 33. 1% halothane increased c.s.f. pressure in every patient studied

PATIENT	MEAN C.S.F. PRESSURE				Pa_{CO_2}
	CONTROL $N_2O + O_2$	DURING 1% HALOTHANE	AFTER 1% HALOTHANE	INCREASE WITH 1% HALOTHANE	
10	72	137	45	+ 65	45
38	190	305	207	+115	38
68	71	154	54	+ 83	38
69	102	211	79	+109	40
MEANS	109 ±56	202 ±76	96 ±75	93 ±23	40.3 ±3.3

Table 46 The effect of 1% halothane on mean c.s.f. pressure (mm. H_2O) in patients during normocapnia.

PATIENT	PULSATIONS OF C.S.F.		
	BEFORE	1% HAL.	AFTER
38	90	112	80
68	62	106	69
69	37	113	45

Table 47 Amplitude of pulsations of c.s.f. pressure (mm. H_2O) before, during and after the administration of 1% halothane in patients.

PATIENT	MEAN C.S.F. PRESSURE				Pa_{co_2}
	CONTROL ($N_2O + O_2$)	DURING 0.5% HALOTHANE	AFTER 0.5% HALOTHANE	INCREASE WITH 0.5% HALOTHANE	
8	21	39	25	18	27
12	20	30	32	10	29
31	44	84	50	40	31
33	9	13	-	4	21
34	16	25	-	9	34
39	-4	21	-24	25	33
MEANS	18 ±16	35 ±25	21 ±37	18 ±13	29.2 ±4.8

Table 48 The effect of 0.5% halothane on mean c.s.f. (mm. H_2O) in patients during hypocapnia (Pa_{co_2} < 35 mm. Hg.).

(see Table 46 and Figure 23). The mean increase was 93 ± 23 mm.H20 (range +65 to +115 mm.H20). After 1% halothane was discontinued, c.s.f. pressure quickly returned to control values. One of these patients was studied immediately after the administration of 0.5% halothane (Case No. 38). With 0.5% halothane c.s.f. pressure rose from 190 mm.H20 to 270 mm.H20; when the concentration of halothane was increased to 1% c.s.f. pressure rose further to reach 305 mm.H20.

All 3 patients given 1% halothane whose c.s.f. pressures were measured electronically showed an increase in the amplitude of c.s.f. pulsations during halothane administration. (Table 47). Central venous pressure was measured in these three cases; in 2 there was no change with halothane and in the third there was a 1 mm.H20 rise.

(3) 0.5% Halothane during Hypocapnia

In 6 patients the influence of 0.5% halothane on c.s.f. pressure was assessed during hypocapnia ($Paco_2$ < 35 mm.Hg.). In 4 of these patients central venous pressure was also measured. The detailed results are given in Table App. 34 and the mean results in Table 48. The mean $Paco_2$ was 29.2 ± 4.8 mm.Hg. The control level of c.s.f. pressure under nitrous oxide-oxygen anaesthesia was considerably lower in this hypocapnic group than in the normocapnic group (18 ± 16 mm.H20 cf. 123 ± 60 mm.H20). When 0.5% halothane was administered there was in each case a rise in c.s.f. pressure but this was much smaller than the increase found during normocapnia (see also Figure 23). The mean increase was 18 ± 13 mm.H20 at a $Paco_2$ of 29.2 mm.Hg. as compared with a mean increase during normocapnia of 64 ± 29 mm.H20.

Central venous pressure did not change in 2 cases while it rose by +4

and +9 mm.H20 in 2 other instances (cases 31 and 33). The increase in central venous pressure could have entirely accounted for the observed rise in c.s.f. pressure in case 33 but not in case 31.

PATIENT	MEAN C.S.F. PRESSURE				Pa_{CO_2}
	CONTROL $N_2O + O_2$	DURING 0.9% T.C.E.	AFTER 0.9% T.C.E.	INCREASE WITH 0.9% T.C.E.	
18	76	135	84	+ 59	40
21	116	220	102	+ 104	37
22	157	333	197	+ 176	37
24	112	229	106	+ 117	37
25	86	156	107	+ 70	42
MEANS	109 ±32	215 ±78	119 ±45	105 ±46	38.6 ±2.1

Table 49 The effect of 0.9% trichloroethylene on mean c.s.f. pressure (mm. H_2O) in patients during normocapnia.

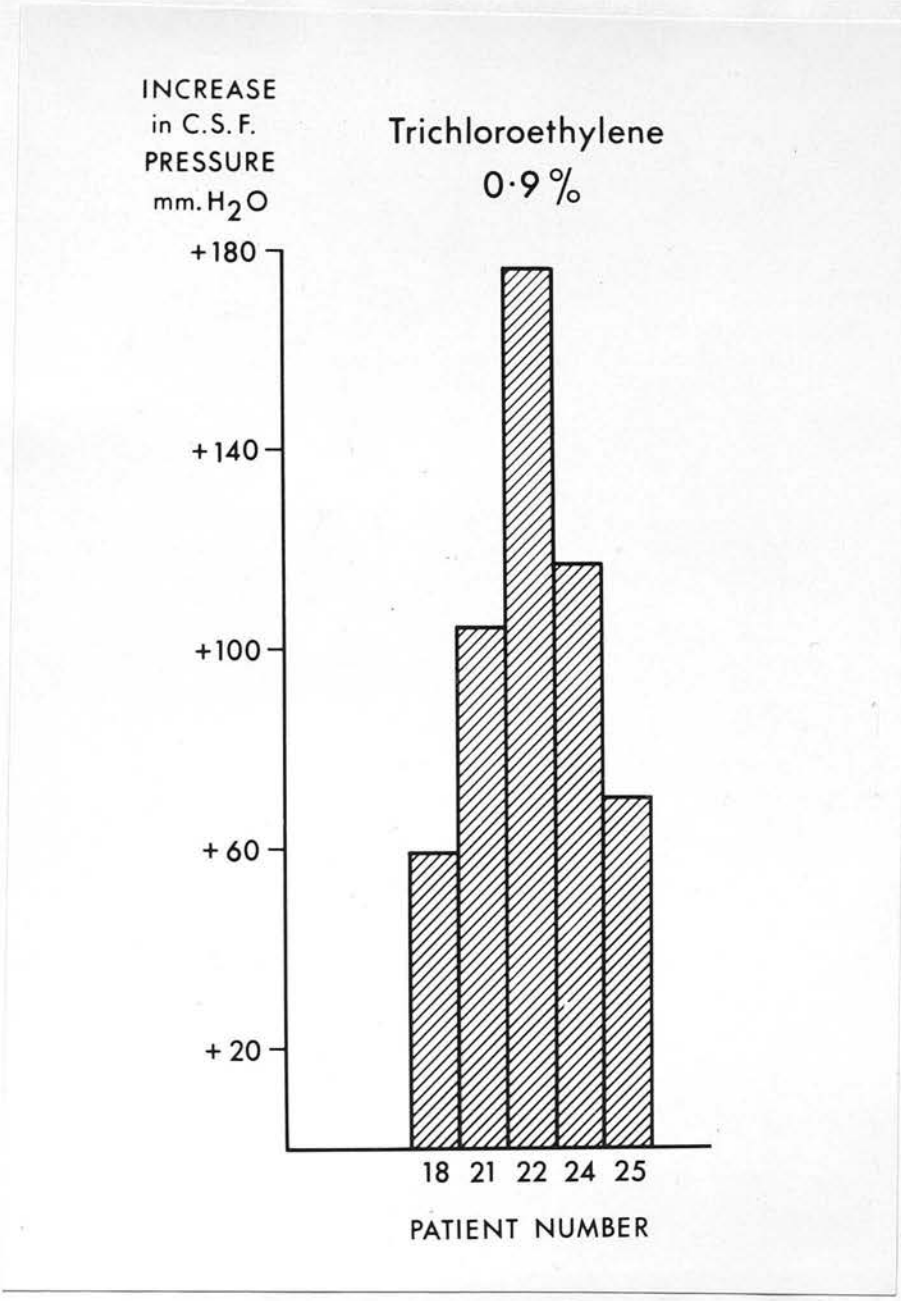


Figure 25 The increases in lumbar c.s.f. pressure produced by 0.9% trichloroethylene administration to patients.

PATIENT	PULSATIONS OF C.S.F.		
	BEFORE	0.9% T.C.E.	AFTER
18	8	14	9
21	24	48	18
22	20	40	20
24	8	10	11
25	13	17	21

Table 50 Amplitude of pulsations of c.s.f. pressure (mm. H_2O) before, during and after the administration of 0.9% trichloroethylene in patients.

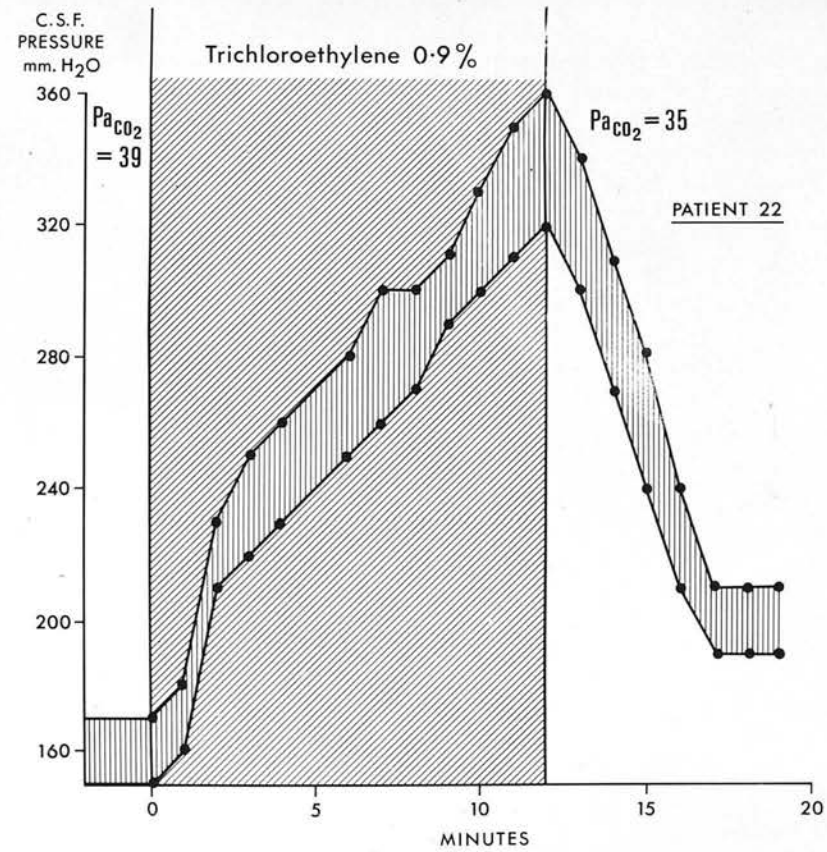


Figure 26 A typical plot from one patient of the c.s.f. pressure changes produced by 0.9% trichloroethylene administration at constant Paco2.

(4) The Influence of Trichloroethylene on c.s.f. Pressure in Man

The influence of trichloroethylene on c.s.f. pressure was studied in 5 cases. In 3 cases central venous pressure was measured prior to and during trichloroethylene administration. All the detailed results are presented in Table App. 35 and the changes in mean pressure in Table 49.

0.9% trichloroethylene produced a rise in c.s.f. pressure in every patient studied. The mean control value for c.s.f. pressure in this group was 109 $\pm$ 32 mm.H20. During trichloroethylene the mean c.s.f. pressure rose to 215 $\pm$ 78 mm.H20, representing an increase of 105 $\pm$ 46 mm.H20 (see Table 49 and Figure 25). All patients were studied during normocapnia; the mean arterial Pco_2 being 38.6 $\pm$ 2.1 mm.Hg. As with halothane, there was an increase in the amplitude of c.s.f. pulsations when trichloroethylene was administered (Table 50). In 1 case however the amplitude of pulsation remained elevated after discontinuance of the trichloroethylene and in another patient the amplitude actually increased at this stage. This latter patient was however breathing against the ventilator at this time and this may well have accounted for this anomalous result.

A typical record of c.s.f. pressure changes with trichloroethylene administration is shown in Figure 26.

CHAPTER 6

Discussion of c.s.f. Pressure Changes in Man and Experimental Animals

These studies have shown that the administration of either halothane or trichloroethylene during nitrous oxide-oxygen anaesthesia leads to definite increases in c.s.f. pressure in man at constant arterial carbon dioxide tension in the normocapnic range and that halothane and chloroform increase c.s.f. pressure in the dog. In man c.s.f. pressure was measured in the lumbar subarachnoid space while in the dog measurement was made in the cisterna magna. However in the horizontal position there is no difference between mean lumbar c.s.f. pressure and mean intracranial pressure (Evans, 1956) though the amplitude of c.s.f. pulsations is lower in the lumbar theca (Bering, 1955). Consequently the changes in mean c.s.f. pressure recorded from the lumbar subarachnoid space in these patients can be considered to indicate the changes produced by halothane and by trichloroethylene in intracranial pressure.

The extent of the rise in c.s.f. pressure produced by these drugs was very variable between individual patients or animals and was not related to either the initial control value for c.s.f. pressure or arterial Pco_2 provided these control values were within the normal range. The increase in c.s.f. pressure produced by halothane was related to the concentration of the drug administered in any individual patient or animal.

The increased amplitude of c.s.f. pulsations noted during the administration of halothane and trichloroethylene can be attributed to the rise in mean c.s.f. pressure for similarly amplified pulsations are seen whenever c.s.f. pressure is elevated (Ryder, Espey, Kimbell, Penka, Rosenauer, Podolsky & Evans,

1952A). Part of the increase may however have resulted from increased intracranial arterial pulsations consequent upon the cerebral vasodilatation produced by halothane and early trichloroethylene (see Part I).

When patients were ~~[illegible]~~ hyperventilated, c.s.f. pressure fell although the initial level was normal. The administration of halothane at this stage caused only minor elevations in c.s.f. pressure. This is in agreement with previous evidence that the influence of any cerebral vasodilator on c.s.f. pressure is less when that pressure is low (Ryder, Espey, Kimbell, Penka, Rosenauer, Podolsky & Evans, 1952B).

There have been several previous studies of the influence of anaesthetic drugs on cerebrospinal fluid pressure. Stephen, Woodhall, Golden, Martin & Nowill (1954) concluded after such a study that "it is doubtful whether anaesthetic drugs per se with the possible exception of avertin, are capable of increasing cerebrospinal fluid pressure". Unfortunately it is not clear from the article whether trichloroethylene or chloroform were studied (halothane was not available at the time). Furthermore these workers made their measurements during the induction of anaesthesia when many factors operate to confuse the picture, e.g. straining and struggling during the excitement stage of anaesthesia. It is therefore not surprising that they failed to detect the relatively small changes in c.s.f. pressure which these anaesthetic drugs have now been shown to produce. Woringer, Brogly and Schneider (1951) have also stated that trichloroethylene has no effect on c.s.f. pressure. Sondergard (1961) found that administration of trichloroethylene produced a rise in c.s.f. pressure in spontaneously breathing patients. However c.s.f. pressure promptly fell "with the re-establishment of a clear airway" and Sondergard therefore concluded that trichloroethylene per se had no effect on c.s.f. pressure.

These findings are interesting in that his observation of an initial rise in c.s.f. pressure with trichloroethylene followed by a fall fits well with the initial but transient increase in cerebral blood flow which has been shown (in Part I) to occur with this drug. Despite these reports, Hunter (1964) in his review of this subject writes "the addition of trichloroethylene to a nitrous oxide-oxygen mixture will cause an immediate small increase in intracranial pressure" and the results reported here fully support his conclusion.

Sondergard also studied the effects of halothane on c.s.f. pressure and he concluded that this agent did increase c.s.f. pressure. Unfortunately his measurements were made on spontaneous breathing patients so that they are obscured by the respiratory depression and consequent hypercapnia which occurs with halothane. It is true that Sondergard measured end tidal Pco_2 but it is difficult to know how much of his observed increases in c.s.f. pressure were due to halothane itself and how much to concomitantly measured increases in end tidal Pco_2.

There have been two reports of the effect of halothane on c.s.f. pressure during controlled ventilation at constant arterial Pco_2. The work of Marx, Andrews & Orkin (1962) performed in this way indicated that halothane increased c.s.f. pressure and that the extent of the rise was related to the concentration of halothane administered. Superficially their results appear to be in agreement with those presented here but in fact the extent of the increase found by them was much smaller, averaging only 17 mm.H2O during 0.5% halothane. These workers also measured "venous pressure" via a catheter introduced into an antecubital vein and this they found to be elevated by halothane by percentage increments similar to the percentage increases in c.s.f. pressure. They therefore concluded "the

increases in cerebrospinal fluid pressure due to halothane per se are related solely to increases in systemic venous pressure". However their mean value for venous pressure of 126 mm.H20 in spontaneously breathing unanaesthetised patients suggest either a falsely low zero reference point or that the venous pressure measured was greatly in excess of central venous pressure. In fact the site of measurement is not specified beyond the information that a catheter was introduced via an antecubital vein. From the high control values quoted it would seem likely that peripheral venous pressure of the arm was monitored. Changes in this pressure may of course be due to changes in central venous pressure but they can equally well result from halothane induced vasodilatation of skin vessels producing increased limb blood flow. Furthermore the expression of changes in pressure as percentages by these authors artificially magnifies any actual increase in venous pressure when compared with c.s.f. pressure since the absolute level of the former is so much less than that of the latter. For these reasons the demonstration of Marx et al. that equal percentage increases in c.s.f. and venous pressure occur with halothane need not imply that the rise in c.s.f. pressure is secondary to a primary rise in venous pressure. In the results reported in this thesis 0.5% and 1% halothane and up to 0.9% trichloroethylene produced either no change in central venous pressure or only small increases. 2% halothane was shown in one animal (Figure 21) to produce a steady and progressive rise in central venous pressure and when this occurred the expected equal and parallel rise in cerebral venous pressure followed. This was the only occasion in all these studies when a change in cerebral venous or c.s.f. pressure appeared to be the result of a primary alteration in central venous pressure. With lower concentrations of halothane and with trichloroethylene administered during

normocapnia, the alterations in central venous pressure did not exceed 10% of the increases in cerebral venous or c.s.f. pressure.

Hunter (1964) has published a record of the changes in intracranial pressure produced in one patient by the intermittent administration of 1% halothane during controlled ventilation. The changes shown closely resemble the pattern observed in the present study.

As regards chloroform, Finesinger and Cobb (1935) noted that the administration of this drug to cats caused increases in c.s.f. pressure. This paper has already been discussed in Part I when it was pointed out that the animals on which these observations were made were certainly hypotensive and possibly hypoxic. Unlike the changes in pial artery diameter, hypotension could not have been the cause of the c.s.f. pressure increases though of course the possible presence of hypoxia could have done so. Koopmans (1939) noted that the administration of chloroform increased the pressure inside a balloon placed under the dura in cats and dogs. Since the pressure inside such a balloon must equal intracranial pressure, this finding indicates that the drug increased c.s.f. pressure. However, like much work carried out at this time, arterial Pco_2 was not controlled in these experiments and therefore the reported change in intracranial pressure could have been due to hypercapnia consequent upon respiratory depression.

Causes of the Pressure Changes

The c.s.f. pressure tends to rise whenever the volume of the intracranial contents increases; this is because, as pointed out by Monro (1783) and by Kellie (1824) the intracranial and spinal theca are relatively rigid or, expressed in other terms, have a low compliance. Therefore changes in the volume of the intracranial contents produce very large changes in intracranial pressure.

The intracranial contents are:-

(1) blood which constitutes about 2% of the intracranial volume (Rosomoff, 1961)

(2) cerebrospinal fluid comprising about 9% of the intracranial volume (Rosomoff, 1961)

(3) the brain itself which consists almost entirely of cellular elements, either neuronal or glial, and with only a small interstitial space (de Robertis, 1963). The fluid in this extracellular space is in free communication with the c.s.f. so that changes in extracellular brain volume can be considered together with changes in c.s.f. volume. Therefore in the subsequent discussion the term "brain volume" is used to indicate intracellular brain volume.

The question of what causes c.s.f. pressure to rise during halothane or trichloroethylene administration therefore becomes "do halothane and trichloroethylene increase the volume of the blood or of the c.s.f. or of the brain within the skull?"

One of the features of the pressure recordings obtained in the present study was the rapidity with which c.s.f. pressure rose on starting halothane or trichloroethylene administration and the equal rapidity with which the pressure fell again when the drug was stopped. Changes in

intracellular volume could scarcely occur with such rapidity.

Changes in c.s.f. volume can be produced by either an increase in the rate of c.s.f. production or a fall in the rate of c.s.f. reabsorption. However when changes in c.s.f. volume are the cause of increases in c.s.f. pressure then there are no associated changes in cerebral venous pressure as measured in the sagittal sinus (Becht, 1920; Weed & Flexner, 1933; Greenfield & Tindall, 1965). This is quite contrary to the situation which has been shown in these experiments to arise when volatile anaesthetic drugs are administered for then both c.s.f. and cerebral venous increase. In the 2 animal experiments described above and illustrated in Figures 17 and 18 when halothane was administered both cerebral venous and c.s.f. pressure rose together and when halothane was withdrawn both pressures fell in parallel. It has also been shown that chloroform and early trichloroethylene increase cerebral venous pressure in dogs. Since primary changes in c.s.f. pressure do not produce secondary changes in cerebral venous pressure these observations must mean that the venous pressure changes were primary and that the c.s.f. changes were the result of increases in cerebral venous pressure. This in turn indicates that the effect of halothane on c.s.f. pressure was not the result of an increase in c.s.f. volume.

Since expansion of either the c.s.f. compartment or of the cerebral intracellular compartment has been excluded the expansion must have been in the intracranial blood volume. The results of the two Parts of this thesis thus become mutually corroborative. When either halothane or trichloroethylene is administered the cerebral arterioles relax and more blood flows through the cerebral circulation, as was shown in Part I. With the increased volume of blood flowing along the venous sinuses the

pressure in these sinuses rises as was shown to occur with halothane, chloroform and early trichloroethylene. The increased venous pressure distends the cerebral veins and this expansion in volume raises the intracranial pressure as demonstrated by the c.s.f. pressure measurements made in the cisterna magna of dogs and in the lumbar subarachnoid space of patients. The volume of the cerebral arterioles is of course also elevated by the vasodilatory action of these drugs but this contributes little to the increase in intracranial volume since the volume of the arterioles is small by comparison with the high capacity of the venous side of the circulation.

In Part I it was shown that the increases in cerebral blood flow produced by halothane were related to the concentration of the drug administered while in this Part the c.s.f. pressure rise has been found also to be related to halothane concentration.

In studying the animal c.s.f. pressure records it has already been pointed out that there was a tendency, during 0.5% halothane administration, for c.s.f. pressure to rise to a peak and then to fall slowly towards the base-line. This late fall in c.s.f. pressure correlates closely with the flow results in which 0.5% halothane was shown to produce an increase in flow at the beginning of its administration with a subsequent return to control values. This may however not be the whole explanation for this pattern of c.s.f. pressure because Draper and Whithead (1944) have demonstrated that a similar rise and subsequent fall in c.s.f. pressure is also seen during hypercapnia although the increase in blood flow is well maintained. Bedford (1935) observed the same sequence of changes in c.s.f. pressure during prolonged venous occlusion in the neck. The probable explanation is that elevation of c.s.f. pressure activates a

regulatory mechanism which operates by increasing the rate of c.s.f. reabsorption. Therefore the end result is that the expansion of the intracranial blood volume is balanced by a reduction in c.s.f. volume and c.s.f. pressure is returned to normal values. Direct evidence of this hypothesis is lacking but Rosomoff (1963) has shown that when cerebral blood flow is reduced by hyperventilation, c.s.f. volume increases; the converse is therefore feasible. Figure 19 tends also to corroborate the hypothesis; in the experiment illustrated in this Figure, halothane was administered for 1 hour and 40 minutes and the c.s.f. pressure rose to a peak and then subsided towards the control value.. The important point to the present discussion is however that c.s.f. pressure fell below the initial control value when the halothane was discontinued. This suggests that the volume of c.s.f. had fallen during the period of halothane administration.

In patients the peak increase in c.s.f. pressure was not reached as quickly as in the animal studies and this may indicate either that the increase in cerebral blood flow produced by 0.5% halothane was more prolonged than in the dogs or alternatively that compensatory adjustments of c.s.f. volume are more slowly accomplished in man.

Clinical Significance of c.s.f. Pressure Changes

Although both halothane and trichloroethylene increased c.s.f. pressure in these investigations, the clinical significance of these findings would appear to be slight. There are two reasons for this view. In the first place the rise in c.s.f. produced by these anaesthetic drugs was small (i.e. of the order of 100 mm.H20 or 7 mm.Hg.) and would scarcely produce a detectable increase in dural tension during neurosurgery. Secondly, particularly with the lower concentration of halothane, the increase in c.s.f. pressure was not sustained so that if halothane were administered from the start of anaesthesia, the c.s.f. pressure would have returned to normal before the surgeon had exposed the dura. These two points almost certainly explain the failure of Bozza, Maspes & Rossandra (1961) to detect any obvious difference in dural tension between patients without intracranial space occupying lesions anaesthetised with different anaesthetic agents.

It should be remembered that although the c.s.f. pressure tends to return to control values during prolonged halothane administration this is probably partly due to reduction in c.s.f. volume. Therefore the surgeon will find the brain itself rather more "engorged" or "swollen" due to the increased brain blood volume while the gap between the pia-arachnoid and the dura will be narrowed by the lowered c.s.f. volume. These theoretical predictions are well borne out by clinical observation.

These are, however, points of little or arguable clinical significance. There is however one group of patients in whom even small elevations in intracranial pressure may be harmful and this group comprises patients who have raised intracranial pressure as a result of the presence of space

occupying lesions within the skull . It was decided therefore as a final part of this study to assess the effect of halothane anaesthesia on patients with intracranial tumours.

CHAPTER 7

The Influence of Halothane on Cerebrospinal Fluid Pressure in Patients with Intracranial Tumours

Methodology

Four patients with intracranial tumours and clinical signs of intracranial hypertension were studied; relevant clinical details are given for each patient below.

Premedication was with pethidine 50 mgs. and atropine 0.6 mg. in every case except A.D. who received atropine 0.6 mg. alone. The technique of anaesthesia was identical to that described in the preceeding study. A metal cannula was inserted into one of the lateral ventricles through a burr hole made as part of the normal surgical procedure. Intracranial pressure was measured via this cannula by means of suitable pressure transducers and amplifiers and was recorded with an ultraviolet recorder. All measurements were completed before a bone flap was reflected. The patient was lying in the supine position with the operating table level and the zero reference point was taken as the mid axillary line.

Blood Pco_2 was held constant by controlling ventilation and was measured on capillary blood by the technique of Andersen et al. (1960) immediately before administering halothane and at the end of the period of administration. The values were corrected for the temperature difference between the patient and the pH electrode by applying Rosenthal's (1948) factor. Systolic blood pressure was measured every minute during halothane administration by upper arm sphygmomanometry and pulse rate by palpation.

Control measurements of intracranial pressure were obtained during

unsupplemented nitrous oxide-oxygen anaesthesia with muscular relaxation obtained with tubocurarine. The effect of the addition of 0.5% or 1% halothane on intracranial pressure was then studied.

PATIENT	MEAN C.S.F. PRESSURE				Pa_{CO_2}
	CONTROL $N_2O + O_2$	DURING HALOTHANE	AFTER HALOTHANE	INCREASE WITH HALOTHANE	
A.D.	167	480(0.5%)	303	313	38
A.McN.	138	680 (1%)	145	542	34
H.T.	128	366 (1%)	130	238	52
M.J.	282	533 (1%)	249	251	39
MEANS	179 ±71	515 ±130	207 ±83	336 ±141	40.8 ±8.2

Table 51 The effect of halothane administration in intracranial pressure (mm. H_2O) in patients with intracranial tumours.

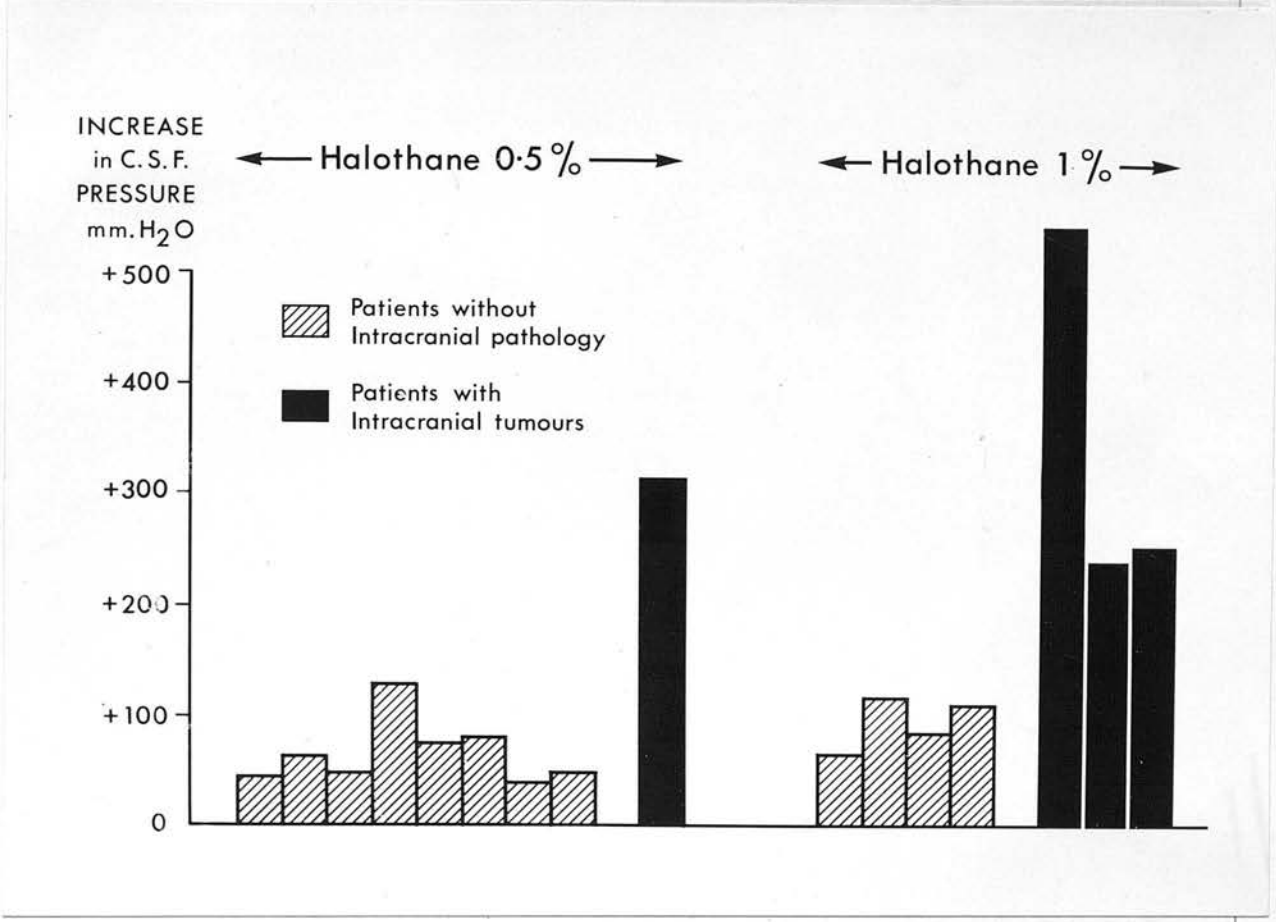


Figure 27 The effect of halothane on mean c.s.f. pressure in patients with intracranial tumours compared with the changes found previously in patients without intracranial pathology.

Results

Table App. 36 records the detailed results while Table 51 shows the changes in mean intracranial pressure produced by halothane in these patients. It will be seen that, as with the patients without intracranial pathology, halothane administration in every case resulted in a rise in c.s.f. pressure. The difference in the present group is in the magnitude of the rise induced by halothane which was 2 to 8 times greater than that in the "normal" patients. This point is illustrated graphically in Figure 27 which shows the pressure increases in these patients with intracranial tumours alongside these obtained from the patients without intracranial pathology.

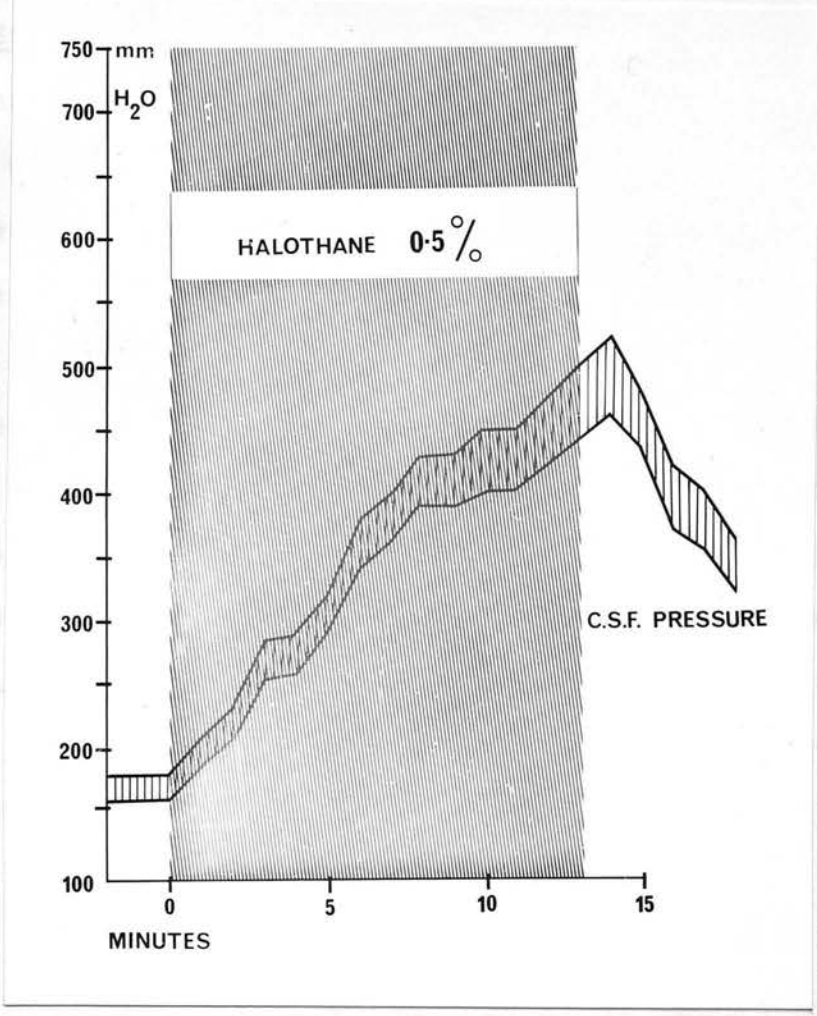


Figure 28 The c.s.f. pressure record in patient A.D.

Individual Results

Patient A.D. (48 years)

Pathology: cerebellar metastatic tumour

Clinical Evidence of Intracranial Hypertension: early papilloedema

Ventriculogram demonstrated symmetrical hydrocephalus.

Pressure Study:

In this patient a burr hole was made under local anaesthesia to allow air ventriculography. Later the same morning the patient was brought to theatre and was anaesthetised in the standard way already described.

Figure 28 is the c.s.f. pressure record from this patient. The c.s.f. pressure, as measured in the lateral ventricle was 180/160 mm.H_2O during unsupplemented nitrous oxide-oxygen anaesthesia and at an arterial Pco_2 of 38 mm.Hg. His systolic blood pressure at this time was 110 mm.Hg. The administration of 0.5% halothane produced a progressive rise in intracranial pressure which showed no sign of levelling off during the 13 minutes of administration. Indeed after discontinuing the halothane, c.s.f. pressure continued to rise for a further minute reaching a peak value of 520/460 mm. H_2O. Thereafter the c.s.f. pressure dropped sharply towards the pre-halothane values. Halothane caused a fall in systolic blood pressure to 90 mm.Hg.

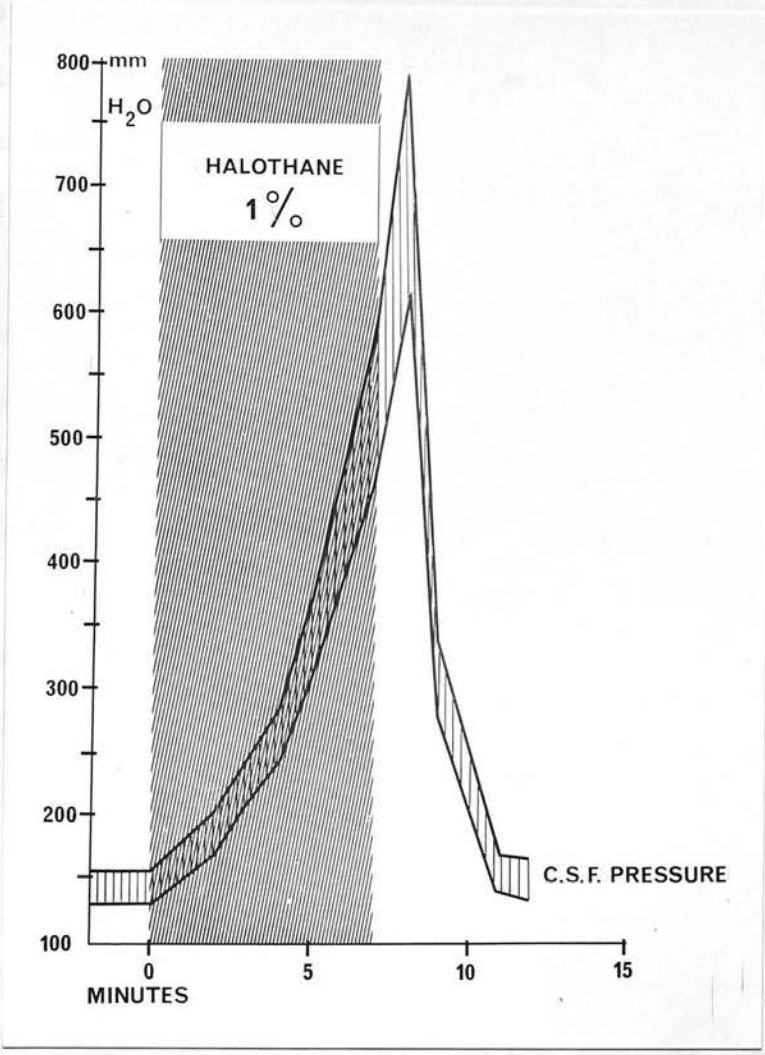


Figure 29 The c.s.f. pressure record in patient A.McN.

Patient A. McN (36 years)

Pathology: Anaplastic astrocytoma of the left frontal lobe.

Clinical Evidence of Intracranial Hypertension: Marked papilloedema.

Pressure Study:

Figure 29 is the c.s.f. pressure record from this patient. The anaesthetic technique and the placement of the ventricular cannula were as described in the general methodology section. During unsupplemented nitrous oxide-oxygen anaesthesia the c.s.f. pressure was 155/130 mm.H20, the arterial Pco_2 was 34 mm.Hg., systolic blood pressure 130 mm.Hg., and the pulse rate 94/minute. The administration of 1% halothane caused a precipitous rise in intracranial pressure, so great indeed that halothane administration was discontinued after only 7 minutes. Intracranial pressure continued to rise for one further minute reaching a peak value of 800/620 mm.H20 at which time systolic blood pressure was down to 100 mm.Hg. and pulse rate was 86/minute. The intracranial pressure then fell rapidly and regained control values 4 minutes after the end of halothane administration.

The minute volume of ventilation was then increased from 6 litres/minute to 9 litres/minute and this produced a fall in $Paco_2$ to 21 mm.Hg. Hyperventilation did not in this patient lower the c.s.f. pressure during nitrous oxide-oxygen anaesthesia which remained at 170/140 mm.H20; however the administration of 1% halothane now caused a much lesser increase in c.s.f. pressure which reached a peak of 530/440 mm.H20 and then fell despite continuing halothane administration to a level of only 340/290 mm.H20. On discontinuing halothane administration intracranial pressure fell to control values in 3 minutes.

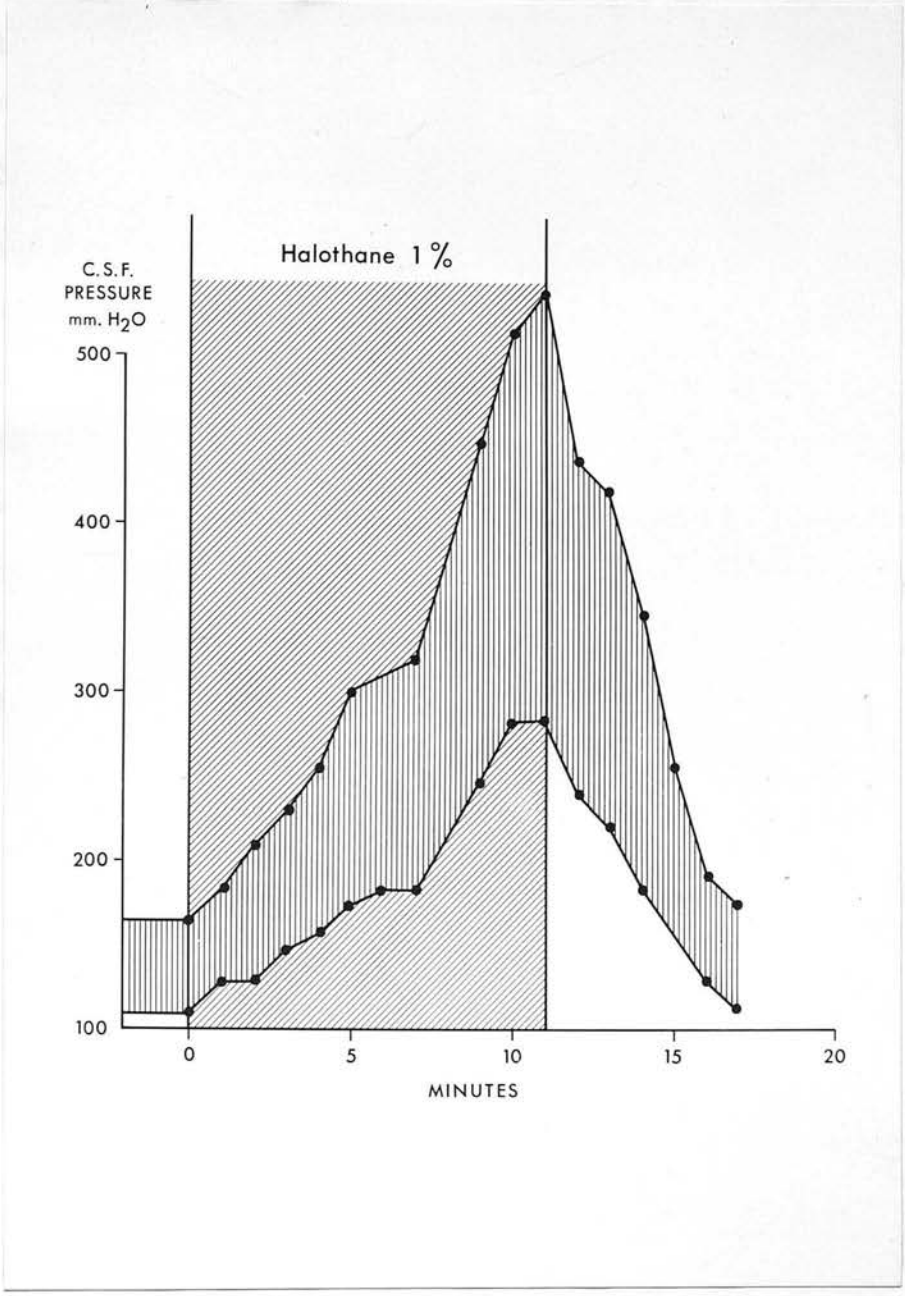


Figure 30 The c.s.f. pressure record in patient H.T.

Patient H.T. (47 years)

Pathology: Astrocytoma in left frontal region.

Clinical Evidence of Intracranial Hypertension: Early papilloedema and X-ray evidence of erosion of dorsum sellae.

Pressure Study:

The record from this patient is shown in Figure 30. During unsupplemented nitrous oxide-oxygen anaesthesia, c.s.f. pressure was 168/108 mm.H20, arterial Pco_2 50 mm.Hg., systolic blood pressure 120 mm.Hg., and pulse rate 92/minute. 1% halothane for 11 minutes produced a rise in intracranial pressure which reached a peak value of 537/281 mm.H20. Intracranial pressure returned to control values 5 minutes after the cessation of halothane. During halothane administration systolic blood pressure fell to 95 mm.Hg. and pulse rate to 84/minute.

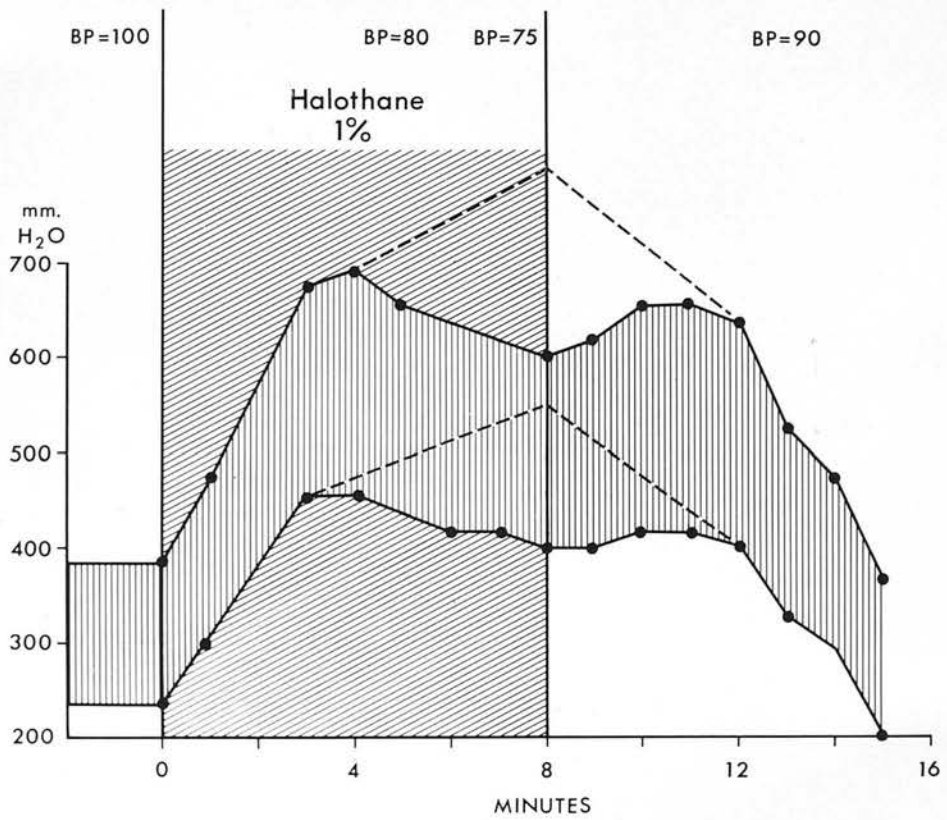


Figure 31 The c.s.f. pressure record in patient M.J.

Patient M.J. (62 years)

Pathology: Glioblastoma left temporal lobe.

Clinical Evidence of Intracranial Hypertension: Angiographic lateral displacement of the anterior cerebral arteries.

Pressure Study:

Figure 31 is the c.s.f. pressure record from this patient. Pre-halothane values were as follows:- c.s.f. pressure 382/232 mm.H_2O; arterial Pco_2 39 mm.Hg., systolic blood pressure 100 mm.Hg., and pulse rate 84/minute.

The administration of 1% halothane at first produced the usual marked rise in intracranial pressure which reached 690/455 at the 4th minute. There then occurred a progressive fall in intracranial pressure which had reached 600/400 mm.H_2O at the 8th minute when halothane was discontinued. The other unusual feature in this case, which will be discussed in detail subsequently, was that when halothane was stopped intracranial pressure rose for 3 minutes before beginning to fall towards the control value. Halothane reduced the systolic blood pressure to 75 mm.Hg; there was no significant alteration in pulse rate.

Discussion of c.s.f. Pressure Changes in Patients with Intracranial Tumours

Without exception, the c.s.f. pressure increases in these patients with intracranial tumours were greater than the increases produced in normal subjects. There is no reason to suppose that the cause of the c.s.f. pressure increase was different between the two groups, i.e. was other than the result of halothane induced cerebral vasodilatation. It would seem unlikely that the greater pressure rise in the tumour group was the result of greater cerebral vasodilatation by halothane in this group though the possibility cannot readily be ruled out. However a more likely explanation would appear to be that the increase in intracranial blood volume produced by halothane in both groups caused a greater pressure rise in the patients with intracranial tumours because the intracranial contents were already compressed by the growth of the tumour. In normal subjects when a sudden increase in intracranial blood volume occurs the consequent rise in intracranial pressure is modified by a compensatory movement of c.s.f. out from the skull. In patients with cerebral tumours such compensatory mechanisms are progressively exhausted by expansion of the tumour and so, when a sudden expansion in intracranial blood volume occurs, intracranial pressure rises precipitously. Lundberg (1960) has demonstrated that in such patients "Plateau waves" of intracranial pressure arise in response to trigger stimuli which act by producing sudden changes in intracranial blood volume. Halothane, because of its cerebral vasodilatatory action, would appear to be such a "trigger".

These results are in direct contradiction to the conclusion of Bozza et al. (1961) that anaesthetic drugs have negligible influence on c.s.f. pressure. However this statement was based upon a comparison of anaesthetic

drugs in patients without intracranial space occupying lesions (patients of Class I of Bozza et al.'s paper) and therefore should not have been extended, as it was, to all neurosurgical patients.

Hunter in 1948 when discussing volatile anaesthetic drugs stated, "During operation on patients with supratentorial tumours even a slight rise in intracranial tension adds to the difficulties of those whose intracranial pressure is already raised.". The present results confirm the truth of this warning but reveal that the situation is not that the volatile anaesthetics produce a small increase in intracranial pressure on top of a high resting level but that these drugs produce very great elevations in intracranial pressure from values which may be only slightly above normal values of intracranial pressure.

The next problem is to decide whether these large changes in intracranial pressure are actually hazardous. It must first be stated that there was in no instance evidence of clinical deterioration in these patients during halothane administration; the pulse rate did not fall dramatically nor was systemic hypertension seen. These are, however, probably late signs of intracranial hypertension. It should also be remembered that halothane administration was stopped in three of the cases while the c.s.f. pressure was still rising so that the maximum effect of halothane was not allowed to develop. Finally, the clinical signs of cerebral ischaemia during anaesthesia have not been adequately studied.

Allowing then that clinical evidence of cerebral dysfunction was not allowed to develop in these patients, is there other evidence that halothane administration without careful c.s.f. pressure monitoring might be detrimental to the brain? There are basically two ways in which a rise

in intracranial pressure can imperil cerebral function. Firstly, an increase in pressure localised to one intracranial compartment may produce brain shifts, brain distortion or brain herniation. In the present studies it was justifiable only to make pressure measurements in the compartment which was being exposed for surgical treatment. All the pressure measurements were made via a cannula in the lateral ventricle. Since the c.s.f. communicating pathways may be obstructed in patients with intracranial space occupying lesions it is possible that pressure equilisation between different intracranial compartments is slow when sudden vasodilatation is produced by halothane. Also because of local compression by tumour growth, the intracranial pressure rise produced by a cerebral vasodilator like halothane will be greatest in the compartment containing the tumour. For these reasons it is likely that halothane administration to patients with intracranial tumours may on occasion produce differential pressure changes and increase the likelihood of brain herniation.

The other way in which intracranial hypertension may impair cerebral function is through reduction of cerebral blood flow. From direct measurement in animals it is known that cerebral blood flow begins to fall when the intracranial pressure rises to within 30-40 mm.Hg. of the mean arterial blood pressure (Zwetnow, 1967). In the four patients presented here systolic and not mean blood pressure was measured but from this a close approximation to mean pressure can be calculated by subtracting 20 mm.Hg. from the systolic pressure at the reduced blood pressure pertaining during halothane anaesthesia, (i.e. assume that the pulse pressure was 30 mm.Hg. and calculate mean pressure in the usual way as diastolic pressure $+\frac{1}{3}$ pulse pressure). It can then be seen that at the

peak values of c.s.f. pressure during halothane administration the difference between mean c.s.f. pressure and mean blood pressure was only 35, 30, 48 and 16 mm.Hg. in the four patients studied. It is clear therefore that halothane administration to patients with intracranial tumours elevates the intracranial pressure to a level at which cerebral perfusion has been shown in animals to be impaired. The hypotensive action of halothane obviously acts synergistically with its effect on intracranial pressure to produce this undesirable situation. It is this systemic hypotension in patients anaesthetised with halothane which makes the situation more serious than in conscious patients. However even if one leaves the question of hypotension out of account for the moment, the level of intracranial hypertension reached in 3 of these patients exceeded the value of 450 mm.H20 stated by Kety, Shenkin and Schmidt (1948) to be the pressure level at which cerebral blood flow begins to fall; all 4 patients exceeded the value of 350 mm.H20 given by Ferris (1941). It should be noted again that in patients A.D., A.McN. and H.T. halothane administration was discontinued before there was any sign that the intracranial pressure had reached its zenith; longer halothane administration would have yielded even greater values but was felt to be clinically contraindicated.

Greenfield and Tindall (1965) measured in man changes in cerebral blood flow produced by artificial elevation of c.s.f. pressure produced by the intradural infusion of saline. Relating cerebral blood flow to c.s.f. pressure is physiologically less meaningful than relating it to cerebral perfusion pressure (i.e. mean blood pressure - mean intracranial pressure) and therefore for the purposes of this discussion Greenfield and Tindall's results have been recalculated to allow this comparison of flow with perfusion pressure. In this way it can be shown that in Greenfield and

Tindall's study cerebral blood flow was reduced to 74% of the initial value when the cerebral perfusion pressure was down to 25 mm.Hg. The mean perfusion pressure during halothane anaesthesia in the patients reported here was 32 mm.Hg. and was as low as 16 mm.Hg. in one.

No direct measurements of cerebral blood flow have been made in these patients but there is a suggestion from the c.s.f. pressure record of patient M.J. that cerebral blood flow was in fact impaired. In Figure 31 it will be seen that when halothane administration was started, intracranial pressure rose steeply in the same way as in the other cases. However, after 4 minutes, intracranial pressure began to fall again and continued to do so until the halothane was stopped. Such a fall from a peak value during halothane administration was not seen in the other patients with intracranial tumours. However the feature of greatest interest in the pressure record of patient M.J. is that when halothane administration was discontinued c.s.f. pressure began to increase again and did so for 2 - 3 minutes before beginning to fall towards control values. A possible interpretation of this unusual pressure pattern is that the fall in c.s.f. pressure seen after the 4th minute of halothane administration was due to a fall in cerebral perfusion and this becomes all the more probable when one notes that the c.s.f. - mean B.P. difference had fallen to only 16 mm.Hg. at this point. The increase in c.s.f. pressure when the halothane was stopped would then be ascribed to an increase in cerebral perfusion as the blood pressure began to recover. At 3 minutes after discontinuing the halothane cerebral vasodilatation was passing off and the c.s.f. pressure fell. In Figure 31 the dotted line indicates the pattern of c.s.f. pressure response to halothane which results in other patients would have led us to expect. In this patient therefore not only did the c.s.f. - B.P.

difference fall to a value which has been shown to be inadequate to sustain cerebral blood flow but the c.s.f. pressure record shows that such a fall in cerebral perfusion may actually have occurred.

One cannot of course infer that because cerebral blood flow may be reduced by the fall in perfusion pressure produced by halothane that cerebral function is thereby imperilled. After all, cerebral blood flow can be halved by hyperventilation without any permanent loss of cerebral function. Indeed the patients in the study of Greenfield and Tindall (1965) remained fully alert and conscious at a cerebral perfusion pressure of only 25 mm.Hg. In considering the question of halothane administration to patients with intracranial tumours, however, it should be emphasised that, unlike the situation with hypocapnic cerebral vasoconstriction, the cerebral arterioles are maximally dilated in an attempt to compensate for the raised intracranial pressure (Fog, 1934) and therefore cerebral blood flow is impaired at a time when the reserves of cerebrovascular compensation are fully extended. The situation is more closely analogous to that existing with systemic hypotension which has been carried to the point at which the cerebral arterioles are maximally dilated and can compensate no further. When halothane is administered to patients with intracranial tumours therefore cerebral perfusion pressure may become inadequate to support neuronal survival at a systemic blood pressure higher than that normally required to maintain adequate cerebral blood flow, the discrepancy being due to the elevated intracranial pressure. In clinical terms the reserves of compensation normally available to the cerebral circulation are exhausted and any further impairment in perfusion pressure, as for example may be produced by a sudden haemorrhage, could produce cerebral damage at a level of blood pressure which would not normally be considered hazardous.

It was demonstrated in the preceding chapter of this thesis that, in patients without intracranial lesions, prior hyperventilation greatly reduced the effect of halothane on c.s.f. pressure. In patient A.McN. of this intracranial tumour group the effect of hyperventilation prior to halothane administration was assessed. It was found that the extent of the halothane induced rise in intracranial pressure was greatly reduced by this procedure. This protective effect of hyperventilation is almost certainly due to the reduction in cerebral blood flow and intracranial blood volume which hypocapnia produces (Rosomoff, 1963). Consequently as suggested but not confirmed by Marx et al. (1962) it is wise to hyperventilate patients with intracranial space occupying lesions prior to administering halothane. It is important however that hyperventilation should not be too long continued before halothane is administered for then a compensatory increase in c.s.f. volume might negate the protective value of this procedure.

Patient A.D. differed from the other patients in this group in that he underwent air ventriculography prior to anaesthesia and prior to the c.s.f. pressure study. Saidman and Eger (1965) have shown that the administration of nitrous oxide to a patient with air inside the skull following air ventriculography can lead to increases in intracranial pressure. These changes are due to the transfer of nitrous oxide to the air bubbles in volumes in excess of the volume of nitrogen removed from the bubbles. The discrepancy between nitrous oxide entry and nitrogen removal from air bubbles is related to the much higher solubility of nitrous oxide in blood than that of nitrogen. However, the c.s.f. pressure rise in this patient is unlikely to have been caused in this way because nitrous oxide had been administered for 30 minutes prior to the study and because a stable value for c.s.f. pressure was obtained during the 5 minutes of measurement prior

to halothane administration. Furthermore the pressure changes which did occur were clearly related in time to the starting and stopping of halothane administration. Transfer of halothane to the intraventricular air bubbles would have been negligible because of the low administered concentration of halothane. By virtue of being compressible the air collections in this patient probably "cushioned" the effects of the increase in intracranial blood volume produced by halothane and indeed the c.s.f. pressure record does show a rather more gentle rise in pressure than that seen in the other tumour patients.

In summary, it has been demonstrated that in patients with intracranial space occupying lesions halothane produces much greater elevations in c.s.f. pressure than it does in patients without intracranial pathology. The increases in pressure in the former group were such that the mean blood pressure - c.s.f. pressure difference (which under these circumstances is the perfusion pressure of the brain) narrowed to levels which in animals are associated with reduction in cerebral perfusion. Prior hyperventilation has been shown to be protective and it is likely that the current anaesthetic practice of hyperventilating patients during neurosurgery accounts for the infrequency of clinical deterioration when halothane is administered. However, sometimes, and especially during cerebral angiography, halothane is administered to patients with intracranial tumours who are allowed to breathe spontaneously. Since such patients usually underventilate intracranial pressure will be elevated both by hypercapnia and halothane itself. This practice would appear to be potentially hazardous.

(The full summary of the thesis has been placed, as required by the regulations, at the beginning immediately after the title page)

APPENDIX

DATE	BLOOD FLOW	OXYGEN UPTAKE	Pa_{co_2}	B.P.
2/4/65	0.96	-	37	150
	1.05	-	37	140
	0.87	-	40	150
	0.87	-	41	130
	0.83	-	41	130
5/4/65	1.26	0.062	36	135
	1.22	0.074	40	148
	1.27	0.068	38	130
23/4/65	1.45	0.072	44	190
	1.40	0.073	44	195
	1.48	-	44	185
26/4/65	1.28	0.074	50	150
	1.28	0.065	50	145
	1.18	0.070	46	157

Table App. 1. Detailed results for blood flow and oxygen uptake of the cerebral cortex and for blood pressure and arterial Pco_2 in four dogs anaesthetised with nitrous oxide-oxygen after non-barbiturate induction of anaesthesia.

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
28/1/64	0.61 0.69	0.85 0.81 0.70 0.70 0.51 0.52	155 155	140 135 130 125 120 115	2.54 2.25	1.65 1.67 1.86 1.79 2.35 2.21
29/1/64	0.67 0.61 0.60 0.70	0.75 0.54 0.48	120 120 120 125	110 110 105	1.79 1.97 2.00 1.79	1.47 2.04 2.19
26/2/64	0.64 0.76	0.61 0.63 0.76	160 150	140 140 140	2.50 1.97	2.30 2.22 1.84
17/3/64	0.98 0.91	1.16 0.94 0.74	140 145	135 143 135	1.43 1.59	1.16 1.52 1.82

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
12/8/64	1.00 1.31 1.08	1.15 1.05 1.12 0.93 0.56 0.49 0.63 0.52 0.64	160 150 150	145 142 138 140 140 142 145 145 145	1.60 1.15 1.39	1.26 1.35 1.23 1.51 2.50 2.90 2.30 2.79 2.27
14/8/64	0.96 1.09 1.12 0.93	1.36 1.36 1.36 1.46 1.46 1.46 1.19 0.91 1.06	150 145 145 148	142 138 132 125 122 125 128 125 125	1.56 1.33 1.29 1.59	1.04 1.01 0.97 0.86 0.84 0.86 1.08 1.37 1.18
11/11/64	1.09 1.19 0.93	1.31 1.03 0.93 0.86	135 140 135	125 110 105 105	1.24 1.18 1.45	0.95 1.07 1.13 1.22
18/11/64	1.36 1.58	1.46 1.22	150 150	135 130	1.10 0.95	0.92 1.07

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
23/11/64	0.69 0.84 0.73	0.96 0.61	160 160 153	130 130	2.32 1.90 2.10	1.35 2.13
25/11/64	1.15 1.34 1.03	1.00 1.26 0.93 1.27	130 130 130	120 115 115 120	1.13 0.97 1.26	1.20 0.91 1.24 0.94
23/12/64	1.01 0.92 0.84 0.92 0.82	1.00 0.74	120 120 120 120 120	100 95	1.19 1.30 1.43 1.30 1.46	1.00 1.28
24/12/64	1.18 0.98 0.87	1.30 1.34 0.96 1.22 1.06	140 140 140	130 125 115 100 95	1.19 1.43 1.61	1.00 0.93 1.20 0.82 0.90
28/12/64	0.72 0.93 0.79 0.82 0.76	0.79 0.72 0.68 0.77	130 130 130 130 130	105 100 95 90	1.81 1.40 1.65 1.59 1.71	1.33 1.39 1.40 1.17

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
26/2/65	0.86 0.95 0.92	1.22 1.35 1.11 1.15	150 150 150	145 150 130 130	1.74 1.58 1.63	1.19 1.11 1.17 1.13
1/3/65	1.05 0.90	0.92 0.97 0.66 0.95 0.82	155 155	145 130 125 120 118	1.48 1.72	1.58 1.34 1.89 1.26 1.44
15/3/65	0.98 0.79 0.86	0.85 0.74 0.74	115 120 120	105 100 95	1.17 1.52 1.40	1.24 1.35 1.28
17/3/65	0.82 0.77 0.71	0.94 0.82 0.89	130 140 150	135 130 130	1.59 1.82 2.11	1.44 1.59 1.46

Table App. 2 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during prolonged administration of 0.5% halothane in nitrous oxide-oxygen.

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
24/5/65	0.80 0.71 0.79 0.80 0.57 0.63	0.79 0.74 0.74 0.70	140 145 148 155 130 140	135 135 128 120	1.75 2.04 1.87 1.94 2.28 2.22	1.71 1.82 1.73 1.71
28/5/65	0.96 0.89 0.81 0.84 0.96 0.73 1.03 0.96	1.31 1.46 0.94 1.12	160 155 150 150 160 160 160 155	155 150 160 155	1.67 1.74 1.85 1.79 1.67 2.19 1.55 1.61	1.18 1.03 1.70 1.38
4/6/65	1.19 0.89 0.94 1.01 0.77 0.65	1.06 1.19 0.82	125 125 130 135 155 145	110 120 135	1.05 1.40 1.38 1.34 2.01 2.23	1.04 1.01 1.65
7/6/65	0.84 0.70 0.82 0.73	0.79 0.76	125 120 135 130	105 118	1.49 1.71 1.65 1.78	1.33 1.55

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
9/7/65	0.79 0.64	0.68	160 150	150	2.03 2.34	2.21
12/7/65	0.84 0.95 0.73 0.90	1.11 1.02	155 138 155 155	90 138	1.85 1.45 2.12 1.72	0.81 1.35
2/8/65	0.64 0.59	0.82	150 140	135	2.34 2.37	1.65

Table App. 3 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during intermittent administration of 0.5% halothane in nitrous-oxide oxygen.

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 0.5% HAL.	B.P. $N_2O + O_2$	B.P. 0.5% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 0.5% HAL.
9/7/65	0.79 0.64	0.68	160 150	150	2.03 2.34	2.21
12/7/65	0.84 0.95 0.73 0.90	1.11 1.02	155 138 155 155	90 138	1.85 1.45 2.12 1.72	0.81 1.35
2/8/65	0.64 0.59	0.82	150 140	135	2.34 2.37	1.65

Table App. 3 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during intermittent administration of 0.5% halothane in nitrous-oxide oxygen.

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{CO_2} $N_2O + O_2$	Pa_{CO_2} 0.5% Hal.
28/1/64	93 94	94 94 93 94 92 90	7.33 7.34	7.32 7.31 7.29 7.32 7.32 7.37	34 34	38 38 43 36 36 37
29/1/64	99 98	98 97 98	7.37 7.38 7.36 7.35	7.36 7.36 7.38	35 32 37 34	40 44 36
26/2/64	91 93	93 90 94	7.24 7.26	7.26 7.24 7.24	41 39	34 40 40
17/3/64	96 96	94 92 94	7.28 7.30	7.31 7.33 7.31	38 40	42 38 37

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{CO_2} $N_2O + O_2$	Pa_{CO_2} 0.5% Hal.
	95	95			36	40
		93			36	39
	95				36	41
		97				43
12/8/64		92				37
						38
		94				38
						40
		95				41
	93	93			38	39
					39	42
	95	91			38	42
					38	39
		93				39
14/8/64						38
		96				37
						35
		95				31
	100	95	7.25	7.23	40	40
	100	97	7.25	7.27	38	38
11/11/64	95	97	7.25	7.27	39	38
		98		7.26		37

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{CO_2} $N_2O + O_2$	Pa_{CO_2} 0.5% Hal.
18/11/64	96 97	96 94	7.25 7.21		40 36	42 40
23/11/64	94 94 93	92 91	7.26 7.27 7.24	7.24 7.24	40 40 40	40 42
25/11/64	96 91 90	91 92 93 92	7.26 7.27 7.26	7.22 7.26 7.28 7.29	40 40 40	44 40 39 37
23/12/64	100 99 100 100 100	96 100	7.32 7.33 7.32 7.28 7.21	7.24 7.27	36 34 34 36 39	38 39
24/12/64	96 96 95	93 94 95 96 96	7.24 7.25 7.24	7.21 7.20 7.22 7.20 7.22	40 40 40	40 45 45 43 39

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{CO_2} $N_2O + O_2$	Pa_{CO_2} 0.5% Hal.
28/12/64	96	95	7.25 7.29 7.26 7.27 7.24	7.23 7.22 7.23 7.22	39 31 39 36 37	40 44 41 43
26/2/65			7.32 7.30 7.33	7.32 7.33 7.32 7.32	40 40 33	33 34 36 35
1/3/65		94 97 96	7.27 7.28	7.31 7.24 7.25 7.25 7.24	40 40	41 44 45 43 45
15/3/65	92 94 96	90 99 97	7.11 7.09 7.18	7.08 7.13 7.17	43 47 44	41 42 44
17/3/65	94 95 95	94 96 95	7.35 7.40 7.38	7.34 7.38 7.36	41 42 40	45 40 39

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{co_2} $N_2O + O_2$	Pa_{co_2} 0.5% Hal.
24/5/65	100	100	7.39	7.39	35	33
	100		7.40		35	
	100	99	7.36	7.38	38	42
	100	100	7.37	7.37	39	43
	100		7.37		44	
	100	100	7.40	7.38	35	37
28/5/65	100	100	7.30	7.31	32	39
	100		7.31		41	
	100	100	7.33	7.32	38	40
	100		7.33		38	
	100	100	7.32	7.32	38	37
	100		7.32		40	
	100	100	7.33	7.35	34	34
	100		7.36		35	
4/6/65	100	100	7.32	7.28	41	46
	100		7.32		45	
	100	100	7.29	7.28	42	46
	100		7.30		46	
	100	100	7.35	7.35	42	39
	100		7.36		42	
7/6/65	100	100	7.33	7.31	35	34
	99		7.27		38	
	99	100	7.30	7.27	36	36
	99		7.31		32	

DATE	Ao_2 $N_2O + O_2$	Ao_2 0.5% Hal.	Art. pH $N_2O + O_2$	Art. pH 0.5% Hal.	Pa_{co_2} $N_2O + O_2$	Pa_{co_2} 0.5% Hal.
9/7/65	100 100	100	7.33 7.35	7.32	36 38	41
12/7/65	98 97 93 95	97 95	7.29 7.29 7.25 7.22	7.25 7.28	54 50 45 54	53 56
2/8/65	99 99		7.36 7.34	7.35	38 41	39

Table App. 4 Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 0.5% halothane in nitrous oxide-oxygen.

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 2% Hal.	B.P. $N_2O + O_2$	B.P. 2% Hal.	C.V.R. $N_2O + O_2$	C.V.R. 2% Hal.
7/6/65	0.79 0.71	0.92	120 115	95	1.52 1.62	1.03
9/7/65	0.64 0.64 0.70 0.64 0.50	0.76 0.76 0.83	150 150 155 155 150	140 130 125	2.34 2.34 2.21 2.42 3.00	1.84 1.71 1.51
12/7/65	0.97	0.86	165	55	1.70	0.64
16/7/65	1.11 1.08 1.01 1.01 1.03 0.86 0.73	1.99 1.75 1.06	140 125 135 130 130 130 115	95 110 90	1.26 1.16 1.34 1.29 1.26 1.51 1.58	0.48 0.63 0.85
23/7/65	0.79 0.77 0.66	0.96 0.74	110 100 130	60 65	1.39 1.30 1.97	0.63 0.88

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 2% Hal.	B.P. $N_2O + O_2$	B.P. 2% Hal.	C.V.R. $N_2O + O_2$	C.V.R. 2% Hal.
26/7/65	0.82 0.49 0.62 0.62	0.96 0.87 0.82	130 120 120 100	100 90 90	1.59 2.45 1.94 1.61	1.04 1.03 1.10
30/7/65	0.70 0.73 1.16 0.79 0.59	1.22 1.33 0.76 0.91	175 170 155 165 160	130 100 90 130	2.50 2.33 1.33 2.09 2.71	1.07 0.75 1.18 1.43
2/8/65	0.54 0.64 0.59	0.76 0.76 0.77	135 150 140	100 85 85	2.50 2.34 2.37	1.32 1.12 1.10
6/8/65	0.97 0.90 0.93 1.08	0.95 1.00 0.80 0.87 0.99 0.99	135 145 135 135	100 95 95 90 90 85	1.39 1.61 1.45 1.25	1.05 0.95 1.19 1.03 0.91 0.86

Table App. 5 Individual results for blood flow, mean blood pressure and cerebrovascular resistance during nitrous oxide-oxygen anaesthesia and during anaesthesia with 2% halothane.

DATE	Ao_2 $N_2O + O_2$	Ao_2 2% Hal.	Art. pH $N_2O + O_2$	Art. pH 2% Hal.	Pa_{co_2} $N_2O + O_2$	Pa_{co_2} 2% HAL.
7/6/65	100 98	100	7.29 7.26	7.255	37 42	43
9/7/65	100 99 99 100 100	100 97 100	7.345 7.30 7.32 7.26	7.34 7.295 7.29	38 39 35 36 37	39 36 36
12/7/65	97	100	7.285	7.285	43	47
16/7/65	95 94 97 97 95 97 98	93 92 97			38 44 42 46 44 40 41	44 44 39
23/7/65	99 98 97	97 99	7.31 7.325 7.32	7.30	35 35 35	34 35

DATE	Ao_2 $N_2O + O_2$	Ao_2 2% Hal.	Art. pH $N_2O + O_2$	Art. pH 2% Hal.	Pa_{co_2} $N_2O + O_2$	Pa_{co_2} 2% HAL.
26/7/65	98 99 99 97	96 97 97	7.29 7.27 7.285 7.325	7.245 7.29 7.25	37 37 34 32	43 40 38
30/7/65	100 100 100 100 100	100 100 100 100	7.305 7.295 7.255 7.26 7.26	7.27 7.26 7.335 7.27	42 38 37 42 41	42 39 32 44
2/8/65	99 99 99	99 99 99	7.33 7.36 7.34	7.37 7.30 7.27	43 38 41	40 42 42
6/8/65					43 40 38 42	37 39 36 37 36 39

Table App. 6 Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 2% halothane in nitrous oxide-oxygen.

DATE	BLOOD FLOW $N_2O + O_2$	BLOOD FLOW 4% HAL.	B.P. $N_2O + O_2$	B.P. 4% HAL.	C.V.R. $N_2O + O_2$	C.V.R. 4% HAL.
23/11/64	0.69 0.84 0.73	0.70 0.63	160 160 153	105 75	2.32 1.90 2.10	1.50 1.19
25/11/64	1.15 1.34 1.03	1.34 0.72	130 130 130	75 40	1.13 0.97 1.26	0.56 0.56
23/12/64	1.01 0.92 0.84 0.92 0.82	0.79 0.72	120 120 120 120 120	70 40	1.19 1.30 1.43 1.30 1.46	0.89 0.56
24/12/64	1.18 0.98 0.87	0.98 0.93	140 140 140	50 45	1.19 1.43 1.61	0.51 0.48
9/8/65	0.91 0.93 1.03 0.84 0.95	0.83 0.60	170 165 165 170 165	65 55	1.87 1.77 1.60 2.02 1.74	0.78 0.92

Table App. 7 Individual results for blood flow, mean blood pressure and cerebrovascular resistance during nitrous oxide-oxygen anaesthesia and during anaesthesia with 4% halothane.

DATE	Ao_2 $N_2O + O_2$	Ao_2 4% HAL.	Art. pH $N_2O + O_2$	Art. pH 4% HAL.	Pa_{co_2} $N_2O + O_2$	Pa_{co_2} 4% HAL.
23/11/64	94 94 93	93 91	7.260 7.270 7.240	7.225 7.210	40 40 40	40 37
25/11/64	96 91 90	93 89	7.260 7.270 7.260	7.290 7.310	40 40 40	38 32
23/12/64	100 99 100 100 100	98 98	7.320 7.330 7.320 7.280 7.210	7.220 7.240	36 34 34	40 40
24/12/64	96 96 95	90 93	7.240 7.245 7.235	7.230 7.250	40 40 40	37 38
9/8/65			7.230 7.240 7.245 7.220 7.200	7.180 7.160	43 41 42 42 40	46 43

Table App. 8 Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 4% halothane in nitrous oxide-oxygen.

DATE	$N_2O + O_2$		0.5% Halothane	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
28/1/64	0.060 0.068	38 37	0.059 0.063 0.052 0.061 0.050 0.047	 36 37 36
29/1/64	0.061 0.069 0.065 0.081	38 38	0.069 0.062 0.070	 38
26/2/64	0.083 0.100		0.087 0.081 0.098	
11/11/64	0.056 0.050 0.053	39 39 39	0.049 0.051 0.058 0.061	39 39 39 38
23/11/64	0.075 0.066 0.056	39 39 39	0.062 0.045	39 39
23/12/64	0.071 0.075 0.059 0.076 0.077	39 39 38 38 38	0.060 0.041	37 37
24/12/64	0.048 0.042 0.036	39 39 39	0.033 0.028 0.020 0.026 0.026	39 39 39 38 38

DATE	$N_2O + O_2$		0.5% Halothane	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
15/3/65	0.077 0.065 0.074	39 39 39	0.065 0.063 0.060	39 39 39
17/3/65	0.057 0.071 0.063	38 38 38	0.074 0.055 0.060	38 38 38
24/5/65	0.060 0.057 0.066 0.065 0.051 0.065	38 38 39 38 38 38	0.046 0.049 0.054 0.058	38 39 39 38
4/6/65	0.098 0.084 0.069 0.092 0.087 0.066	39 38 38 38 38 38	0.069 0.081 0.075	39 38 38
7/6/65	0.066 0.061 0.064 0.068	39 39 39 39	0.065 0.061	39 39
9/7/65	0.090 0.081	38 38	0.057	38
12/7/65	0.044 0.058 0.041 0.041	38 38 37 37	0.055 0.035	38 37

DATE	$N_2O + O_2$		0.5% Halothane	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
2/8/65	0.056 0.053	38 38	0.061	38

Table App. 9 Individual results for oxygen uptake of the cerebral cortex during nitrous oxide-oxygen anaesthesia and during anaesthesia with 0.5% halothane. The pharyngeal temperature at the time of the measurement is also displayed.

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH.	Ven. pH	A-V pH
28/1/64	93 94	55 56	38 38						
29/1/64	99 99 98 98	72 65 66 64	27 33 32 34						
26/2/64	91 93	54 55	37 38						
11/11/64	100 100 95	75 77 65	25 23 30	38 39	47 48	9 9	7.25 7.25 7.25	7.22 7.20 7.20	0.03 0.05 0.05
23/11/64	94 94 93	44 57 57	50 37 36	40 40 40	50 53 52	10 13 12	7.26 7.27 7.24	7.20 7.18 7.18	0.06 0.09 0.06
23/12/64	100 99 100 100 100	56 48 56 48 41	44 51 34 52 59	36 34 34 36 39	47 47 47 50 52	11 13 13 14 13	7.32 7.33 7.32 7.28 7.21	7.23 7.25 7.24 7.17 7.19	0.09 0.08 0.08 0.11 0.02

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH.	Ven. pH	A-V pH
24/12/64	96	63	33	40	48	8	7.24	7.20	0.04
	96	61	35	40	45	5	7.25	7.22	0.03
	95	57	38	4o	49	9	7.24	7.18	0.06
15/3/65	92	49	43	43	57	14	7.11	7.05	0.06
	94	45	49	47	63	16	7.09	7.03	0.06
	96	43	53	44	56	12	7.18	7.11	0.07
17/3/65	94	59	35						
	95	52	43						
	95	51	44						
24/5/65	100	68	32				7.39	7.37	0.02
	100	66	34				7.40	7.33	0.07
	99	67	32				7.36	7.29	0.07
	100	61	39				7.37	7.31	0.06
	100	57	43				7.37	7.30	0.07
	100	48	52						
4/6/65	100	63	37	41	52	11	7.32	7.29	0.03
	100	58	42	45	57	12	7.32	7.25	0.07
	100	56	44	42	56	14	7.32	7.29	0.03
	100	45	55	46	62	16	7.38	7.30	0.08
	100	41	59	42	60	18	7.35	7.27	0.08
	100	44	56	42	57	15	7.36	7.24	0.12

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
7/6/65	100	71	29	35	46	11	7.33	7.26	0.07
	99	67	32	38	53	15	7.27	7.22	0.05
	99	67	32	36	46	10	7.30	7.23	0.07
	99	60	39	32	49	17	7.31	7.25	0.06
9/7/65	100	58	42	36	57	21			
	100	53	47	38	55	17			
12/7/65	98	73	25	54	64	10			
	97	68	29	50	64	14			
	93	65	28	45	65	20			
	95	67	28	54	77	23			
2/8/65	99	60	39	38	52	14	7.36	7.30	0.06
	99	58	41	41	52	11	7.34	7.28	0.06

Table App. 10A

Values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen saturation difference, for arterial and cerebral venous Pco_2, for cerebral arterio-venous Pco_2 difference, for arterial and cerebral venous pH and cerebral arterio-venous pH difference during anaesthesia with nitrous oxide-oxygen (i.e. control values from study of effect of 0.5% halothane on oxygen uptake of the cerebral cortex).

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
28/1/64	94	67	27						
	94	64	30						
	93	64	29						
	94	60	34						
	92	54	38						
	90	55	35						
29/1/64	98	71	27						
	97	63	34						
	98	55	43						
26/2/64	93	52	41						
	90	53	37						
	94	57	37						
11/11/64	95	70	25	40	44	4	7.23	7.22	0.01
	97	67	30	38	47	9	7.27	7.23	0.04
	97	62	35	38	47	9	7.27	7.21	0.06
	98	58	40	37	50	13	7.26	7.19	0.06
23/11/64	92	57	35	40	52	12	7.24	7.17	0.07
	91	50	41	42	55	13	7.24	7.17	0.07
23/12/64	96	48	48	38	50	12	7.24	7.18	0.06
	100	56	44	39	58	19	7.27	7.17	0.10

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
24/12/64	93	72	21	40	49	9	7.21	7.18	0.03
	94	72	22	45	49	4	7.20	7.18	0.02
	95	74	21	45	49	4	7.22	7.20	0.02
	96	77	19	43	47	4	7.20	7.17	0.03
	96	75	21	39	45	6	7.22	7.21	0.02
15/3/65	90	45	45	41	54	13	7.08	7.09	-0.01
	99	46	53	42	60	18	7.13	7.11	0.02
	97	45	52	44	54	10	7.17	7.16	0.01
17/3/65	94	58	36						
	96	57	39						
	95	58	37						
24/5/65	100	75	25				7.39	7.34	0.05
	100	74	26				7.38	7.35	0.03
	100	65	35				7.37	7.32	0.05
	100	58	42				7.38	7.30	0.08
4/6/65	100	71	29	46	57	11	7.28	7.25	0.03
	100	59	41	46	59	13	7.34	7.28	0.06
	100	52	48	39	54	15	7.35	7.28	0.07
7/6/65	100	70	30	34	50	16	7.31	7.25	0.06
	100	67	33	36	52	16	7.27	7.18	0.09

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
9/7/65	100	69	31	41	50	9			
12/7/65	97 95	73 74	24 21	53 56	62 66	9 10			
2/8/65	99	66	33	39	52	13	7.35	7.32	0.03

Table App. 10B Values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen saturation difference, for arterial and cerebral venous Pco_2, for cerebral arterio-venous Pco_2 difference, for arterial and cerebral venous pH and cerebral arterio-venous pH difference during anaesthesia with 0.5% halothane (from the study of effect of 0.5% halothane on oxygen uptake of the cerebral cortex).

DATE	$N_2O + O_2$		2% Halothane	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
7/6/65	0.068 0.055	39 39	0.048	39
9/7/65	0.081 0.073 0.090 0.079 0.059	38 37 38 38 38	0.045 0.046 0.064	38 38 38
12/7/65	0.053	38	0.051	38
23/7/65	0.072 0.050	39 39	0.041	39
26/7/65	0.047 0.038 0.044 0.051	39 38 39 39	0.023 0.033 0.030	39 38 39
2/8/65	0.045 0.056 0.053	38 38 38	0.037 0.033 0.033	38 38 38

Table App. 11 Individual results for oxygen uptake of the cerebral cortex during nitrous oxide-oxygen anaesthesia and during anaesthesia with 2% halothane. The pharyngeal temperature at the time of the measurement is also displayed.

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
7/6/65	100 98	59 61	41 37	37 42	58 62	21 20	7.29 7.26	7.14 7.19	0.15 0.07
9/7/65	100 99 99 100 100	53 55 55 55 57	47 44 44 45 43	38 39 35 36 37	55 55 51 50 55	17 16 16 14 18	7.35 7.30 7.32	7.27 7.27 7.24	0.08 0.03 0.08
12/7/65	97	72	25	43	59	16	7.29	7.23	0.06
23/7/65	99 98	50 60	49 38	35 35	46 44	11 9	7.31 7.33	7.28 7.21	0.03 0.12
26/7/65	98 99 99 97	67 52 59 43	31 47 40 54	37 37 34 32	46 48 42 45	9 11 10 13	7.29 7.27 7.29 7.33	7.24 7.21 7.24 7.30	0.05 0.06 0.05 0.03

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
2/8/65	99	72	27	43	48	5	7.33	7.31	0.02
	99	60	39	38	52	14	7.36	7.30	0.06
	99	58	41	41	52	11	7.34	7.28	0.06

Table App. 12A Values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen saturation difference, for arterial and cerebral venous Pco_2, for cerebral arterio-venous Pco_2 difference, for arterial and cerebral venous pH and for cerebral arterio-venous pH difference during anaesthesia with nitrous oxide-oxygen (i.e. control values from the study of the effect of 2% halothane on oxygen uptake of the cerebral cortex).

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
7/6/65	100	75	25	43	53	10	7.26	7.21	0.05
9/7/65	100	77	23	39	47	8	7.34	7.32	0.02
	97	76	21	36	45	9	7.30	7.27	0.03
	100	72	28	36	44	8	7.29	7.18	0.11
12/7/65	100	73	27	47	60	13	7.29	7.22	0.07
23/7/65	97	73	24	34	53	19	7.30	7.26	0.04
26/7/65	96	82	14	43	47	4	7.25	7.24	0.01
	97	73	20	40	44	4	7.29	7.21	0.08
	97	73	24	38	43	5	7.25	7.22	0.03
2/8/65	99	76	23	40	48	8	7.37	7.32	0.05
	99	78	21	42	51	9	7.30	7.27	0.03
	100	72	28	32	42	10	7.32	7.30	0.02

Table App. 12B Values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen saturation difference, for arterial and cerebral venous Pco_2, for cerebral arterio-venous Pco_2 difference, for arterial and cerebral venous pH and cerebral arterio-venous pH difference during anaesthesia with 2% halothane (from study of the effect of 2% halothane on oxygen uptake of the cerebral cortex).

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
7/5/63	0.74 0.79 0.67	1.11 0.87 0.71 0.61 0.80 0.79 0.76	145 120 120	135 140 145 145 150 155 155	1.89 1.48 1.74	1.13 1.53 1.94 2.31 1.83 1.91 1.99
9/5/63	0.73 0.80 0.79	0.96 0.90 0.81 0.76	120 120 120	120 110 110 115	1.59 1.46 1.48	1.20 1.17 1.30 1.45
13/5/63	0.71 0.82 0.80	0.77 0.79 0.70 0.80 0.76	145 145 155	145 140 150 145 145	1.94 1.69 1.86	1.80 1.71 2.07 1.74 1.85
20/6/63	0.84 0.76 0.72	0.58 0.54 0.61 0.58 0.60 0.61 0.60 0.62	145 145 145	140 140 135 135 135 135 135 130	1.69 1.88 1.98	2.36 2.55 2.16 2.26 2.18 2.15 2.18 2.03

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
27/6/63	0.53 0.57 0.58	0.59 0.54 0.58 0.61 0.53	200 195 190	180 185 185 190 180	3.70 3.36 3.21	2.99 3.35 3.12 3.06 3.32
2/7/63	0.88 0.90 0.97	0.90 0.93	160 160 190	170 170	1.82 1.78 1.96	1.89 1.83

Table App. 13 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during prolonged administration of trichloroethylene.

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
7/5/63	97 100 99	100 100 100 100 99 99 99	7.31 7.35 7.35	7.32 7.37 7.37 7.36 7.37 7.36 7.35	36 37 34	42 31 36 34 35 34 36
9/5/63	100 99 100	100 99 99 99	7.26 7.26 7.26	7.23 7.24 7.25 7.23	35 36 38	38 40 34 37
13/5/63	100 98 100	100 100 92 100 100	7.33 7.32 7.33	7.33 7.31 7.34 7.35 7.34	35 37 31	32 36 34 30 34
20/6/63	97 100 97	98 98 98 98 99 98 98 98	7.31 7.31 7.29	7.31 7.31 7.31 7.30 7.30 7.30 7.28 7.29	40 37 38	38 36 36 37 38 36 34 36

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
27/6/63	93 93 98	97 98 98 95 98	7.36 7.33 7.34	7.35 7.35 7.33 7.30 7.31	34 40 38	36 34 35 36 35
2/7/63	97 96 95	98 98	7.29 7.29 7.34	7.29 7.31	38 38 30	36 32

Table App. 14 Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during prolonged anaesthesia with trichloroethylene in nitrous oxide-oxygen.

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
7/5/63	0.74 0.79 0.67	1.11	145 120 120	135	1.89 1.48 1.74	1.13
9/5/63	0.73 0.80 0.79	0.96	120 120 120	120	1.59 1.46 1.48	1.20
13/5/63	0.71 0.82 0.80	0.77	145 145 145	145	1.94 1.69 1.86	1.80
20/6/63	0.84 0.76 0.72	0.58	145 145 145	140	1.69 1.88 1.98	2.36
27/6/63	0.53 0.57 0.58	0.59	200 195 190	180	3.70 3.36 3.21	2.99
2/7/63	0.88 0.90 0.97	0.90	160 160 190	170	1.82 1.78 1.96	1.89

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
17/1/66	1.03 1.24 1.16 1.43 1.16 1.16 0.93 0.84	1.62 1.43 1.69 1.43	130 135 135 130 115 125 145 168	140 145 145 145	1.26 1.09 1.16 0.91 0.99 1.08 1.56 2.00	0.86 1.01 0.86 1.01
18/2/66	0.70 0.73	1.80 0.86	160 170	160 145	2.29 2.33	0.89 1.69
21/2/66	0.79 0.64 0.65 0.57 0.57 0.77	0.86 0.84 1.00	160 160 175 170 165 175	170 175 170	2.03 2.50 2.69 2.98 2.89 2.27	1.98 2.08 1.70
6/5/66	0.88 1.35 0.95 0.86 0.82 0.76 0.76	1.80 0.97 1.11	190 185 185 190 185 190 190	190 190 190	2.16 1.37 1.95 2.21 2.26 2.50 2.50	1.06 1.96 1.71

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
9/5/66	0.80 0.80 0.86 0.87 0.84 0.71 0.60 0.64	1.09 1.03 0.91	140 145 145 140 140 145 145 145	145 145 145	1.75 1.81 1.69 1.61 1.67 2.04 2.42 2.27	1.33 1.41 1.59

Table App. 15 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during first 20 minutes of trichloroethylene administration.

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
7/5/63	97 100 99	100	7.310 7.350 7.350	7.320	36 37 34	42
9/5/63	100 99 100	100	7.260 7.265 7.260	7.230	35 36 38	38
13/5/63	100 98 100	100	7.330 7.320 7.330	7.330	35 37 31	32
20/6/63	97 100 97	98	7.305 7.310 7.295	7.310	40 37 38	38
27/6/63	93 93 98	97	7.360 7.330 7.340	7.350	34 40 38	36
2/7/63	97 96 95	98	7.290 7.290 7.335	7.290	38 38 30	36

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
17/1/66			7.195	7.195	43	40
		98	7.165	7.165	43	40
	97	99	7.175	7.145	37	39
	97	99	7.160	7.130	40	40
	98		7.145		43	
	98		7.145		39	
	99		7.130		44	
	98		7.140		42	
18/2/66	99	98	7.320	7.280	41	42
	99	99	7.320	7.340	39	35
21/2/66	100	99	7.365	7.350	32	34
	100	97	7.310	7.320	39	37
	100	96	7.340	7.300	36	36
	100		7.350		30	
	96		7.310		40	
	100		7.310		40	
6/5/66	100	100	7.275	7.310	45	46
	100	100	7.300	7.300	48	44
	99	99	7.320	7.270	50	44
	100		7.295		43	
	99		7.285		43	
	99		7.310		41	
	99		7.300		39	

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.	$N_2O + O_2$	T.C.E.
9/5/66	100	100	7.290	7.300	40	44
	100	100	7.290	7.300	43	43
	100	100	7.300	7.295	43	42
	98		7.280		46	
	100		7.295		45	
	99		7.280		46	
	100		7.280		43	
	100		7.280		41	

Table App. 16 Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during the 1st 20 minutes of anaesthesia with trichloroethylene in nitrous oxide-oxygen.

DATE	$N_2O + O_2$		Trichloroethylene	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
7/5/63	0.051 0.055 0.047	37.0 37.0 37.0	0.044 0.036 0.052 0.041 0.042 0.049 0.052	38.0 38.0 38.0 37.0 37.0 36.5 36.5
9/5/63	0.096 0.098 0.093	38.0 38.0 38.0	0.088 0.079 0.074 0.086	38.0 38.0 38.0 38.0
20/6/63	0.066 0.089 0.079	38.0 38.0 37.0	0.060 0.055 0.063 0.057 0.060 0.062 0.057 0.051	37.0 37.0 37.0 36.5 36.5 36.5 37.0 37.0
27/6/63	0.056 0.055 0.060		0.057 0.062 0.040 0.034 0.042	 38.0 38.5
17/1/66	0.054 0.058 0.064 0.071 0.073 0.066	38.5 38.7 39.2 39.0 38.4 38.5	0.046 0.059 0.054	38.7 39.2 39.0

DATE	$N_2O + O_2$		Trichloroethylene	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
18/2/66	0.088 0.099	39.0 38.0	0.097 0.067	38.5 38.5
21/2/66	0.051 0.043 0.056 0.073 0.075 0.076	37.5 38.0 39.0 39.0 39.0 39.0	0.040 0.043 0.077	38.0 39.0 39.0
6/5/66	0.043 0.029 0.036 0.051 0.064 0.053 0.065	38.0 39.0 38.0 38.5 38.5 38.5 38.5	0.011 0.018 0.039	38.0 38.0 38.5
9/5/66	0.048 0.048 0.058 0.040 0.040 0.047 0.041 0.050	38.0 38.0 38.0 38.0 38.0 38.5 39.0 39.0	0.049 0.010 0.047	38.0 38.0 38.5

Table App. 17 Individual results for oxygen uptake of the cerebral cortex during nitrous oxide-oxygen anaesthesia and during anaesthesia with trichloroethylene. The pharyngeal temperature at the time of the measurement is also displayed.

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
7/5/63	97 100 99	56 58 57	41 42 42						
9/5/63	100 99 100	51 53 56	49 46 44						
20/6/63	97 100 97	62 48 48	35 52 49						
27/6/63	93 93 98	52 55 58	41 38 40						
17/1/66	97 97 98 99 99 98	81 83 79 76 71 70	16 14 19 23 28 28				7.175 7.160 7.145 7.145 7.130 7.140	7.140 7.135 7.125 7.120 7.095 7.110	.035 .025 .020 .025 .035 .030

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
18/2/66	99	62	37				7.320	7.255	.065
	99	59	40				7.320	7.260	.060
	97	71	26				7.310	7.255	.055
	98	61	37				7.350	7.290	.060
	99	58	41				7.345	7.280	.065
21/2/66	100	80	20				7.365	7.330	.035
	100	79	21				7.310	7.290	.020
	100	73	27				7.340	7.295	.045
	100	65	35				7.350	7.320	.030
	96	55	41				7.310	7.280	.030
	100	59	41				7.310	7.250	.060
6/5/66	100	75	25	45	56	11	7.275	7.240	.035
	100	89	11	48	56	8	7.300	7.280	.020
	99	80	19	50	56	6	7.320	7.270	.050
	100	70	30	43	50	7	7.295	7.270	.025
	99	60	39	43	60	17	7.285	7.230	.055
	99	64	35	41	52	11	7.310	7.240	.070
	99	57	42	39	52	13	7.300	7.250	.050

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
9/5/66	100	64	36	40	53	13	7.290	7.250	.040
	100	64	36	43	54	11	7.290	7.270	.020
	100	59	41	43	53	10	7.300	7.235	.065
	98	70	28	46	56	10	7.280	7.240	.040
	100	71	29				7.295	7.250	.045
	99	59	40				7.280	7.230	.050
	100	58	42	43	52	9	7.280	7.230	.050
	100	52	48	41	53	12	7.280	7.230	.050

Table App. 18A Values for arterial and cerebral venous oxygen saturation, for cerebral arterio-venous oxygen saturation difference, for arterial and cerebral venous Pco_2, for cerebral arterio-venous Pco_2 difference, for arterial and cerebral venous pH and for cerebral arterio-venous pH difference during anaesthesia with nitrous oxide-oxygen (i.e. control values from the study of the effect of trichloroethylene on the oxygen uptake of the cerebral cortex).

DATE	Ao_2	Vo_2	$A\text{-}Vo_2$	Pa_{co_2}	Pv_{co_2}	$Pa\text{-}v_{co_2}$	Art. pH	Ven. pH	A-V pH
7/5/63	100 100 100 100 99 99 99	77 75 56 59 68 62 58	23 25 44 41 31 37 41						
9/5/63	100 99 99 99	67 66 65 56	33 33 34 43						
20/6/63	98 98 98 98 99 98 98 98	52 53 52 54 54 53 56 61	46 45 46 44 45 45 42 37						
27/6/63	97 98 98 95 98	59 53 71 73 67	38 45 27 22 31						

DATE	Ao_2	Vo_2	A-Vo_2	Pa_{co_2}	Pv_{co_2}	Pa-v_{co_2}	Art. pH	Ven. pH	A-V pH
	98	87	11				7.165	7.145	.020
	99	86	13				7.145	7.105	.040
17/1/66	99	83	16				7.130	7.110	.020
	99	82	17				7.280	7.260	.020
18/2/66	99	76	23				7.340	7.310	.030
	100	73	27				7.360	7.300	.060
	99	84	15				7.350	7.305	.045
21/2/66	97	81	16				7.320	7.300	.020
	96	73	23				7.300	7.270	.030
	100	94	6	46	50	4	7.310	7.290	.020
6/5/66	100	90	10	44	47	3	7.300	7.300	.000
	99	82	17	44	51	7	7.270	7.255	.015
	100	73	27	44	52	8	7.300	7.240	.060
9/5/66	100	94	6	43	48	5	7.300	7.270	.030
	100	69	31	42	49	7	7.295	7.250	.045

Table App. 18B Values for arterial and cerebral venous oxygen saturation, cerebral arterio-venous oxygen saturation difference, arterial and cerebral venous Pco_2 and cerebral arterio-venous Pco_2 difference and for arterial and cerebral venous pH and cerebral arterio-venous pH difference during anaesthesia with trichloroethylene (from the study of the effect of trichloroethylene on the oxygen uptake of the cerebral cortex).

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform
5/7/63	0.73 0.97 0.83	1.19	170 170 170	140	2.33 1.75 2.05	1.18
9/7/63	1.19 1.19 1.36	1.27 1.23 1.09 1.12	170 160 160	150 155 155 155	1.43 1.34 1.18	1.18 1.26 1.42 1.38
12/7/63	0.76 0.79 0.68	0.91 0.75	175 175 175	180 165	2.30 2.22 2.57	1.98 2.20
12/8/63	0.54 0.59 0.55	0.88 0.78 0.75 0.81	150 160 165	150 140 120 140	2.78 2.71 3.00	1.70 1.79 1.60 1.73
27/8/63	0.78 0.84 0.81	1.00 0.78 0.66	165 160 155	150 145 120	2.12 1.90 1.91	1.50 1.86 1.82

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform
8/10/63	0.85 0.75 0.90	0.83 0.76 0.95	125 140 140	125 130 135	1.47 1.87 1.56	1.51 1.71 1.42
11/10/63	0.64 0.61	1.00 0.86 0.82	160 155	160 130 115	2.50 2.54	1.60 1.51 1.40
18/10/63	0.54 0.54 0.56	0.64 0.69	150 150 160	140 120	2.78 2.78 2.86	2.19 1.74
26/10/63	0.70 0.59 0.67 0.68	0.95	160 165 150 140	150	2.29 2.80 2.24 2.06	1.57
29/10/63	0.72 0.71 0.76	0.88 0.86 0.95	155 170 175	150 140 130	2.15 2.39 2.30	1.70 1.63 1.37
20/1/64	0.67 0.61	0.76 0.68	165 160	155 150	2.46 2.62	2.04 2.21

DATE	BLOOD FLOW		B.P.		C.V.R.	
	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform	$N_2O + O_2$	Chloroform
	0.83 0.83 0.86	1.23 1.36 1.36 1.15	145 145 145	145 135 130 125	1.75 1.75 1.69	1.18 0.99 0.96 1.09

Table App. 19 Cerebral cortical blood flow, cerebrovascular resistance and mean blood pressure during unsupplemented nitrous oxide-oxygen anaesthesia and during anaesthesia with 1% chloroform in nitrous oxide-oxygen.

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	Chloroform	N_2O	Chloroform	N_2O	Chloroform
5/7/63	92 95 99	97	7.360 7.330 7.345	7.335	32 39 36	37
9/7/63	95 99	89 96 95 99	7.275 7.320 7.290	7.270 7.310 7.305 7.280	45 36 41	45 36 35 39
12/7/63	92 99 95	99 99	7.360 7.365 7.360	7.300 7.330	40 38 38	44 37
12/8/63	100 100 98	99 96 97 96	7.245 7.265 7.275	7.270 7.240 7.230 7.060	41 41 38	39 40 40 40
27/8/63	100 98 100	100 100	7.320 7.290 7.300	7.300 7.245 7.255	34 34 34	34 42 30

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	Chloroform	N_2O	Chloroform	N_2O	Chloroform
8/10/63	95 94 90	92 89 92	7.330 7.335 7.330	7.340 7.330 7.280	40 40 39	39 34 43
11/10/63	92 99	93 98 97	7.295 7.295	7.305 7.270 7.180	37 38	39 38 35
18/10/63	99 99 97	99 98	7.350 7.360 7.355	7.315 7.260	33 28 28	28 29
26/10/63	95 95 100 97	90	7.300 7.340 7.300 7.300	7.320	34 27 37 40	31
29/10/63	99 98 98	94 96 98	7.390 7.400 7.410	7.400 7.370 7.320	35 35 32	28 28 30
20/1/64	97 94	97 95	7.350 7.340	7.280 7.270	34 34	45 48

DATE	Ao_2		Art. pH		Pa_{co_2}	
	$N_2O + O_2$	Chloroform	N_2O	Chloroform	N_2O	Chloroform
19/8/64	97 97 97	98 97 97 97	7.370 7.315 7.300	7.280 7.290 7.290 7.300	36 38 39	40 40 38 35

Table App. 20. Arterial oxygen saturation, pH and Pa_{co_2} during nitrous oxide-oxygen anaesthesia and during anaesthesia with 1% chloroform in nitrous oxide-oxygen.

DATE	$N_2O + O_2$		1% CHLOROFORM	
	Oxygen Uptake	Temp. °C.	Oxygen Uptake	Temp. °C.
12/7/63	0.060 0.094 0.073	37.0 36.5 37.0	0.065 0.061	37.0 37.5
11/10/63	0.052 0.067	36.5 37.0	0.070 0.049 0.040	37.0 37.0 37.0
18/10/63	0.057 0.056 0.072	- - -	0.059 0.065	- -
26/10/63	0.067 0.056 0.070 0.065	- - -	0.041	-
20/1/64	0.050 0.045	39.5 39.5	0.048 0.040	39.5 39.5
19/8/64	0.047 0.048 0.049	39.0 39.0 39.0	0.054 0.059 0.060 0.056	39.0 39.0 39.0 39.0

Table App. 21 Individual results for oxygen uptake of the cerebral cortex during nitrous oxide-oxygen anaesthesia and during anaesthesia with 1% chloroform. The pharyngeal temperature at the time of the measurement is also displayed.

DATE	$N_2O + O_2$			1% CHLOROFORM		
	Ao_2	Vo_2	$A\text{-}Vo_2$	Ao_2	Vo_2	$A\text{-}Vo_2$
12/7/63	92 99 95	61 52 53	31 47 42	99 99	71 67	28 32
11/10/63	92 99	62 58	30 41	93 98 97	67 77 79	26 21 18
18/10/63	99 99 99	61 62 51	38 37 48	99 98	66 64	33 34
26/10/63	95 95 100 97	60 60 62 62	35 35 38 35	90	74	16
20/1/64	97 94	71 69	26 25	97 95	75 75	22 20
19/8/64	97 97 97	65 65 65	32 32 32	98 97 97 97	74 73 72 70	24 24 25 27

Table App. 22 Values for arterial and cerebral venous oxygen saturation and for cerebral arterio-venous oxygen saturation difference during nitrous-oxygen anaesthesia and during anaesthesia with 1% chloroform.

DATE	HALOTHANE CONCENTRATION	HALOTHANE & NORMOCAPNIA			HALOTHANE & HYPOCAPNIA		
		Blood Flow	Pa_{CO_2}	Mean B.P.	Blood Flow	Pa_{CO_2}	Mean B.P.
23/7/65	2%	0.74	35	65	0.59	27	50
30/7/65	2%	1.33	39	100	0.76	32	90
2/8/65	2%	0.77	42	85	0.65	32	70

Table App. 23 The effect of hypocapnia on blood flow through the cerebral cortex during halothane anaesthesia.

DATE	HALOTHANE CONCENTRATION	HALOTHANE & NORMOCAPNIA			HALOTHANE & HYPERCAPNIA		
		Blood Flow	Pa_{CO_2}	Mean B.P.	Blood Flow	Pa_{CO_2}	Mean B.P.
25/11/64	0.5%	1.00	44	120	2.12	75	130
2/8/65	2%	0.77	42	85	0.88	63	65

Table App. 24 The effect of hypercapnia on blood flow through the cerebral cortex during halothane anaesthesia.

DATE	TRICHLOROETHYLENE & NORMOCAPNIA			TRICHLOROETHYLENE & HYPOCAPNIA		
	Blood Flow	Pa_{CO_2}	Mean B.P.	Blood Flow	Pa_{CO_2}	Mean B.P.
9/5/63	0.76	37	115	0.57	24	105
13/5/63	0.76	34	145	0.56	21	140
20/6/63	0.62	36	130	0.51	21	120
27/6/63	0.53	35	180	0.41	23	140

Table App. 25 The effect of hypocapnia on blood flow through the cerebral cortex during trichloroethylene anaesthesia (< 1% trichloroethylene).

DATE	TRICHLOROETHYLENE & NORMOCAPNIA			TRICHLOROETHYLENE & HYPERCAPNIA		
	Blood Flow	Pa_{CO_2}	Mean B.P.	Blood Flow	Pa_{CO_2}	Mean B.P.
20/6/63	0.62	36	130	1.09	79	140
27/6/63	0.53	35	180	1.80	84	170

Table App. 26 The effect of hypercapnia on blood flow through the cerebral cortex during trichloroethylene anaesthesia ($<$ 1% trichloroethylene).

DATE	CHLOROFORM & NORMOCAPNIA			CHLOROFORM & HYPOCAPNIA		
	Blood Flow	Pa_{co_2}	Mean B.P.	Blood Flow	Pa_{co_2}	Mean B.P.
27/8/63	0.78	42	145	0.66	30	120
19/8/64	1.15	35	125	0.93	25	110

Table App. 27 The effect of hypocapnia on blood flow through the cerebral cortex during chloroform anaesthesia (1% chloroform).

DATE	CHLOROFORM & NORMOCAPNIA			CHLOROFORM & HYPERCAPNIA		
	Blood Flow	Pa_{CO_2}	Mean B.P.	Blood Flow	Pa_{CO_2}	Mean B.P.
27/8/63	0.78	42	145	1.65	58	125
8/10/63	0.95	43	135	1.46	68	100
19/8/64	1.15	35	125	1.81	62	95

Table App. 28 The effect of hypercapnia on blood flow through the cerebral cortex during chloroform anaesthesia (1% chloroform).

DOG NO.	EXPERIMENT PROTOCOL
1	1% chloroform on c.s.f. pressure.
2	0.5% halothane and 1% chloroform separately on c.s.f. and central venous pressures. Also 0.5% halothane during hyperventilation.
3	Experiment abandoned because of hypotension.
4	Experiment abandoned. Catheter accidentally dislodged from cisterna magna.
5	Prolonged 0.5% halothane on c.s.f. and cerebral venous pressures.
6	Experiment abandoned because of hypoxic incident.
7	Experiment not relevant. Hypothermia on c.s.f. pressure.
8	0.5% and 2% halothane on c.s.f., cerebral venous and central venous pressures.
9	0.5% and 2% halothane on c.s.f. and cerebral venous pressures.

Table App. 29 Protocols of individual experiments in animal study of influence of volatile anaesthetic drugs on cerebrospinal fluid and cerebral venous pressures.

PATIENT	REASON FOR EXCLUSION
5	No blood gas results.
7	Loss of C.S.F. from L.P. needle.
9	Recorder failure.
13	No stable control value for c.s.f pressure.
15	No stable control value for c.s.f. pressure.
23	Pressure transducer faulty.
26	No stable control value for c.s.f. pressure.
28	Pressure transducer faulty.
29	Pressure transducer faulty.
30	Pressure transducer faulty.
42	No stable control value for c.s.f. pressure.

Table App. 30 Patient studies excluded from results section together with reasons for exclusion.

PATIENT	SEX	AGE	INVESTIGATION
6	M	57	0.5% halothane during normocapnia on c.s.f. and central venous pressures.
38	M	42	0.5% halothane during normocapnia on c.s.f. and central venous pressures.
40	M	27	0.5% halothane during normocapnia on c.s.f. and central venous pressures.
43	F	47	0.5% halothane during normocapnia on c.s.f. and central venous pressures.
14	M	40	0.5% halothane during normocapnia on c.s.f. pressure.
16	M	37	0.5% halothane during normocapnia on c.s.f. pressure.
17	F	34	0.5% halothane during normocapnia on c.s.f. pressure.
32	M	47	0.5% halothane during normocapnia on c.s.f. pressure.
31	F	50	0.5% halothane during hypocapnia on c.s.f. and central venous pressures.
33	F	22	0.5% halothane during hypocapnia on c.s.f. and central venous pressures.
34	M	52	0.5% halothane during hypocapnia on c.s.f. and central venous pressures.
39	F	44	0.5% halothane during hypocapnia on c.s.f. and central venous pressures.
8	M	39	0.5% halothane during hypocapnia on c.s.f. pressure.
12	F	38	0.5% halothane during hypocapnia on c.s.f. pressure.

PATIENT	SEX	AGE	INVESTIGATION
38	M	42	1% halothane during normocapnia on c.s.f. and central venous pressures.
68	M	47	1% halothane during normocapnia on c.s.f. and central venous pressures.
69	M	25	1% halothane during normocapnia on c.s.f. and central venous pressures.
10	M	37	1% halothane during normocapnia on c.s.f. pressure.
25	M	30	0.9% trichloroethylene during normocapnia on c.s.f. and central venous pressures.
18	M	42	0.9% trichloroethylene during normocapnia on c.s.f. pressure.
21	F	34	0.9% trichloroethylene during normocapnia on c.s.f. pressure.
22	M	45	0.9% trichloroethylene during normocapnia on c.s.f. pressure.
24	M	29	0.9% trichloroethylene during normocapnia on c.s.f. pressure.
20	F	43	0.9% trichloroethylene during normocapnia on central venous pressure.
35	M	32	0.9% trichloroethylene during normocapnia on central venous pressure.

Table App. 31 Details of age, sex and investigation performed in the patients studied.

PATIENT	C.S.F. PRESSURE			Pa_{co_2}		TEMP.	SYSTOLIC B.P.		CENTRAL VENOUS PRESSURE
	BEFORE	0.5% HAL.	AFTER	BEFORE	AFTER		BEFORE	0.5% HAL.	
6	216/213*	260/255*	208/204*	39	-	-	110	105	NO CHANGE*
14	24/20	84/68	33/27	45	41	37.3	95	85	-
16	125	172	-	45	-	36.8	100	85	-
17	113/75	265/188	105/68	40	40	34.7	100	80	-
32	164/111	253/179	-	39	39	34.2	120	105	-
38	250/160	330/240	260/180	37	37	36.4	100	90	+ 8
40	117/92	167/125	100/75	39	39	35.2	120	100	NO CHANGE*
43	157/93	222/130	193/107	45	46	35.7	90	75	NO CHANGE*

Table App. 32 Individual results for c.s.f. and central venous pressures, for Pa_{co_2}, oesophageal temperature and systolic blood pressure prior to, during and after administration of 0.5% halothane (normocapnic results) in patients. C.S.F. and central venous pressures marked with * were measured with saline manometer; all other measurements made electronically.

PATIENT	C.S.F. PRESSURE			Pa_{co_2}		TEMP.	SYSTOLIC B.P.		CENTRAL VENOUS PRESSURE
	BEFORE	1% HAL.	AFTER	BEFORE	AFTER		BEFORE	1% HAL.	
10	75/71*	140/135*	48/44*	45	45	35.4	110	90	-
38	250/160	380/268	260/180	38	38	36.4	100	85	+1
68	112/50	225/119	100/31	40	35	36.1	125	80	NO CHANGE*
69	127/90	286/173	109/64	38	42	34.7	110	90	NO CHANGE*

Table App. 33 Individual results for c.s.f. and central venous pressure, for Pa_{co_2}, oesophageal temperature and systolic blood pressure prior to, during and after administration of 1% halothane in patients. C.s.f. and central venous pressure marked * were measured with saline manometer; all other measurements made electronically.

PATIENT	C.S.F. PRESSURE			Pa_{co_2}		TEMP.	SYSTOLIC B.P.		CENTRAL VENOUS PRESSURE
	BEFORE	0.5% HAL.	AFTER	BEFORE	AFTER		BEFORE	0.5% HAL.	
8	21*	39*	25*	-	27	35.1	95	82	-
12	22/19*	31/29*	33/31*	31	27	35.3	110	90	-
31	63/35	112/70	81/35	32	29	36.1	100	92	+ 4
33	16/5	20/9	-	21	-	35.3	88	85	+ 9
34	24/12	36/20	-	36	32	36.4	107	90	NO CHANGE
39	3/-7	30/17	-17/-27	33	33	36.0	110	100	NO CHANGE

Table App. 34 Individual results for c.s.f. and central venous pressures, for Pa_{co_2}, oesophageal temperature and systolic blood pressure prior to, during and after 0.5% halothane (hypocapnic results) in patients. C.S.F. and central venous pressures marked * were measured with saline manometer; all other measurements made electronically.

PATIENT	C.S.F. PRESSURE			Pa_{co_2}		TEMP.	SYSTOLIC B.P.		CENTRAL VENOUS PRESSURE
	BEFORE	0.9% T.C.E.	AFTER	BEFORE	AFTER		BEFORE	0.9% T.C.E.	
18	81/73	144/130	90/81	41	39	36.9	95	85	-
20	-	-	-	-	-	-	-	-	NO CHANGE
21	132/108	252/204	114/96	39	34	-	110	78	-
22	170/150	360/320	210/190	39	35	35.2	90	75	-
24	117/109	236/226	113/102	40	34	35.8	120	100	-
25	96/83	167/150	121/100	43	40	35.4	110	95	NO CHANGE*
35	-	-	-	-	-	-	-	-	+ 30*

Table App. 35 Individual results for c.s.f. and central venous pressures (mm. H_2O), for Pa_{co_2}, oesophageal temperature and systolic blood pressure prior to, during and after 0.9% trichloroethylene in patients. Central venous pressures marked * were measured with saline manometer.

PATIENT	HAL. CONC.	C.S.F. PRESSURE			Pa_{co_2}		TEMP.	SYSTOLIC B.P.	
		BEFORE	HALOTHANE	AFTER	BEFORE	AFTER		BEFORE	HALOTHANE
A.D.	0.5%	180/160	520/460	330/290	38	37	36.3	110	90
A.McN.	1%	155/130	800/620	165/135	34	-	35.6	130	100
H.T.	1%	168/108	537/281	173/109	50	54	35.8	120	95
M.J.	1%	382/232	690/455	346/200	39	39	36.4	110	75

Table App. 36 Individual results for c.s.f. pressure, Pa_{co_2}, oesophageal temperature and systolic blood pressure prior to, during and after halothane administration to patients with intracranial tumuours.

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THE EFFECTS OF CLINICAL CONCENTRATIONS OF HALOTHANE ON THE BLOOD FLOW AND OXYGEN UPTAKE OF THE CEREBRAL CORTEX

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SUMMARY

Clinical concentrations of halothane vaporized in nitrous oxide-oxygen caused vasodilatation in the cerebral cortex of anaesthetized dogs at constant arterial carbon dioxide tension. The vasodilatory action on the cerebral circulation was greater the higher the concentration of halothane. Consequently 2 per cent halothane increased blood flow through the cerebral cortex more than did 0.5 per cent halothane. However, the administration of 4 per cent halothane reduced mean blood pressure so markedly that blood flow was not elevated above the control value. The oxygen uptake of the cerebral cortex was depressed by halothane and this depression was greater with 2 per cent halothane than with 0.5 per cent. These results are discussed with reference to the effects of halothane on intracranial pressure and on the oxygenation of the brain.

Over the past three years, evidence has accumulated which indicates that halothane is a cerebral vasodilator. However, there is no knowledge of the relationship between cerebral blood flow and concentration of halothane administered nor is there agreement on the effect of the drug on the oxygen uptake of the brain. The following studies were undertaken to elucidate the effects of a range of concentrations of halothane on the blood flow and oxygen uptake of the cerebral cortex.

METHODS

Unselected mongrel dogs were anaesthetized with a dose of thiopentone just sufficient to produce sleep. Following endotracheal intubation, the animals were ventilated by intermittent positive pressure using a non-return circuit and anaesthesia was maintained with 70 per cent nitrous oxide and 30 per cent oxygen. Muscular relaxation was obtained with intermittent doses of a dilute solution of suxamethonium in order to allow control of ventilation and so of arterial carbon dioxide tension. One or occasionally two supplemental doses of thiopentone were administered during the early stages of the surgical preparation.

The femoral artery and vein on one side were exposed and cannulated; the arterial cannula allowed measurement of mean arterial blood pressure and sampling of arterial blood. The venous cannula was for the injection of suxamethonium. The common carotid artery on one side was exposed and its superior thyroid branch cannulated.

After exposing the skull by reflection of skin and temporalis muscle, a trephine was made over the parietal cortex. The dura was opened, carefully avoiding trauma to the cortical surface. The exposed brain was immediately covered with a plastic membrane 6μ in thickness ("Melinex"; ICI—polyethylene teraphthalate) to prevent drying and heat loss. A second trephine was made in the midline of the skull to expose the superior sagittal sinus and into this a cannula was inserted for the sampling of cerebral venous blood. Anterior to this trephine the bone overlying the sinus was removed in order to sever diploic connections.

Blood flow in the cerebral cortex was measured by the radioactive inert gas clearance technique of Lassen and Ingvar (1961). The radioactive gas employed was krypton 85, the beta emissions of which were counted by a Geiger Muller tube mounted above the exposed cerebral cortex. The krypton, dissolved in saline, was injected into the cerebral circulation via the cannula in the common carotid artery. The speed of its injection was controlled to give a relatively constant counting

rate from the cortex over a period of 2–3 minutes. During this time, equilibration between the concentration of krypton in the arterial blood and the concentration in the cerebral cortex was achieved (Harper, 1966a). The injection was then suddenly stopped and the rate of clearance of krypton from the brain tissue was measured. After transposition to semilogarithmic paper, the slope of the initial part of this clearance curve was measured. The time to half-clearance so obtained was inserted into the following equation to yield cortical flow (Ingvar and Lassen, 1962).

$$\text{Flow (ml/g/min)} = \frac{\lambda \log_e 2 \times 60}{T\frac{1}{2}}$$

where λ = brain-blood partition coefficient for krypton.

Mean arterial blood pressure was monitored with a damped mercury manometer. Pharyngeal temperature was measured by a mercury-in-glass thermometer. Heating was applied as necessary to maintain the pharyngeal temperature close to 38°C. Arterial and venous blood samples were withdrawn from the femoral artery and sagittal sinus following each determination of blood flow and were analyzed for oxygen saturation, pH and Pco_2.

The oxygen saturation measurements were carried out on a Kipp haemoreflector which was calibrated for each experiment with the animal's own blood. Arterial and venous pH were measured with a capillary glass electrode (Radiometer); arterial and venous Pco_2 were measured with a carbon dioxide electrode of the type described by Severinghaus and Bradley (1958) (Electronic Instruments Ltd.). Calibration of the pH electrode was with two known phosphate buffers and of the Pco_2 electrode with humidified gases of three known carbon dioxide concentrations.

Haemoglobin concentration of arterial blood was measured by the cyanmethaemoglobin method with spectrophotometric analysis at 540 mμ wavelength.

Experimental procedure.

Measurements of blood flow were started when a time interval of at least 1 hour had elapsed since opening the dura or of at least 2 hours after administering the last dose of thiopentone, whichever was the longer. It was known, from preliminary studies, that within these time limits blood flow through the cerebral cortex reached a value which thereafter remained constant for many hours if the experimental conditions were not altered. Cerebral cortical blood flow was measured during nitrous oxide-oxygen anaesthesia and during anaesthesia with 0.5 per cent halothane, 2 per cent halothane or 4 per cent halothane. The halothane was vaporized in nitrous oxide-oxygen from a Fluotec II vaporizer, the output of which was checked by refractometry; the actual concentrations delivered by the particular Fluotec used at each setting of the control dial are given in table I.

TABLE I

The halothane output of the Fluotec used.

Indicated dial reading (%)	Actual halothane output (%)
0.5	0.46
2.0	1.98
4.0	4.12

In most animals only one halothane concentration was studied but in some experiments measurements were made during the administration of two different concentrations of halothane. All comparisons were made with the values for blood flow obtained during unsupplemented nitrous oxide-oxygen anaesthesia in the same animals. In all, there were 88 measurements of flow during 0.5 per cent halothane in 24 dogs (with 84 control measurements), 26 measurements of flow during 2 per cent halothane in 9 dogs (with 34 control measurements) and 10 measurements during 4 per cent halothane in 5 dogs (with 19 control measurements).

RESULTS

Blood flow through the cerebral cortex.

The blood flow through the cerebral cortex during administration of 0.5 per cent halothane (table II and fig. 1) was not significantly different from that under unsupplemented nitrous oxide anaesthesia while mean blood pressure was reduced by 11 per cent. However, analysis of the flow data, with reference to duration of halothane administration, shows that there was a 16 per cent increase in flow during the first 20 minutes of

TABLE II

The effect of 0.5% halothane on blood flow through the cerebral cortex.

		Nitrous oxide +oxygen	0.5% halothane all measurements	Nitrous oxide +oxygen	0.5% halothane 1st 20 min	Nitrous oxide +oxygen	0.5% halothane over 60 min
Blood flow (ml/g/min)	Mean	0.88	0.94	0.88	1.02†	0.96	0.84
	SD	0.19	0.27	0.19	0.25	0.18	0.27
Blood pressure (mm Hg)	Mean	141	126‡	142	132†	143	123‡
	SD	14	17	14	17	11	16
Pa_{CO_2} (mm Hg)	Mean	38.9	39.9	39.0	40.0	38.2	39.0
	SD	4.2	4.0	4.4	5.1	2.3	3.4

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$

TABLE III

The effect of 2% halothane on blood flow through the cerebral cortex.

		Nitrous oxide + oxygen	2% halothane all measurements	Nitrous oxide + oxygen	2% halothane with blood pressure greater than 90 mm Hg
Blood flow (ml/g/min)	Mean	0.79	0.98*	0.79	1.07†
	SD	0.19	0.36	0.20	0.36
Blood pressure (mm Hg)	Mean	138	97‡	139	110‡
	SD	19	21	18	17
Pa_{CO_2} (mm Hg)	Mean	39.2	39.3	39.5	40.1
	SD	3.4	3.6	3.3	3.2

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$

0.5 per cent halothane despite a 7 per cent fall in mean blood pressure.

Two per cent halothane (table III and fig. 1) produced a 24 per cent increase in flow through the cerebral cortex but lowered mean blood pressure by 30 per cent. When the animals which were rendered very hypotensive by this concentration of halothane (i.e. with mean blood pressures of 90 mm Hg and below) were excluded, the increase in blood flow with 2 per cent halothane was 36 per cent.

During the administration of 4 per cent halothane (table IV) flow was not significantly different from the value during unsupplemented nitrous oxide anaesthesia. However, 4 per cent halothane reduced the mean blood pressure by 57 per cent (to 62 ± 20 mm Hg).

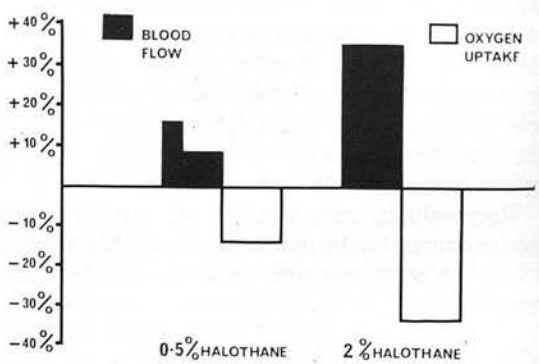

FIG. 1

The effect of 0.5 per cent halothane and of 2 per cent halothane on the blood flow and oxygen uptake of the cerebral cortex.

TABLE IV

The effect of 4% halothane on blood flow through the cerebral cortex.

		Nitrous oxide + oxygen	4% halothane
Blood flow (ml/g/min)	Mean	0.95	0.82
	SD	0.16	0.22
Blood pressure (mm Hg)	Mean	143	62‡
	SD	19	20
Pa_{CO_2} (mm Hg)	Mean	39.3	39.1
	SD	2.5	3.8

* P <0.05; † P<0.01; ‡ P<0.001

TABLE V

The effect of 0.5% halothane on cerebrovascular resistance and on blood pressure.

		Nitrous oxide + oxygen	0.5% halothane all measurements	Nitrous oxide + oxygen	0.5% halothane 1st 20 minutes
Cerebrovascular resistance	Mean	1.67	1.45‡	1.68	1.36‡
	SD	0.37	0.47	0.37	0.36
Blood pressure (mm Hg)	Mean	141	126‡	142	132†
	SD	14	17	14	17

* P<0.05; † P<0.01; ‡ P<0.001

It will be seen in tables II and III that the mean values for flow, blood pressure and Pa_{CO_2} during nitrous oxide anaesthesia are slightly different between different subgroups. The reason for this is that not all animals were represented in each group, e.g. in table II not all animals were studied during more than 60 minutes of halothane anaesthesia, and therefore the nitrous oxide measurements from such animals were excluded in calculating the mean nitrous oxide values for this subgroup. This step was, of course, necessary to ensure that in each subgroup comparisons between nitrous oxide results and halothane results were made in the same animals.

Cerebrovascular resistance.

Cerebrovascular resistance was calculated according to the following equation:

$$\text{c.v.r.} = \frac{\text{mean arterial blood pressure}}{\text{blood flow through cerebral cortex}}$$

Since cerebrovascular resistance relates flow to perfusion pressure, the cerebral venous pressure should theoretically be subtracted from the arterial pressure. However, the error introduced into the calculated c.v.r. by ignoring cerebral venous pressure is less than 5 per cent because the venous pressure in the superior sagittal sinus of the supine dog is only 5–10 cm H_2O (McDowall, Harper and Jacobson, 1964).

With 0.5 per cent halothane, cerebrovascular resistance fell by 19 per cent during the first 20 minutes of administration and by 13 per cent overall, both changes being highly significant (see table V and fig. 2); 2 per cent halothane caused a fall of 43 per cent, and 4 per cent halothane a fall of 49 per cent in c.v.r. (see table VI and fig. 2). As discussed below, the varying degrees of hypotension which occurred with halothane administration complicate the interpretation of these changes (see table VII).

Oxygen uptake of the cerebral cortex.

The mean results for the oxygen uptake of the cerebral cortex are shown in table VIII and figure 1; 0.5 per cent halothane reduced the oxygen uptake of the cortex by 14 per cent of the value existing during unsupplemented nitrous oxide anaesthesia; 2 per cent halothane caused a greater (– 33 per cent) reduction in oxygen uptake. All these results were obtained at the same pharyngeal temperature (see table VIII).

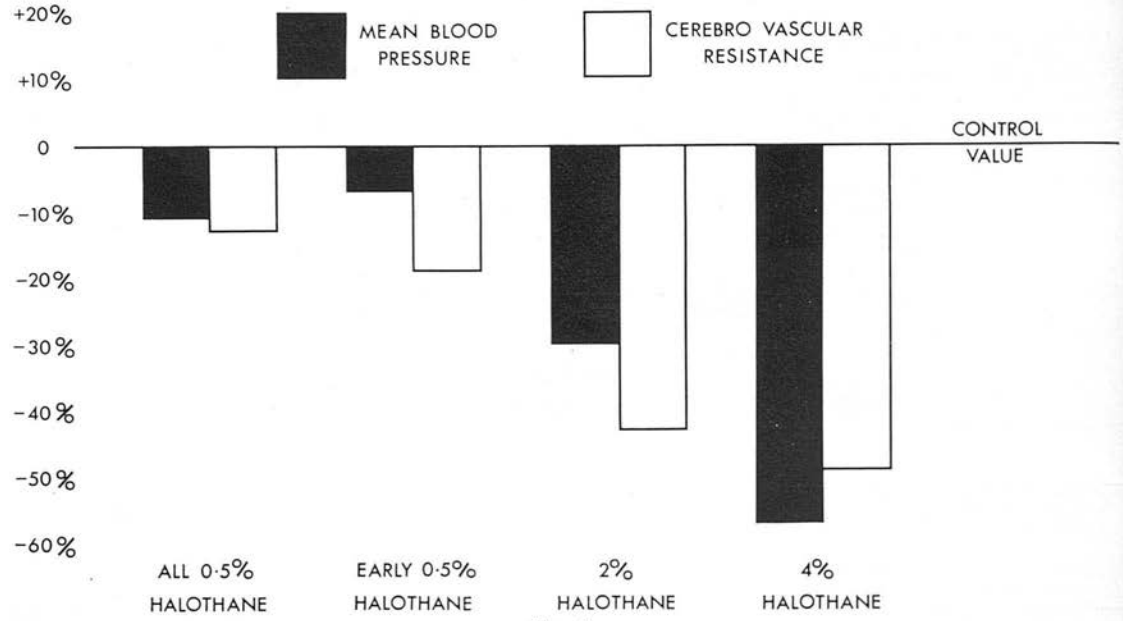

FIG. 2

Changes in cerebrovascular resistance compared with changes in mean blood pressure produced by 0.5–4 per cent halothane

TABLE VI

The effect of 2% and 4% halothane on cerebrovascular resistance and mean blood pressure.

		Nitrous oxide + oxygen	2% halothane	Nitrous oxide + oxygen	4% halothane
Cerebrovascular resistance	Mean	1.84	1.05‡	1.56	0.80‡
	SD	0.52	0.32	0.37	0.34
Blood pressure (mm Hg)	Mean	138	97‡	143	62‡
	SD	19	21	19	20

* $P<0.05$; † $P<0.01$; ‡ $P<0.001$

TABLE VII

Comparison of changes in cerebrovascular resistance with changes in mean blood pressure.

Concentration of halothane (%)	% change in c.v.r.	% change in b.p.	% c.v.r. change / % b.p. change
0.5	−13	−11	1.18
0.5 1st 20 minutes	−19	−7	2.71
2	−43	−30	1.43
4	−49	−57	0.86

In order to analyze statistically the significance of the apparently greater reduction in oxygen uptake with 2 per cent halothane as compared with 0.5 per cent it was necessary to reduce the influence of variations in the control values for oxygen uptake since the comparisons were made in two separate groups of animals. To do this the mean value for oxygen uptake during nitrous oxide anaesthesia in each individual animal was designated 100 per cent and all determinations calculated as percentages of this. Calculated in this way 0.5 per cent halothane was associated with a cortical oxygen uptake of 87.8 ± 16.0 per cent of the nitrous oxide value; while 2 per cent halothane gave a value of 69.8 ± 11.8 per cent of the nitrous oxide value. The depression of oxygen uptake produced by 2 per cent halothane was significantly greater than that produced by 0.5 per cent halothane ($0.001 > P$).

Arteriovenous differences across the cerebral cortex.

The arteriovenous differences for oxygen saturation, carbon doxide tension and pH across the cerebral cortex during nitrous oxide anaesthesia and during halothane anaesthesia are shown in table IX. All these arteriovenous differences narrowed when 0.5 per cent halothane was administered. Two per cent halothane caused the A–V differences for oxygen and for carbon dioxide to narrow even further but the change in A–V pH difference did not reach statistical significance.

TABLE VIII

The effect of 0.5% and 2% halothane on the oxygen uptake of the cerebral cortex.

		Nitrous oxide + oxygen	0.5% halothane	Nitrous oxide + oxygen	2% halothane
Oxygen uptake (ml/g/min)	Mean	0.066	0.057†	0.060	0.040‡
	SD	0.014	0.016	0.015	0.011
Pharyngeal temperature (°C)	Mean	38.4	38.2	38.4	38.3
	SD	0.6	0.9	0.6	0.5

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

TABLE IX

The effect of 0.5% and 2% halothane on the arteriovenous differences across the cerebral cortex for oxygen, Pco_2, and pH.

		Nitrous oxide + oxygen	0.5% halothane	Nitrous oxide + oxygen	2% halothane
Arteriovenous oxygen saturation difference (%)	Mean	39.0	34.0†	40.7	23.2‡
	SD	9.1	8.7	7.6	3.9
Arteriovenous Pco_2 difference (mm Hg)	Mean	13.2	10.8*	13.6	8.9†
	SD	3.8	4.3	4.3	4.1
Arteriovenous pH difference	Mean	0.062	0.045†	0.063	0.045
	SD	0.023	0.027	0.035	0.029

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

TABLE X

The effect of 0.5% and 2% halothane on the oxygen saturation of cerebral venous blood sampled from the superior sagittal sinus.

		Nitrous oxide + oxygen	0.5% halothane	Nitrous oxide + oxygen	2% halothane
Cerebral venous oxygen saturation	Mean	58.3	62.2*	58.1	75.0‡
	SD	9.1	9.1	7.4	3.0

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$

Table X shows the effect of halothane on the oxygen saturation of cerebral venous blood, sampled from the superior sagittal sinus; 0.5 per cent halothane raised the venous oxygen saturation by 3.9 per cent while 2 per cent halothane caused a rise of 16.9 per cent.

DISCUSSION

Methodology.

The method of flow measurement used in this study indicates the tissue perfusion of the area of cerebral cortex lying below the Geiger Muller tube. The diameter of this area was 1–2 cm. Furthermore, since the beta radiation of krypton has a limited range in tissue, only flow occurring within the superficial 1–1.5 mm of cerebral cortex is measured, with negligible contribution from the underlying white matter. The measurements reported then refer only to the grey matter of localized areas of parietal cortex. Harper, Glass and Glover (1961), however, have shown that flow throughout the superolateral surfaces of the cerebral hemispheres is fairly uniform in the dog during nitrous oxide anaesthesia and the present author (unpublished observations) has established that a similar flow relationship exists between different areas of the cortex during administration of 0.5 per cent halothane. There is, therefore, evidence for accepting that measurements of flow in the parietal cortex are applicable to the entire cerebral cortex under the conditions of this study. Since flow through grey matter is about 5 times that through white (Landau et al., 1955) and since the cortical surface accounts for a considerable proportion of the total brain volume, the observations made are indicative of changes occurring in a sizeable component of total cerebral blood flow.

The calculation of the oxygen uptake of the cerebral cortex from the flow measurements and the arteriovenous oxygen content differences requires that flow over the entire drainage area of the superior sagittal sinus be the same as that measured in the localized area studied. The venous blood in the superior sagittal sinus has drained almost entirely from the cerebral cortex (after destruction of the diploic connections) (Gleichmann et al., 1962). The validity of the oxygen uptake calculations is, therefore, also established by the above evidence that flow over the cortical surface is uniform under the conditions of these experiments.

The influence of halothane on flow and cerebrovascular resistance.

These studies have demonstrated that the volatile anaesthetic drug, halothane, acts as a dilator of the cerebral cortical circulation. This vasodilatation results in increases in cerebral cortical blood flow despite falls in mean arterial blood pressure with 0.5 and 2 per cent halothane. Four per cent halothane reduces cerebral perfusion pressure so greatly that flow is not increased; also in the case of 2 per cent halothane, the flow increase is greater when measurements made at blood pressures above 90 mm Hg only are considered.

It is well known that cerebral blood flow autoregulates to compensate for changes in perfusion pressure (reviewed by Lassen, 1959, and Harper, 1966b). In a study by Harper in the dog (1965) no change in the cerebral cortical flow occurred as the mean arterial pressure was reduced (by controlled bleeding) from 150 to 90 mm Hg; greater reductions in arterial pressure led to proportionate reductions in blood flow. Very similar results were obtained by Häggendal (1965) also in the dog. In the experiments described in this paper, 4 per cent halothane reduced the mean blood pressure to 62 mm Hg and flow was close to control values. At such levels of hypotension, therefore, it is not possible to demonstrate halothane vasodilatation because the hypotension itself produces maximal cerebral vasodilatation. This is understandable when one recalls that at this level of perfusion pressure even hypercapnia is ineffective in raising cerebral flow (Harper and Glass, 1965). It is for the same reason that the flow increase with 2 per cent halothane was greater when measurements made at blood pressures above 90 mm Hg only were considered.

Cerebrovascular resistance fell whenever halothane was administered. However, the autoregulation of cerebral blood flow, which has been repeatedly demonstrated to occur in the face of moderate hypotension, implies that cerebrovascular resistance must fall proportionately with blood pressure during hypotension, however

produced. The problem is, therefore, to determine whether the observed changes in cerebrovascular resistance during halothane administration could or could not be entirely ascribed to the associated falls in mean blood pressure. The results have been analyzed from this point of view in table VII and figure 2, from which it will be seen that c.v.r. fell more than did blood pressure during the first 20 minutes of 0.5 per cent halothane and during 2 per cent halothane administration. The drug was, therefore, under these circumstances producing relaxation of the cerebral arterioles in excess of that due to the concomitant blood pressure changes. With 4 per cent halothane the fall in c.v.r. was less than the fall in blood pressure and this must mean that the point of maximum vasodilatation due to hypotension had been passed; since the blood pressure was reduced to 62 mm Hg such a conclusion is in accord with the pressure-flow curve of Harper (1965).

Galindo and Baldwin (1963) reported that halothane administered in unspecified concentrations, did not alter internal carotid artery flow in dogs though the blood pressure was reduced by 40.7 per cent. Since the mean blood pressure during halothane administration in their study was 80 mm Hg, maximum vasodilatation due to hypotension was probably present and, therefore, changes in cerebrovascular resistance due to halothane would have been difficult to demonstrate. However, these authors observed an increase in internal carotid flow early in the administration of halothane before the blood pressure had fallen greatly. Flow in the internal carotid artery of the dog is so uncertain a measure of cerebral blood flow, however, that it is not possible to draw firm conclusions with regard to the cerebral circulation from such observations (De La Torre, Netsky and Meschan, 1959).

Wollman and associates (1964) reported that 1.2 per cent halothane increased the total cerebral blood flow of man by 15 per cent, a result which agrees quantitatively with the findings of the present study. However, the 55 per cent increase in total cerebral blood flow reported by McHenry and others (1965) with 1 per cent halothane administration is much greater than the increase reported here, or the increase found by Wollman and associates (1964). McHenry and co-workers explain the greater change with halothane, as compared with that of Wollman's group, as being due to higher mean blood pressure and to different methods of calculating flow. The former point may explain part of the discrepancy but their method of flow calculation would introduce an error in the direction of underestimating the halothane effect. A more likely cause of the difference is that the mean arterial carbon dioxide tension was 47 mm Hg during the halothane measurements, whereas the "control" measurements, made on conscious subjects, were presumably at arterial tensions of carbon dioxide within the normal range.

Lassen (personal communication) has recently studied halothane anaesthesia in man using a radioactive clearance technique with external counting. He found that 1 per cent halothane caused an elevation of 27 per cent in regional cerebral blood flow.

In an earlier study from this laboratory (McDowall, Harper and Jacobson, 1963) a decrease in cerebral cortical flow with halothane in dogs was reported. This result was due to the use of very low concentrations of halothane (less than 0.5 per cent) vaporized in air (McDowall and Harper, 1965). It seems that at such low concentrations regional differences in cerebral cortical flow may occur.

In summary, all workers are agreed that halothane in clinical concentrations is a cerebral vasodilator. The present study has, however, demonstrated that this is true only under certain conditions. At low levels of perfusion pressure, halothane is without effect on cerebrovascular resistance; the same is probably also the case when maximum vasodilatation by hypercapnia precedes halothane administration. The cerebral vasodilatation produced by halothane increases with increasing concentration but 4 per cent halothane has less effect than 2 per cent because of concomitant hypotension. The effect of 0.5 per cent halothane is relatively weak and is not well sustained so that after more than 20 minutes of administration flow returns to close to control values.

The influence of halothane on oxygen uptake.

0.5 per cent halothane reduces the oxygen uptake of the cortex by 14 per cent and 2 per cent halothane produces a reduction of 33 per cent.

These measurements were made at constant pharyngeal temperature. It must be emphasized that these reductions occurred in animals already anaesthetized with nitrous oxide after thiopentone induction of anaesthesia. This technique of general anaesthesia in man has been shown to reduce the oxygen uptake of the brain (Wollman et al., 1965) and consequently the "control" value for oxygen uptake in these experiments may certainly have been below the value in conscious dogs. If the comparison could have been made with conscious values, then the percentage depression of oxygen uptake with halothane would probably have been greater.

Cohen and co-workers (1964) also found that cerebral oxygen uptake was reduced by halothane; they noted a 15 per cent fall with 1.2 per cent halothane but ascribed most of this reduction to a drop in oesophageal temperature in their anaesthetized subjects. The results of McHenry and co-workers (1965) and of Lassen (personal communication) agree with the present study in demonstrating a depression of cerebral oxygen uptake with halothane at constant body temperature (in both quoted studies the fall was 26 per cent with 1 per cent halothane). The relationship between oxygen uptake and administered concentration of halothane revealed in the present study has not been previously ascribed.

The relationship between blood flow and oxygen uptake during halothane anaesthesia.

It is paradoxical that halothane increases cerebral blood flow while reducing cerebral metabolic oxygen requirements, the discrepancy becoming wider with higher concentrations of halothane (until hypotension intervenes). The paradox is all the greater because the brain is often stated to be an organ in which flow is regulated to metabolic demand. This metabolic regulation of flow is conceived as being exercised by means of local tissue levels of carbon dioxide, oxygen and pH.

From tables IX and X it can be seen that as a result of these changes in flow and oxygen uptake, halothane narrows the arteriovenous differences for oxygen and for carbon dioxide by elevating venous oxygen saturation and reducing venous Pco_2. It is well known that tissue oxygen tension is related inter alia to arterial and venous oxygen tensions (Thews, 1963). Ponten and Siesjö (1966) have similarly demonstrated a relationship between arterial and venous Pco_2 and the level of tissue Pco_2. It follows, therefore, that one may consider the data in table IX to indicate that halothane raises tissue Po_2 and lowers tissue Pco_2 in the brain.

Arterial and venous pH were also measured but, unlike the situation with oxygen and carbon dioxide, it is not justifiable to calculate changes in tissue pH from measured values of blood pH (because of the blood brain barrier).

The above experiments do not provide any evidence to indicate the mechanism by which halothane produces these changes. It is probably reasonable to accept provisionally that halothane exerts a direct relaxing effect on the smooth muscle of the cerebral arterioles and that this action resets the "resting tone" of these vessels without impairing their responsiveness to changes in blood carbon dioxide tension (Alexander et al., 1964; McHenry et al., 1965; McDowall, 1966). This direct action apparently more than counteracts the normal constrictive effect of the observed reductions in cerebral metabolic rate both with 0.5 per cent and with 2 per cent halothane. Smith and Vane (1966) have reported that high tensions of oxygen in media perfusing isolated vascular smooth muscle cause increases in the tone of such smooth muscle. They have suggested that one possible explanation of this response might be that vascular tone is dependent upon an enzyme-controlled process and that the rate of this enzymatic reaction is limited by the amount of oxygen in the surrounding medium. If halothane inhibited this enzymatic reaction then vascular relaxation such as that observed in the present study would occur.

Clinical implications.

As halothane increases cerebral blood flow while reducing cerebral metabolic demand, the oxygenation of the brain rises. Furthermore, because these effects are related to the concentration of halothane administered, deep halothane anaesthesia, especially if combined with infusion of vasopressors, will produce high tissue oxygen tensions in the brain. Such an approach has been utilized during operations involving carotid artery occlusion by Wells, Keats and Cooley (1963) and by Lyons

and others (1964), though, as pointed out by Spencer (1964), there was at the time of these reports no evidence for the belief that the metabolic rate of the brain was reduced by general anaesthesia other than barbiturate anaesthesia.

As a result of the cerebral vasodilatation, the cerebrospinal fluid pressure rises during halothane administration even when the arterial carbon dioxide tension is held constant (Marx, Andrews and Orkin, 1962; Hunter, 1964; Jennett and McDowall, 1964). The increasing dilatation with increasing halothane concentration demonstrated in this paper is mirrored in the observed relationship between magnitude of c.s.f. pressure rise and inspired halothane concentration (Marx et al., 1962; McDowall, Barker and Jennett, 1966). The changes in c.s.f. pressure produced by halothane are quantitatively small and probably clinically insignificant in patients with normal c.s.f. pathways. However, this is not the case in certain patients with intracranial tumours in whom halothane administration may elevate the intracranial pressure by several hundred millimetres of water (Jennett, McDowall and Barker, 1967).

The effects of halothane on the cerebral circulation and metabolism can, therefore, in different situations be clinically advantageous or disadvantageous; a detailed knowledge of the actions of this commonly used drug should thus be of clinical value.

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EFFETS DE L'HALOTHANE A DES CONCENTRATIONS CLINIQUES SUR LE DEBIT SANGUIN ET LA CONSOMMATION EN OXYGENE DU CORTEX CEREBRAL

SOMMAIRE

Vaporisé à des concentrations cliniques dans un mélange de protoxyde d'azote et d'oxygène, l'halothane provoque chez le chien anesthésié une vasodilatation dans le cortex cérébral avec des pressions partielles de CO_2 artériel constantes. Cette action vasodilatatrice est d'autant plus marquée que les concentrations en halothane sont plus élevées. En conséquence, une concentration en halothane de 2% augmente plus le débit sanguin dans le cortex cérébral qu'une concentration de 0,5%. Cependant, avec une concentration en halothane de 4%, la diminution de la pression sanguine moyenne est si prononcée que le débit sanguin n'est pas plus grand que chez les animaux témoins. L'halothane diminue la consommation d'oxygène du cortex cérébral; cette diminution est plus marquée pour une concentration en halothane de 2% que pour une concentration de 0,5%. On discute ces résultats en tenant compte des effets de l'halothane sur la pression intracrânienne et sur l'oxygénation du cerveau.

WIRKUNG KLINISCHER HALOTHAN-KONZENTRATIONEN AUF DURCHBLUTUNG UND SAUERSTOFFAUFNAHME DER GROSSHIRNRINDE

ZUSAMMENFASSUNG

Klinische Konzentrationen von Halothan in Lachgas-Sauerstoffgemisch führten bei Hunden zur Vasodilatation der Grosshirnrindengefässe. Die arterielle CO_2-Spannung war konstant. Die cerebrale Vasodilatation stieg mit der Halothan-Konzentration an, d.h. das cerebrale Durchflussvolumen war unter 2 prozent Halothan grösser als unter 0,5 prozent. Bei Anwendung von 4 prozent Halothan sank der mittlere Blutdruck jedoch so stark ab, dass die Durchblutungsgrösse den Kontrollwert nicht überschritt. Die Sauerstoffaufnahme der Grosshirnrinde verschlechterte sich unter Halothan. Sie war bei 2 prozent Halothan geringer als bei 0,5 prozent. Die Ergebnisse werden in Hinsicht auf intrakraniellen Blutdruck und cerebrale Sauerstoffversorgung diskutiert.

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THE EFFECT OF HALOTHANE ON INTRACRANIAL PRESSURE IN CEREBRAL TUMORS. REPORT OF TWO CASES

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The Effect of Halothane on Intracranial Pressure in Cerebral Tumors*

Report of Two Cases

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Halothane in anesthetic concentrations causes a marked increase in cerebrospinal fluid (C.S.F.) pressure as reported by Sondergard,[10] Marx,[7] Hunter,[3] and McDowall, *et al.*[5] The observations in our own study were made on patients with normal C.S.F. pathways who were anesthetized with nitrous oxide-oxygen during controlled ventilation to produce normocapnia. The addition of 0.5% Halothane to the anesthetic gases increased lumbar C.S.F. pressure in every case (Fig. 1), the mean increase being 68.2 mm H_2O (S.D. $\pm$31.2 mm H_2O; statistical significance $P < 0.001$). It was suggested that this rise in C.S.F. pressure might prove dangerous to patients in whom the pressure was already high due to an intracranial space-occupying lesion. Our report concerns the effect of Halothane on the intracranial pressure in two such patients.

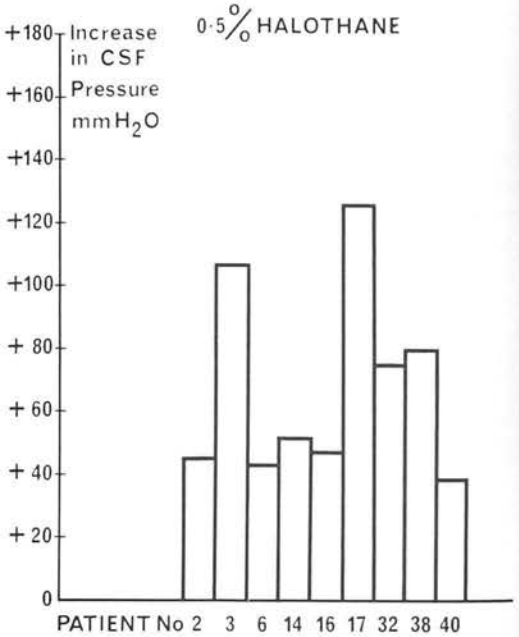

Fig. 1. Effect of Halothane on cerebrospinal fluid pressure in patients with normal C.S.F. pathways. (Reproduced from *Anaesthesia* by courtesy of the editor.)

Case Reports

Case 1. A 48-year-old man with headache of 2 months' duration was admitted to the hospital after noticing visual hallucinations on the left side for 3 weeks. On examination he had left homonymous hemianopia, mild left hemiparesis, and early papilledema; there was nystagmus and left-sided cerebellar ataxia. Carotid angiography suggested hydrocephalus, and air ventriculography showed a cerebellar tumor. At operation on the same day as the ventriculogram, a metastatic tumor was removed from the cerebellum; it was thought likely that there was at least one other metastasis in the right cerebral hemisphere to account for his visual signs.

Case 2. A 36-year-old woman was admitted to the hospital after 5 weeks of headache and vomiting. She had had a major epileptic fit during the puerperium 4 years earlier, and for 2 years had been slowing down mentally. She had marked papilledema; the only neurological sign was facial weakness. Angiography revealed a large frontal tumor. At operation this proved to be an extensive infiltrating glioma, reported histologically to be an anaplastic astrocytoma.

Method

Each case was premedicated with 0.6 mg atropine. Anesthesia was induced with a sleep dose of thiopentone and, after the intravenous injection of suxamethonium chloride, a cuffed endotracheal tube was

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passed. Controlled ventilation with nitrous oxide-oxygen was instituted, and tubocurare was administered at the earliest indication of returning muscle tone. A period of about 30 minutes was then allowed for stabilization during which the head was draped for craniotomy and a frontal burr hole was made. A metal brain cannula was inserted into the lateral ventricle through a burr hole and connected to a Statham pressure transducer, amplifier, and ultraviolet recorder. Stability of the intracranial pressure was assessed for 10 minutes, and Halothane (0.5% in Case 1 and 1.0% in Case 2) was then introduced. No further surgery was undertaken until all measurements of intracranial pressure were completed. Blood pressure was measured intermittently by upper arm sphygmomanometry, the systolic pressure being determined by palpation. The minute volume was measured with a Dräger Volumeter on the expiratory limb of the non-return anesthetic circuit. Arterial pH and Pco_2 were measured on capillary blood before, during, and after the Halothane administration by the micro-Astrup technique (Andersen, *et al.*[1]). Esophageal temperature was monitored to allow correction of the arterial Pco_2 ($PaCo_2$) for temperature, using Rosenthal's factor.

Results

Case 1. The intracranial pressure rose from 180/160 mms H_2O to 500/440 mms H_2O after 13 minutes of administration, at which time the Halothane was discontinued. In the following minute the intracranial pressure rose further to 520/460 mms H_2O, but thereafter fell rapidly towards the control value (Fig. 2).

Throughout the period of measurement the $PaCo_2$ was 38 mm Hg, and the mean esophageal temperature was 36.3°C.

Case 2. After 7 minutes of 1% Halothane, intracranial pressure rose from 155/130 mm H_2O to 590/470 mm H_2O and the Halothane was then discontinued. During the next minute the intracranial pressure continued to rise precipitously, reaching a peak value of 800/620 mm H_2O, after which it returned rapidly to the control value (Fig. 3). During these measurements, $PaCo_2$ was 34 mm Hg; the mean esophageal temperature was 35.8°C; and the systolic blood pressure was

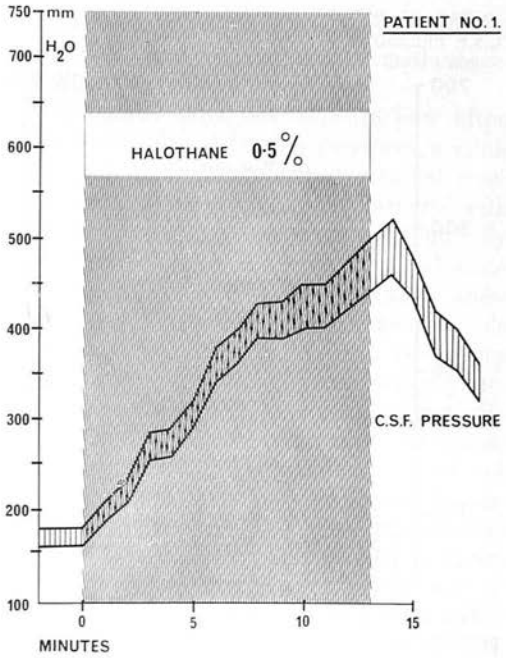

FIG. 2. Effect of Halothane on cerebrospinal fluid pressure in Case 1.

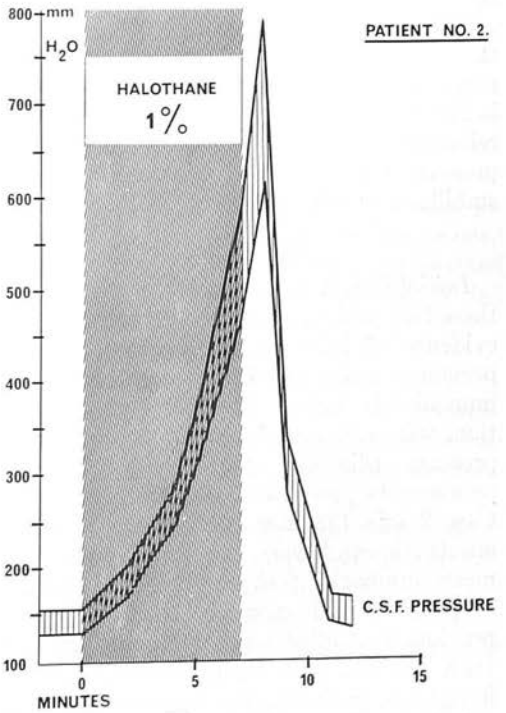

FIG. 3. Effect of Halothane on cerebrospinal fluid pressure in Case 2.

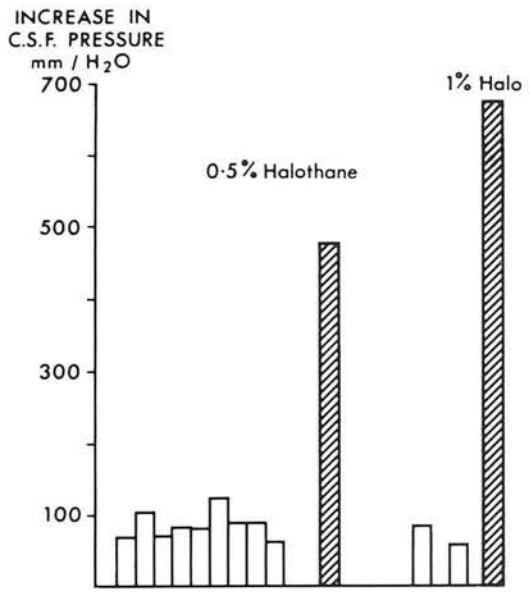

FIG. 4. Comparison of the "Halothane rise" in C.S.F. pressure in patients whose C.S.F. pathways were normal (clear blocks) with that in two patients who had cerebral tumors (lined blocks). The three cases on the right had 1% Halothane, the rest, 0.5%.

130 mm Hg, falling to 100 mm Hg during Halothane administration.

After these measurements were completed the ventilation was increased from 6.0 liters/min to 9.0 liters/min, which resulted in a fall in $PaCo_2$ to 19 mm Hg. When Halothane was reintroduced at this low $PaCo_2$, the C.S.F. pressure rise was much less marked and stabilized at 350/300 mm H_2O.

Discussion

Initial C.S.F. Pressure. Although each of these two patients had definite preoperative evidence of intracranial hypertension, the pressures measured during anesthesia, but immediately before Halothane administration, were not very high. The mean C.S.F. pressure (diastolic plus one-third pulse pressure) in Case 1 was 167 mm H_2O and in Case 2 was 138 mm H_2O. Under identical anesthetic conditions, the control values for mean (lumbar) C.S.F. pressure in two groups of patients with normal C.S.F. pathways previously studied were 118 and 109 mm H_2O. The fact that the intracranial pressure in our two patients was not more markedly raised may be ascribed to two factors: the $PaCo_2$ was rather low (38 mm Hg and 34 mm Hg), and the esophageal temperature was only 36.3°C and 35.8°C. The length of the clinical histories suggests that a considerable degree of compensation had already taken place.

Response to Halothane. In spite of the initial C.S.F. pressures being only modestly increased, the administration of Halothane produced dramatic and alarming increases, which necessitated discontinuing the Halothane administration after 13 and 7 minutes respectively (Fig. 4). We of course do not know to what level the intracranial pressure might finally have risen had Halothane administration been continued. It should be noted that the routine clinical monitoring of blood pressure and pulse rate gave no indication that these large increases in intracranial pressure had occurred. It is likely, therefore, that in many clinical situations, Halothane administration would not be terminated so early.

Mechanism of Raised Intracranial Pressure. We have previously presented evidence[5] supporting the hypothesis that the increase in C.S.F. pressure during Halothane administration is the result of the increase in total cerebral blood flow. Other workers have demonstrated this increase with this drug.[6,12] In our two patients, we postulated that the increased cerebral blood flow induced by Halothane produced a very much greater elevation in C.S.F. pressure than in normal subjects because of the presence of an intracranial space-occupying lesion. We have so far failed to reproduce this pattern of intracranial pressure response to Halothane in animals with experimental space-occupying lesions. This is probably because the experimental animal has only a few hours to compensate for the space-occupying lesion (saline-filled extradural balloon) while patients have had weeks or months in which to do so. Compensation, which must involve a readjustment to the volumes contributed by blood, brain, tumor, and C.S.F., must have been exhausted in the human cases, since clinical signs of intracranial hypertension had already appeared. A further increase in the volume of any one component, in this case of intracranial blood volume with Halothane administration, then resulted in large and progressive increases in pressure because no further compensation was possible.

One patient (Case 1) had been investigated by air ventriculography 2 hours before this study was undertaken. Saidman and Eger[8] have shown that the administration of nitrous oxide under these circumstances leads to a rise in C.S.F. pressure, since the nitrous oxide enters the intracranial air bubbles from the blood more rapidly than the nitrogen can leave. This effect is related to the widely different solubilities of the two gases in blood. However, in our investigation, the C.S.F. pressure had had time, during the preceding 30 minutes of nitrous oxide anesthesia, to restabilize before the effect of Halothane on the intracranial pressure was studied. The influence of transfer of Halothane into the intracranial air collection would be very small because of the low partial tension of Halothane in the arterial blood. It is more likely that the presence of intracranial air damped the extent of the Halothane-induced pressure rise. It can indeed be seen, by comparing Figs. 2 and 3, that the intracranial pressure rise was slower and less marked in the patient who had had an air ventriculogram.

Influence of Hyperventilation. Hyperventilation has been shown to reduce the amount of the increase in C.S.F. pressure with Halothane administration.[5] The results in our Case 2 confirm that this is also true in patients with intracranial space-occupying lesions. It would therefore seem wise to use hyperventilation before Halothane is used in patients with clinical signs of raised intracranial pressure.

Clinical Significance. In recent years there has been a tendency to dismiss as unimportant the changes produced in intracranial pressure by general anesthetic drugs (Stephen, *et al.*,[11] Small, *et al.*,[9] Bozza, *et al.*[2]). This view may have arisen because of the failure to detect consistent changes with these agents or because the changes found were so small as to be insignificant in patients with normal C.S.F. pathways. Hunter,[3] however, has cautioned that even a slight increase produced by an anesthetic drug might produce a dangerous level of intracranial pressure in patients with pre-existing intracranial hypertension. The situation revealed by our present study is even more serious, for Halothane, which in normal patients produces only small changes in C.S.F. pressure, has been shown to produce much more marked elevations of pressure in patients with space-occupying lesions.

This study does not indicate how often Halothane administration produces a clinically important effect on intracranial pressure. Sudden deterioration of patients with raised intracranial pressure undoubtedly does occur on occasion during general anesthesia, but is often ascribed to faulty anesthetic technique. The measurements made on these two patients indicate that very large rises in intracranial pressure can sometimes be produced in this group of patients by Halothane despite adequate ventilation and oxygenation. That difficulties do not more commonly arise may be due to the current anesthetic practice of hyperventilating many neurosurgical patients prior to Halothane administration. However, spontaneous ventilation with Halothane is often used for radiological investigations in patients with space-occupying lesions, and we believe this to be potentially hazardous.

A similar situation can arise when anesthesia has to be administered to a patient with a head injury who requires surgical treatment for associated injuries. Under these circumstances, there is no surgical demand for controlled respiration, let alone for hyperventilation, yet increased intracranial pressure is commonly present, either due to multiple cerebral contusions and swelling, or to a hematoma. The dangers of anesthesia in the early stages after head injury are well recognized by neurosurgeons,[4] although they too have usually been ascribed to anesthetic difficulties rather than to the influence of particular anesthetic drugs.

Summary

1. An acute rise in intracranial pressure was observed on administering Halothane to two patients with intracranial space-occupying lesions.

2. This rise in C.S.F. was much greater than that previously reported in patients with normal C.S.F. pathways.

3. Prior hyperventilation, to produce hypocapnia, greatly diminished this response to Halothane.

4. The possible dangers of Halothane anesthesia in patients with intracranial space-occupying lesions have been discussed.

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Cerebro–spinal fluid pressure measurements during anæsthesia*

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In recent years the potent influences of hypercapnia, hypoxia and respiratory obstruction on the intracranial pressure during anæsthesia have rightly been stressed. This emphasis on factors related to good anæsthetic technique has led to the belief that, provided respiratory depression is avoided, general anæsthetic drugs have negligible effects on intracranial pressure [1,2,3]. The present study was undertaken to determine quantitatively the effects of halothane and trichlorethylene on the cerebrospinal fluid (CSF) pressure in the absence of changes in arterial carbon dioxide tension and to correlate any changes found with alterations in central and cerebral venous pressures.

METHOD

Patient Study

This study was carried out on 24 patients whose prior consent had been obtained. Ages ranged from 22–64 years; 16 were male and 8 female. Most were about to undergo surgery for prolapsed lumbar disc lesions and all were presumed to have normal CSF pathways and pressure.

Premedication was with pethidine 100mg and atropine 0.6mg. Anæsthesia was induced with a sleep dose of thiopentone and maintained with nitrous oxide and oxygen. D-tubocurarine was administered and intubation performed with a flexometallic cuffed endotracheal tube after laryngeal spraying with 4% lignocaine. Ventilation was controlled with a Barnet ventilator set at a minute volume predicted to produce normocapnia. An oesophageal thermoelectric probe was inserted and oesophageal temperature recorded intermittently.

*Based on a paper read at the 1965 Annual Meeting of the Association of Anæsthetists of Great Britain and Ireland at Edinburgh

The patients were placed in the lateral position and a needle inserted into the lumbar subarachnoid space and connected to a pressure transducer; care was taken that only minimal quantities of CSF escaped. In some patients a catheter was inserted into an antecubital vein and advanced until its tip was judged by measurement to lie within the subclavian vein.

In patients numbers 1–12, pressures were measured with a fine bore saline manometer. In patients numbers 14–20, the measurements were made with Elema–Schonander low-pressure transducers, amplifiers and ink jet recorder. In the remaining patients the recording system consisted of Statham transducers, connected via suitable amplifiers to an ultra–violet recorder.

Control pressure measurements were made during ventilation with nitrous oxide and oxygen only. 0.5% or 1% halothane was added to the nitrous oxide–oxygen mixture using a Fluotec II vaporiser and the changes in CSF and central venous pressures were followed, usually for ten minutes. The halothane was then discontinued and the pressures observed for a further five to ten minutes.

In 3 patients after making the control measurements the minute volume was increased to produce hyperventilation. Halothane was added only after the arterial carbon dioxide tension had been lowered.

A similar procedure without hyperventilation was followed in 6 patients to whom trichlorethylene was administered in a concentration of 0.9% (the trichlorethylene was also vaporised from a Fluotec II vaporiser for which Cyprane Ltd supplied conversion factors).

Capillary (finger tip) blood was withdrawn at the beginning and at the end of the period of observation. It was analysed for pH and for P_{CO_2} by the Astrup interpolation technique[4]. The pH electrode was maintained at 38°C and corrections for differences between the patients' oesophageal temperature and the electrode temperature were made by applying Rosenthal's factor. The mean oesophageal temperature during the period of measurement was 35.7°C (range 34.2–37.3°C).

Animal Experiments

Unselected, unpremedicated mongrel dogs were anæsthetised with a sleep dose of thiopentone, intubated and ventilated by a Starling ventilator with 70% nitrous oxide and 30% oxygen. Muscular paralysis was obtained by intermittent administration of a dilute solution of suxamethonium chloride (0.5mg/ml). The pharyngeal temperature was measured and maintained at 38°C.

CSF pressure was measured via a plastic cannula inserted into the cisterna magna. Cerebral venous pressure was measured via a needle inserted through a midline trephine into the superior sagittal sinus. A

venous cannula placed in the right atrium via an external jugular vein indicated the central venous pressure. All measurements were made with pressure transducers and an ultra-violet recorder.

RESULTS

Patients

The influence of 0.5% halothane was studied in 9 patients in whom the arterial P_{CO_2} was in the range 37–45mm/Hg (mean 40.2 ± 2.6mm/Hg). The control value for CSF pressure in this group was 117.1 ± 62.6mm/H_2O. On the administration of 0.5% halothane the CSF pressure increased in every case; the mean increase was 68.2 ± 31.2mm/H_2O but the range was wide, from +39 to +126mm/H_2O. These

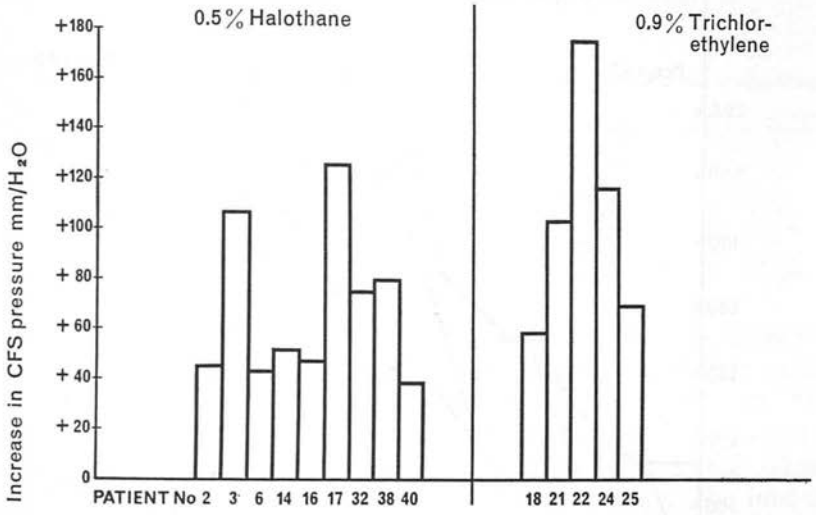

FIGURE 1 Absolute increases in CSF pressure with halothane and with trichlorethylene in patients (The numbers are not consecutive because the present study was carried out on certain patients only in a series of 40)

TABLE 1
Influence of halothane in patients during normocapnia

PATIENT NO	CSF PRESSURE					ART. P_{CO_2}
	CONTROL	0.5% HALOTHANE	1—2% HALOTHANE	AFTER HALOTHANE DISCONTINUED	INCREASE WITH 0.5% HALOTHANE	
	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/Hg
2	147	192	—	147	45	38
3	45	152	—	54	107	42
6	214	257	—	205	43	39
14	21	73	—	29	52	43
16	125	172	—	—	47	45
17	88	214	—	80	126	40
32	129	204	(2%) 252	—	75	39
38	190	270	(1%) 307	207	80	37
40	100	139	—	83	39	39
MEANS	117.7 ±62.6	185.9 ±60.8	—	115 ±71.8	68.2 ±31.2	40.2 ±2.6

results are illustrated in detail in table 1 and figure 1. In 7 of these 9 patients, the changes in CSF pressure were also measured after withdrawing the halothane; there was in each case a return almost to the initial level (table 1 and figure 2).

The magnitude of the fluctuations of the CSF pressure induced by the arterial pulse pressure was difficult to determine with the saline manometer because of the slow response time and heavy damping. In 4 of the 5 patients receiving halothane whose pressures were measured electronically the size of the arterial CSF pulsations increased with halothane administration; in the fourth there was no change (table 2).

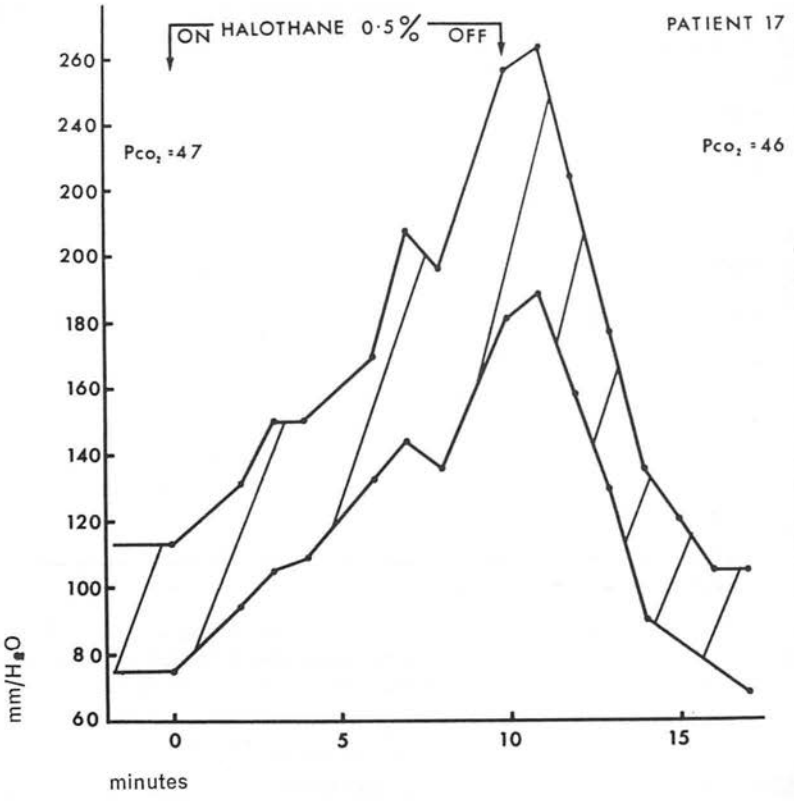

FIGURE 2 The effect of halothane on CSF pressure in one patient

TABLE 2

Amplitude of the arterial pulsations of the CSF

PATIENTS NO	CONTROL	0.5% HALOTHANE	AFTER HALOTHANE DISCONTINUED
	mm/H_2O	mm/H_2O	mm/H_2O
14	4	16	6
17	38	77	37
32	53	74	—
38	90	90	80
40	25	42	25

The increases in CSF pressure occurred very quickly after introducing halothane – within one minute in 5 cases and within 2 minutes in the other 3. The time to reach peak pressure was very variable (from 3 to 16 minutes) while the return to the baseline occurred within 3–10 minutes of discontinuing the halothane.

In 2 patients the halothane concentration was increased after observing the effect of 0.5% halothane. In one (no. 32), the CSF pressure rose from 129 to 204mm/H_2O with 0.5% halothane and increased further to 252mm/H_2O with 2% halothane. In the other (no. 38) 0.5% led to a rise from 190 to 270mm/H_2O, while 1% produced a CSF pressure of 307mm/H_2O.

Central venous pressure (as defined in methodology section) was measured in 10 patients receiving halothane and a mean rise of 6mm/H_2O was noted (range 0 to +30mm/H_2O) (see table 3).

TABLE 3

Comparison of changes in CSF and central venous pressures in patients with halothane administration

PATIENT NO	CSF CHANGE WITH 0.5% HALOTHANE	CENTRAL VENOUS CHANGE WITH 0.5% HALOTHANE	PATIENT NO	CSF CHANGE WITH 0.5% HALOTHANE	CENTRAL VENOUS PRESSURE CHANGE WITH 0.5% HALOTHANE
	mm/H_2O	mm/H_2O		mm/H_2O	mm/H_2O
3	+107	+ 30	36	NOT DONE	NO CHANGE
6	+ 43	NO CHANGE	37	NOT DONE	NO CHANGE
31	+ 84	+ 4	38	+ 80	+ 8
33	+ 4	+ 13	39	+ 25	NO CHANGE
34	+ 9	NO CHANGE	40	+ 39	NO CHANGE

Trichlorethylene. 5 patients received trichlorethylene in a concentration of 0.9%. In all these patients CSF pressure rose sharply on the introduction of trichlorethylene into the anæsthetic mixture. The mean control value was 109.4 ± 31.5mm/H_2O and the mean average increase with trichlorethylene was 105.2mm/H_2O ±46.2 (range +59 to +176mm/H_2O). The mean arterial P_{CO_2} at the time of these measurements was 38.6mm/Hg ± 2.1 (see table 4 and figures 1 and 3). Measurements of central venous pressure showed no change in 2 patients during trichlorethylene administration and in a third a rise of 30mm/H_2O.

TABLE 4

Influence of trichlorethylene in patients

PATIENT NO	CSF PRESSURE: CONTROL	CSF PRESSURE: 0.9% TRICHLORETHYLENE	CSF PRESSURE: AFTER TRICHLORETHYLENE DISCONTINUED	INCREASE WITH TRICHLORETHYLENE	ART. P_{CO_2}
	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/Hg
18	76	135	84	59	40
21	116	220	102	104	37
22	157	333	197	176	37
24	112	229	106	117	37
25	86	156	107	70	42
MEANS	109.4 ±31.5	214.6 ±77.5	119.2 ±44.5	105.2 ±46.2	38.6 ±2.1

Hyperventilation with halothane. 3 of the patients who received 0.5% halothane were inadvertently hyperventilated to an arterial P_{CO_2} of less than 35mm/Hg and a further 3 patients were deliberately hyperventilated before the administration of halothane. All of these patients had low levels of CSF pressure during hyperventilation with nitrous oxide–oxygen; under these circumstances the administration of 0.5% halothane produced only very small rises in CSF pressure. The mean increase was 17.7mm/H_2O (range +4 to +40mm/H_2O) at a mean arterial P_{CO_2} of 28.2mm/Hg (table 5).

Animals

In 4 dogs the administration of 0.5% halothane during controlled ventilation with nitrous oxide–oxygen resulted in increases in CSF pressure ranging from +40mm/H_2O to +105mm/H_2O at a mean

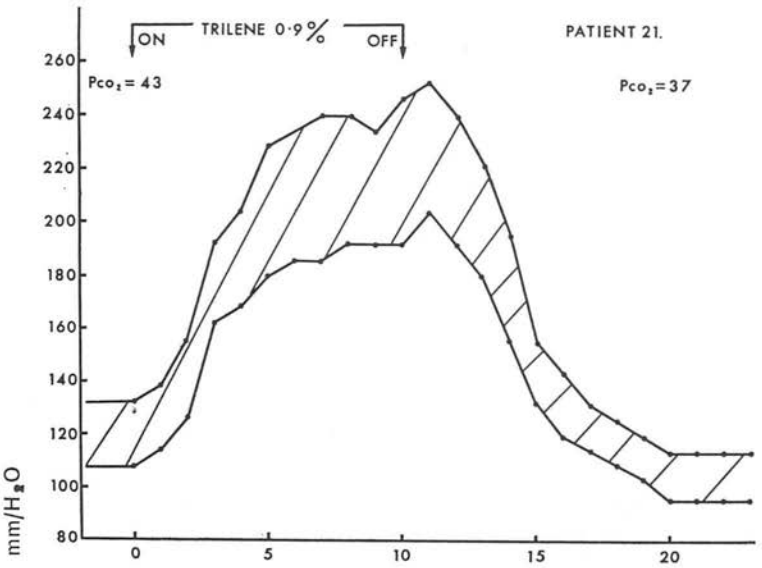

FIGURE 3 The effect of trichlorethylene on CSF pressure in one patient

TABLE 5

Influence of halothane in patients during hypocapnia

PATIENT NO	CSF PRESSURE				ART. P_{CO_2}
	CONTROL	0.5% HALOTHANE	AFTER HALOTHANE DISCONTINUED	INCREASE WITH HALOTHANE	
	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/Hg
12	20	30	32	10	29
31	44	84	50	40	31
39	—4	21	—24	25	33
8	21	39	—	18	27
33	9	13	—	4	21
34	16	25	—	9	—

arterial P_{CO_2} of 44mm/Hg. The administration of 2% halothane increased the CSF pressure further in the two dogs in which this was studied (table 6).

In 2 of these animals (nos. 8 and 9) cerebral venous pressure was also measured. At all times the cerebral venous pressure was slightly less than the CSF pressure. With the administration of halothane, cerebral venous pressure increased in parallel with the CSF pressure and on the withdrawal of halothane both pressures fell together (see figure 4). In the other 2 animals (nos. 2 and 5) central venous pressure was measured and no significant change occurred in this parameter with halothane.

In every instance the increases in CSF pressure with halothane occurred within one minute of starting the administration and the peak of CSF pressure was reached in from 3–13 minutes. With con-

TABLE 6

Influence of halothane in dogs

DOG NO	CSF PRESSURE: CONTROL	WITH 0.5% HALOTHANE	WITH 2% HALOTHANE	AFTER HALOTHANE DISCONTINUED	INCREASE WITH 0.5% HALOTHANE	ART P_{CO_2}
	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/H_2O	mm/Hg
2	139	212	—	141	73	37
5	183	264	—	71	81	43
8	170	210	240	160	40	43
9	146	251	276	118	105	38

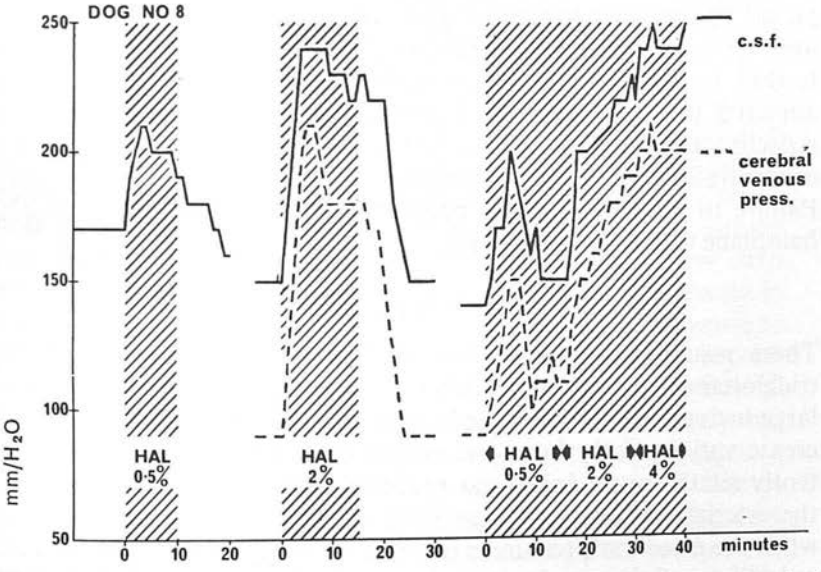

FIGURE 4 The effect of various concentrations of halothane on CSF and cerebral venous pressures in one dog

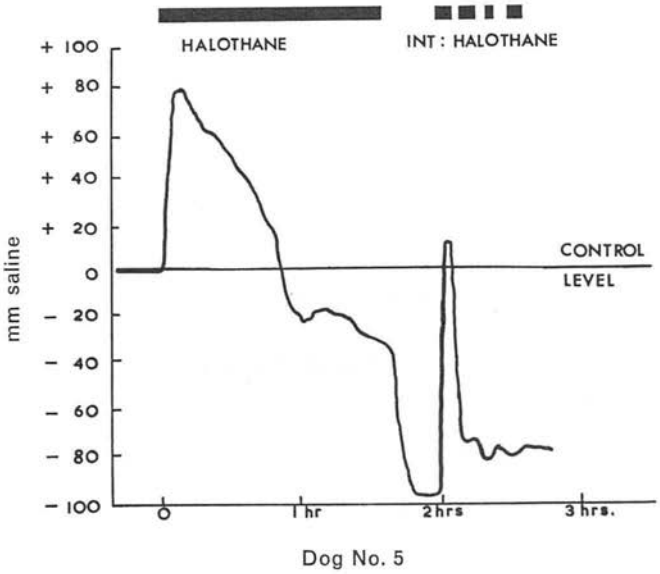

FIGURE 5 The effect of prolonged halothane administration on CSF pressure in one dog

tinued administration beyond this peak, the CSF pressure began to decline again in 6 out of 7 occasions. In one animal, in which 0.5% halothane was administered for one hour and 40 minutes (see figure 5), the CSF pressure had fallen again to the initial level after 52 minutes. On withdrawal of halothane in this animal, the CSF pressure fell further, to a level that was 100mm/H_2O below the control value. In animal 8, 0.5% halothane produced a peak at 5 minutes followed by a decline almost to baseline in 12 minutes; increasing the halothane concentration to 2% then produced a further rise in CSF pressure. Failure to maintain the CSF pressure rise with either 0.5% or 2% halothane was also seen in dog 9.

DISCUSSION

These results demonstrate that both 0.5% halothane and 0.9% trichlorethylene, vaporised with nitrous oxide and oxygen, produce large increases in CSF pressure in man and dog. The degree of the increase varies greatly from one subject to another and is not consistently related to the initial CSF pressure, when this is normal, nor to the arterial P_{CO_2} in the range 37 to 45mm/Hg. As always happens when the mean CSF pressure is elevated for any reason[5,6], the arterial pulsations of the CSF increase in amplitude during halothane and trichlorethylene administration.

Stephen and his colleagues[3] concluded that anæsthetic drugs do not alter CSF pressure. They measured CSF pressure during induction of anæsthesia with various drugs including trichlorethylene, but halothane was not yet available. These workers may have failed to detect trichlorethylene-induced pressure changes against the background of the large pressure alterations which normally accompany induction of anæsthesia. Some of the results of Sondergaard[7] are similarly obscured by the events of induction including hypercapnia during respiratory depression; although end-tidal P_{CO_2} was measured there was no method of attributing the proportion of the rise in CSF pressure due to the rise in arterial P_{CO_2} and that due to the drug itself. Nonetheless Sondergaard[7] concluded that part of the increase in CSF pressure during halothane administration was due to the drug directly. With trichlorethylene he found that CSF pressure and end-tidal P_{CO_2} rose during induction but that the establishment of a clear airway caused a fall in both parameters; he therefore concluded that trichlorethylene of itself had no effect on CSF pressure.

CSF pressure and central venous pressure

Marx *et al.*[8] observed that halothane anæsthesia increased the CSF pressure above the resting level (*i.e.* before induction of anæsthesia). The mean CSF pressure before anæsthesia found by these workers was abnormally high ($244 \pm 32mm/H_2O$) and the increases with halothane were much smaller than those obtained in the present study; they recorded a mean rise in CSF pressure with 0.5% halothane of only $17mm/H_2O$ at P_{CO_2} values 'within the normal range'. The 'venous pressure' rose with halothane by percentage increases which closely resembled the percentage increases in CSF pressure. They therefore concluded that increases in CSF pressure due to halothane *per se* are related solely to increases in systemic venous pressure. However, their mean value for venous pressure of $126 \pm 6mm/H_2O$ in spontaneously breathing unanæsthetised patients suggests either a misleadingly low zero reference point or that the venous pressure measured was greatly in excess of central venous pressure and therefore had little relevance to CSF pressure. In fact the site of measurement is not specified beyond the information that a catheter was introduced via an antecubital vein. From the absolute control values quoted it would seem likely that peripheral venous pressure of the arm was monitored. Changes in this pressure may of course be due to changes in central venous pressure but they can equally well result from halothane-induced vasodilatation of skin vessels producing increased limb blood flow. Furthermore the expression of changes in pressure as percentages by these authors artificially magnifies any actual increase in venous

pressure when compared with CSF pressure since the absolute level of the former is so much less than that of the latter. For these reasons the demonstration by Marx *et al.*[8] that equal percentage increases in CSF and venous pressures occur with halothane need not imply that the rise in CSF pressure is secondary to a primary rise in venous pressure. In the present study the administration of 0.5% halothane or of 0.9% trichlorethylene produced either no change in central venous pressure or only a very small increase.

Marx *et al.*[8] demonstrated that the elevation in CSF pressure with halothane varied with the concentration of the drug administered. In the present study both patients (32 and 38) and both dogs (8 and 9) receiving more than 0.5% halothane showed further increases in CSF pressure when the concentration of halothane exceeded 0.5%.

Hunter[9] has published a record of the changes in intracranial pressure in a patient produced by the intermittent administration of 1% halothane during controlled ventilation. The changes shown closely resemble the pattern observed in the present study.

Causes of pressure changes

The possible causes of increased CSF pressure are:

1 Increased volume of brain parenchyma or of CSF
2 Increased volume of intracranial blood secondary to an increase in cerebral blood flow (CBF) or in central venous pressure (both of which increase cerebral venous pressure).

Only intracranial blood volume can alter rapidly and changes in this are therefore likely to account for the transient alterations in CSF pressure during anæsthesia. However, an experiment was performed in two dogs to explore the relationship between cerebral venous pressure and CSF pressure, because it has been asserted that increases in CSF volume cause increases only in CSF pressure and not in cerebral venous pressure[10,11]. In these two dogs the increase in CSF pressure with halothane was associated with a parallel change in cerebral venous pressure, which is strong evidence against the hypothesis that the CSF pressure rise caused by halothane is secondary to increased CSF volume. Of the two factors affecting intracranial blood volume, central venous pressure was shown in this study to change very little during the administration of 0.5% halothane or 0.9% trichlorethylene; it seems that increase in CBF is the most likely explanation for the CSF pressure changes induced by these two agents.

Total CBF has been directly measured in a group of anæsthetised volunteers; during administration of 1.2% halothane CBF was 14% greater than in a group of conscious subjects[12]. This would correlate well with the rise in CSF pressure in the present study, but Christensen

et al.[13] reported that 1% halothane did not appear to act as a cerebral vasodilator in man.

Measuring blood flow through a localised area of cortex in dogs, McDowall *et al.*[14] reported a 46% fall in CBF during the administration of 0.5% halothane or less in air. Subsequently McDowall and Harper[15] reported that the administration of 0.5% halothane in nitrous oxide and oxygen caused a progressive fall in CBF after an apparent early increase; flow fell in the second half hour of administration by 16% and in the second hour by 23%. These workers[16] have since found that after ten minutes of 0.5% halothane CBF is 9% higher than the control value; this difference, however, failed to reach statistical significance. With 2% halothane flow was increased by 36%, a statistically significant increase. It would seem that alterations in both CBF and in CSF pressure are related to halothane concentration.

Time relations of pressure changes

Another interesting correlation between changes in CBF and in CSF pressure under halothane anæsthesia is that both show a return towards the resting level after an initial increase. On 6 out of 7 occasions in dogs CSF pressure rose to a peak in 3 to 13 minutes and then fell towards the control level despite continuing halothane administration. In dog 5, in which the changes were followed for the longest period of time, the CSF pressure returned to the baseline after 52 minutes of administration and then dropped below it. On withdrawal of halothane in this dog there was a further sharp reduction in CSF pressure.

There are two possible interpretations of this sequence of events. The first is that compensation for increased CBF occurs during halothane administration by means of a compensatory reduction in CSF volume. The effect of such a fall in CSF volume would be to restore the CSF pressure to its initial value despite the augmented CBF. The other possibility is that, as described by McDowall and Harper[15] CBF falls during the administration of 0.5% halothane after an initial vasodilatation. In favour of this hypothesis is our observation that cerebral venous pressure falls as the CSF pressure declines during continuing halothane administration; such a fall in cerebral venous pressure would occur from a reduction in CBF but would not, according to Becht[10] and Weed and Flexner[11], occur with a reduction in CSF volume. Compensatory CSF changes have been demonstrated during the increase in CBF produced by CO_2 inhalation[17], during the increase in cerebral venous pressure produced by jugular ligation[18] and, in the opposite direction, during the reduction in CBF associated with hyperventilation[19].

It was not possible, because of the obvious limitations on time, to follow these relatively slow adjustments of CSF pressure in man. However, it is interesting that in three of the patients in this study the CSF pressure had already started to fall from its peak level during the period of observation. Such a secondary fall in pressure could account for the results of Bozza *et al.*[1] who found no change in dural tension at craniotomy under halothane anæsthesia; by the time the surgeon had exposed the dura (from the appearance of which these workers assessed intracranial pressure the,) pressure would already have fallen from its peak level. The CSF pressure increases during the administration of trichlorethylene may also be the result of increases in cerebral blood flow. Such increases in CBF with trichlorethylene have been briefly described by Nowill *et al.*[20] The report by McDowall *et al.*[21] that no change in cortical blood flow occurs during trichlorethylene administration to dogs requires further investigation; it may be that the duration of administration is critical here as with halothane.

When patients in this study were deliberately hyperventilated, CSF pressure fell although the initial level was normal. When 0.5% halothane was administered during hypocapnia only insignificant increases in CSF pressure occurred. Ryder *et al.*[6] have shown that any increase in CBF has less influence on CSF pressure when that pressure is initially low and this is the likely explanation for the failure of halothane to induce a rise in CSF pressure in hypocapnia.

It seems clear that appreciable increases in intracranial pressure occur with the introduction of 0.5% halothane or 0.9% trichlorethylene when the arterial P_{CO_2} is above 35mm/Hg. The CSF pressure may decline after the initial rise despite continuing administration of the volatile agent so that by the time the dura is exposed no obvious increase in dural tension is noticeable. Such gradual compensation could prove too slow for the patient whose intracranial pressure is already high, and there could be a risk of precipitating a critical rise of intracranial pressure during the early stages of anæsthesia with halothane. This could be averted, as suggested by Marx *et al.*[8], if the patient were previously hyperventilated.

SUMMARY

CSF pressure was measured during anæsthesia in patients via lumbar puncture and in dogs via cisternal puncture.

Introduction of 0.5% halothane or 0.9% trichlorethylene in normocapnic subjects caused an appreciable rise in CSF pressure, associated with little or no rise in central venous pressure. With hypocapnia the rise in CSF pressure was much less pronounced.

With continued administration of these agents the CSF pressure is gradually restored to normal.

Increased cerebral blood flow is proposed as the most likely explanation for the rise in CSF pressure.

To avoid precipitating a crisis in patients with raised intracranial pressure it is recommended that a period of hyperventilation should precede the introduction of halothane or trichlorethylene.

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CEREBRAL BLOOD FLOW DURING TRICHLOROETHYLENE ANAESTHESIA: A COMPARISON WITH HALOTHANE

BY

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SUMMARY

Cerebral blood flow has been measured in dogs using the method of Ingvar and Lassen (1962) in which flow is calculated from the rate of clearance from the exposed cerebral cortex of krypton 85 after its injection into the carotid artery. It was found that the addition of trichloroethylene in concentrations of 0.4–0.9 per cent to a nitrous oxide-oxygen anaesthetic mixture did not alter the cerebral blood flow significantly. Trichloroethylene did, however, reduce the oxygen consumption of the cerebral cortex by 20 per cent. These findings are compared with the previously reported effects of halothane. The striking differences in the response of the cerebral blood vessels to the two agents is discussed.

Trichloroethylene and halothane are the inhalational agents most generally recommended for neurosurgical anaesthesia (Lee, 1959; Wylie and Churchill-Davidson, 1959). In attempting to produce optimal conditions for neurosurgery, a knowledge of the effects of anaesthetic drugs on cerebral haemodynamics is obviously important. Halothane has been studied recently (Galindo and Baldwin, 1963; McDowall, Harper and Jacobson, 1963), but little is known about the effects of trichloroethylene on cerebral blood flow and cerebral oxygen uptake.

METHOD

Blood flow through the cerebral cortex was measured by the method of Lassen and Ingvar (1961), and Ingvar and Lassen (1962). This involves the measurement of the rate of clearance of krypton 85 from an area of exposed cerebral cortex. We have previously given a detailed account of our experimental technique in using this method for the assessment of the effects of halothane on cerebral haemodynamics (McDowall, Harper and Jacobson, 1963). The same procedure was followed in the present series of experiments, except for the following points.

Forty-nine measurements of blood flow through the cerebral cortex were made in six unselected mongrel dogs. A cannula in the sagittal sinus was connected to a saline manometer for the measurement of cerebral venous pressure and for the collection of samples of cerebral venous blood. The right atrial pressure was monitored in one dog through a cannula passed via the external jugular vein and connected to a saline manometer.

In four of the experiments the level of anaesthesia was monitored by an Offner electroencephalograph, using stainless steel electrodes. Bipolar, bifrontal and right frontal-occipital recordings were taken during each blood flow measurement.

Trichloroethylene was administered from a Fluotec Mark II vaporizer, the drug being vaporized by the same mixture of nitrous oxide and oxygen as was used for the control flow measurements. The setting on the vaporizer dial was 1.5 per cent in two experiments and 3 per cent in four. (These settings represent 0.43 and 0.87 per cent trichloroethylene respectively.*)

In each experiment three measurements of cerebral blood flow were made during ventilation with nitrous oxide and oxygen alone. Blood flow was then measured during the administration of trichloroethylene. In four experiments the effects of carbon dioxide and hyperventilation during trichloroethylene anaesthesia were observed.

*Correction factor kindly supplied by Messrs. Cyprane Ltd.

TABLE I

Details of results obtained for cerebral blood flow, cerebral oxygen uptake and cerebrovascular resistance (c.v.r.) with nitrous oxide and oxygen and with trichloroethylene, nitrous oxide and oxygen.

Dog No.	Nitrous oxide and oxygen only			Trichloroethylene, nitrous oxide and oxygen		
	Blood flow (ml/g/min)	c.v.r.	Oxygen uptake (ml/g/min)	Blood flow (ml/g/min)	c.v.r.	Oxygen uptake (ml/g/min)
1	0·74	1·89	0·051	1·11	1·13	0·044
	0·79	1·48	0·055	0·87	1·53	0·036
	0·67	1·74	0·047	0·71	1·94	0·052
				0·61	2·31	0·041
				0·80	1·83	0·042
				0·79	1·91	0·049
				0·76	1·99	0·052
2	0·73	1·59	0·096	0·96	1·20	0·088
	0·80	1·46	0·098	0·90	1·17	0·079
	0·79	1·48	0·093	0·81	1·30	0·074
				0·76	1·45	0·086
3	0·71	1·94	—	0·77	1·80	—
	0·82	1·69	—	0·79	1·71	—
	0·80	1·86	—	0·70	2·07	—
				0·80	1·74	—
				0·76	1·85	—
4	0·84	1·69	0·066	0·58	2·36	0·060
	0·76	1·88	0·089	0·54	2·55	0·055
	0·72	1·98	0·079	0·61	2·16	0·063
				0·58	2·26	0·057
				0·60	2·18	0·060
				0·61	2·15	0·062
				0·60	2·18	0·057
				0·62	2·03	0·051
5	0·53	3·70	0·056	0·59	2·99	0·057
	0·57	3·36	0·055	0·54	3·35	0·062
	0·58	3·21	0·060	0·58	3·12	0·040
				0·61	3·06	0·034
				0·53	3·32	0·042
6	0·88	1·82	—	0·90	1·89	—
	0·90	1·78	—	0·93	1·83	—
	0·97	1·96	—			

TABLE II

Means of value for cerebral blood flow, cerebrovascular resistance (c.v.r.) and cerebral oxygen uptake.

Means	Blood flow	c.v.r.	Oxygen uptake
Nitrous oxide+oxygen (All dogs)	0·76±0·11	2·03±0·67	0·070±0·019
Trichloroethylene+nitrous oxide+oxygen (All dogs)	0·72±0·15	2·08±0·60	0·056±0·015*
Trichloroethylene+nitrous oxide+oxygen (excluding Dog 4)	0·76		

*Statistically significant $0{\cdot}01 > P > 0{\cdot}005$

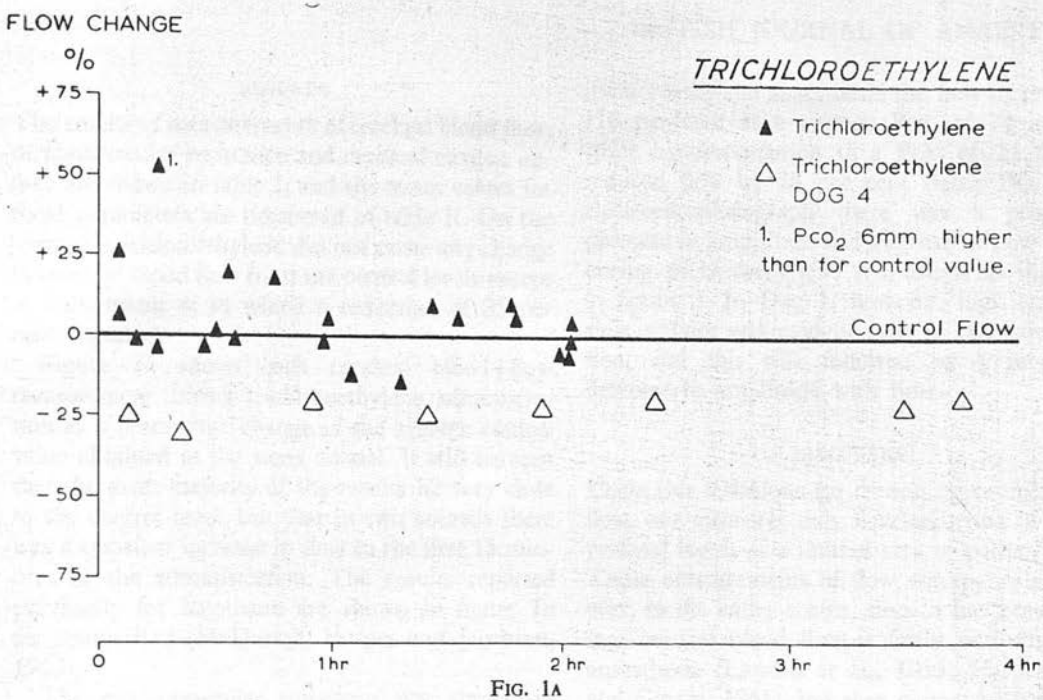

FIG. 1A

Cerebral blood flow during trichloroethylene anaesthesia expressed as percentage increase (+) or decrease (−) of the control value in the same animal. The time scale indicates the duration of trichloroethylene administration.

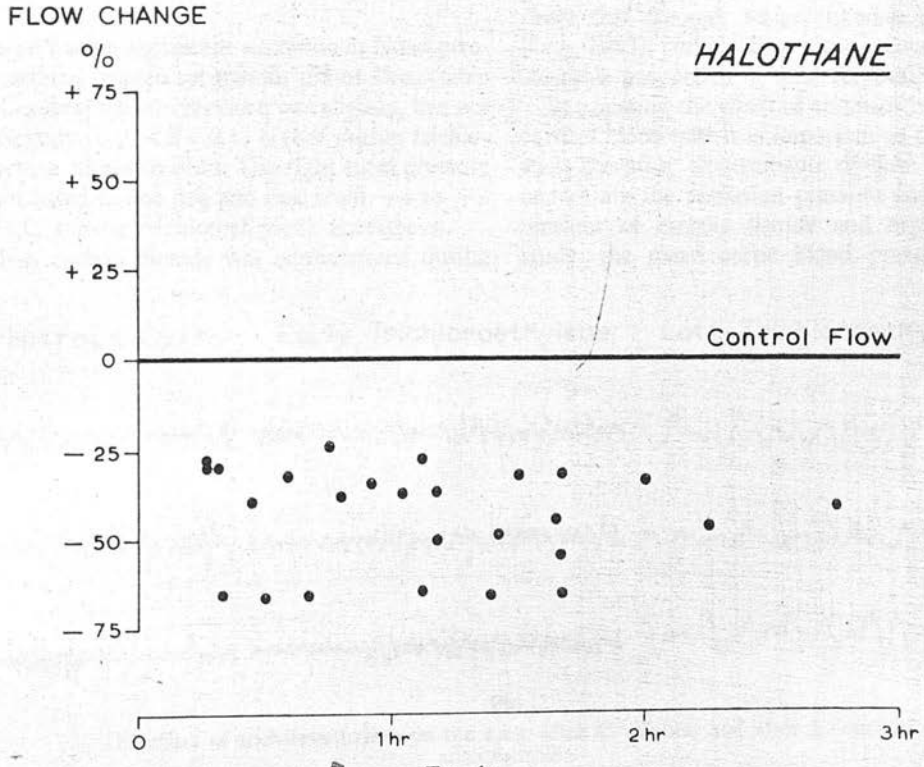

FIG. 1B

Cerebral blood flow during halothane anaesthesia expressed as percentage increase (+) or decrease (−) of the control value in the same animal. The time scale indicates the duration of halothane administration.

RESULTS

The results of measurements of cerebral blood flow, cerebrovascular resistance and cerebral oxygen uptake are shown in table I, and the mean values for these parameters are presented in table II. On the average, trichloroethylene did not cause any change in cerebral blood flow from the control levels except in experiment 4, in which a reduction of 25 per cent occurred.

Figure 1A shows each cerebral blood flow measurement during trichloroethylene administration as a percentage change of the average control value obtained in the same animal. It will be seen that the great majority of the results lie very close to the control level, but that in two animals there was a transient increase in flow in the first 15 minutes of the administration. The results reported previously for halothane are shown in figure 1B for comparison (McDowall, Harper and Jacobson, 1963).

The cerebrovascular resistance was similar in the control and trichloroethylene groups. Trichloroethylene administration reduced the oxygen uptake of the cerebral cortex by an average of 20 per cent.

There was no significant alteration in blood pressure, arterial oxygen saturation, pH or Pco_2 (table III). Cerebral venous pressure was slightly, but not significantly ($0.05<P<0.1$) higher during trichloroethylene administration. The right atrial pressure was recorded in one dog and rose from -1 to $+2$ cm H_2O during trichloroethylene anaesthesia.

When carbon dioxide was administered during trichloroethylene anaesthesia the flow increased by 116 per cent at a average Pco_2 of 74 mm Hg, while hyperventilation to a Pco_2 of 21 mm Hg reduced flow by 28 per cent (table IV). In the electroencephalograph there was a progressive decrease in amplitude and increase in slow activity during trichloroethylene anaesthesia as illustrated in figure 2. In Dog 1, however, high amplitude slow activity was evident early in the administration, and this was followed by a progressive decrease in amplitude with time.

DISCUSSION

Using this technique for measuring cerebral blood flow, one measures only flow occurring in the superficial layers of a limited area of parietal cortex. These measurements of flow are applicable, however, to the entire cortex, since it has been shown that cortical blood flow is fairly uniform during anaesthesia (Landau et al., 1955; Harper, Glass and Glover, 1961), but they cannot be considered as necessarily indicating changes in total cerebral blood flow. Nevertheless, as blood flow through grey matter has been shown to be three to five times that through white (Landau et al., 1955; Kety, 1963), cortical flow must account for a considerable proportion of total cerebral flow.

In assessing the effect of an anaesthetic agent on cortical blood flow it is important to maintain constant the other determinants of flow. These other factors are the perfusion pressure and the arterial tensions of carbon dioxide and oxygen. In this study, the mean aortic blood pressure was not

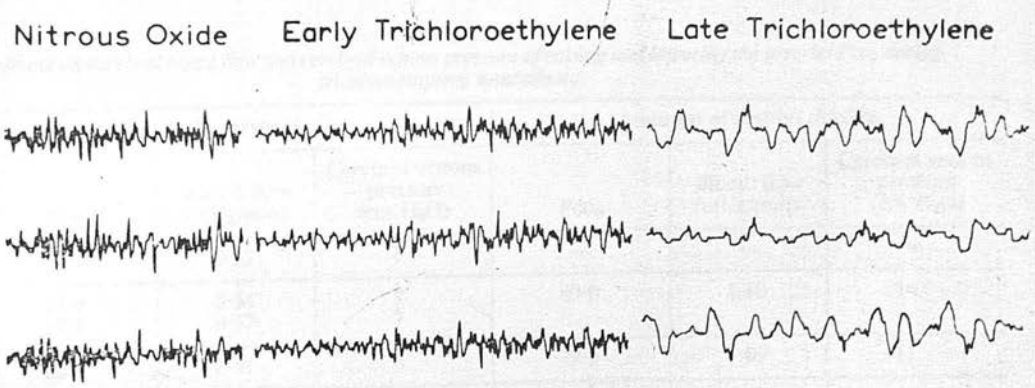

FIG. 2

The effect of trichloroethylene on the e.e.g. after 45 minutes and after 2 hours of administration.

TABLE III

Values for mean blood pressure, cerebral venous pressure, central venous pressure, arterial pH, arterial Pco_2, arterial and venous oxygen saturations during each measurement of cerebral blood flow.

Dog No.	Nitrous oxide and oxygen							Trichloroethylene, nitrous oxide and oxygen						
	Blood pressure (mm Hg)	Cerebral venous pressure (cm H_2O)	Central venous pressure (cm H_2O)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.	Blood pressure (mm Hg)	Cerebral venous pressure (cm H_2O)	Central venous pressure (cm H_2O)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.
1	145	7	—	7·31	35·5	97	56	135	12	—	7·32	41·5	100	76·5
	120	4	—	7·35	37·0	100	58	140	10	—	7·37	31·0	99·5	74·5
	120	4	—	7·35	34·0	99	57	145	7	—	7·37	36·0	100	56
								145	5	—	7·36	34·0	99·5	59
								150	4	—	7·37	35·0	99	67·5
								155	6	—	7·36	34·0	99	62
								155	5·5	—	7·35	35·5	99	58
2	120	5·5	—	7·26	35·0	100	51	120	7	—	7·23	38·0	100	67
	120	4	—	7·26	36·0	99	53	110	8	—	7·24	40·0	99	66
	120	5	—	7·26	37·5	100	56	110	7	—	7·25	34·0	99	65
								115	8	—	7·23	37·0	98·5	56
3	145	10	—	7·33	35·0	100	—	145	8	—	7·33	32·0	100	—
	145	10	—	7·32	36·5	98	—	140	7	—	7·31	35·5	100	—
	155	8	—	7·33	31·0	100	—	150	7	—	7·34	34·0	92	—
								145	8	—	7·35	30·0	100	—
								145	7	—	7·34	34·0	100	—
4	145	4	0	7·31	39·5	97	62	140	4	−1	7·31	38·0	98	52
	145	3	0	7·31	36·5	100	48	140	3	−1	7·31	36·0	98	53
	145	3	0	7·29	37·5	97	48	135	4	+1	7·31	36·0	98	52
								135	5	+1	7·30	37·0	98	54
								135	6	+2	7·30	38·0	98·5	54
								135	5	+2	7·30	35·5	98	52·5
								135	5	+2	7·28	34·0	98	56
								130	6	+2	7·29	36·0	97·5	61
5	200	4	—	7·36	33·5	93	52	180	5	—	7·35	35·5	97	59
	195	5	—	7·33	39·5	93	55	185	6	—	7·35	33·5	98	53
	190	5	—	7·34	37·5	98	58	185	6	—	7·33	35·0	98	71
								190	6	—	7·30	35·5	95	73
								180	6	—	7·31	35·0	98	67
6	160	—	—	7·29	37·5	97	—	170	—	—	7·29	36·0	98	—
	160	—	—	7·29	37·5	96	—	170	—	—	7·31	32·0	98	—
	190	—	—	7·34	29·5	95	—							
	151·1 ±27·1	5·4 ±2·3			35·9 ±2·6	97·7 ±2·3	54·5 ±4·2	146·8 ±21·6	6·3 ±3·1			35·3 ±2·5	98·4 ±1·6	61·0 ±7·7

TABLE IV

The effects on cerebral blood flow and cerebral venous pressure of raising and lowering the arterial Pco_2 during trichloroethylene anaesthesia.

Dog No.	Passive hyperventilation			Addition of carbon dioxide		
	Pco_2	Blood flow (ml/g/min)	Cerebral venous pressure (cm H_2O)	Pco_2	Blood flow (ml/g/min)	Cerebral venous pressure (cm H_2O)
2	23·5	0·57	8	—	—	—
3	22·0	0·54	7	60·0	1·80	14
	18·5	0·57	7			
4	20·5	0·51	6	79·0	1·09	11
5	23·0	0·41	5·5	84·0	1·80	13
Mean	21·5	0·52	6·7	74·0	1·56	12·7

altered significantly by the administration of trichloroethylene. Since ventilation was controlled throughout each experiment, it was possible to maintain the arterial carbon dioxide tension within narrow limits, while the oxygen content of the inspired gases was adjusted to maintain a steady level of arterial oxygen saturation.

The effect of trichloroethylene on cerebral blood flow.

Under these controlled conditions, the addition of trichloroethylene (in concentrations of 0.4–0.9 per cent) to the nitrous oxide-oxygen anaesthetic mixture did not alter the average cortical blood flow. In two of the six animals there was a transient 30 per cent increase in flow which settled during the first half-hour of administration, and in one dog the flow was reduced by approximately 25 per cent throughout.

Nowill, Stephen and Searles (1953) used the thermoelectric technique of Gibbs (1933) to measure cerebral blood flow during trichloroethylene anaesthesia in rabbits and one monkey. They found that trichloroethylene, vaporized in oxygen, produced an increase in flow which was less than that which resulted from the administration of 5 per cent carbon dioxide. The authors do not state what anaesthetic, if any, was used in obtaining their control levels. Bozza, Maspes and Rossanda (1961) estimated intracranial tension by the look and feel of the dura at operation and found that "general anaesthesia" (which included the use of trichloroethylene in an unspecified number of patients) "did not appreciably modify the conditions of the operating field". However, as their technique did not detect a significant difference in the operating conditions between hypoventilation and normal ventilation, quite large changes due to trichloroethylene could have been missed.

The effect of trichloroethylene compared with halothane on cerebral oxygen uptake.

Oxygen consumption was calculated from the cerebral cortical flow and the arteriovenous oxygen difference, the venous sample being obtained from the superior sagittal sinus. As the superior sagittal sinus in the dog contains mainly cortical venous blood (Gleichmann et al., 1962), the oxygen consumption obtained is that of the grey matter of the cerebral cortex. For this reason the values given here are considerably higher than those obtained when cerebral oxygen consumption is calculated from total cerebral flow and arterial-internal jugular oxygen difference.

The oxygen uptake of the cerebral cortex was 20 per cent lower during trichloroethylene administration than during unsupplemented nitrous oxide anaesthesia. There are no previous measurements of the effect of trichloroethylene on cerebral oxygen uptake. Halothane in concentrations of 0.5 per cent or less has been shown to depress cerebral oxygen uptake by about 50 per cent, and, while the exact relationship between cerebral oxygen uptake and anaesthesia is uncertain (Butler, 1950; Hunter and Lowry, 1956), these results fit well with clinical experience of the relative potency of the two agents.

Other observations during trichloroethylene anaesthesia.

Although the average cerebral blood flow during trichloroethylene administration was no higher than the control level, the cerebral venous pressure rose slightly. In one dog, central venous pressure was recorded and was found to rise by 3 cm H_2O during 2 hours of trichloroethylene administration, perhaps due to direct cardiac depression (Krantz et al., 1935). As the cerebral venous pressure rose by the same amount at the same time, it is suggested that the increase in cerebral venous pressure was due to the change in central venous pressure. However, this explanation is not supported by the work of Dobkin, Harland and Fedoruk (1962), who found no change in inferior vena caval pressure in dogs anaesthetized with trichloroethylene.

Nowill, Stephen and Searles (1953) described the changes which occurred in the electroencephalogram of rabbits and one monkey during their study of trichloroethylene as consisting only of slight slowing and a small decrease in amplitude. In the experiments reported here, the electrocorticogram showed similar small changes in the first hour, but with more prolonged administration the changes became quite marked.

As has been previously reported (Nowill, Stephen and Searles, 1953; Ostlere, 1953; Dobkin, Harland and Fedoruk, 1962), even prolonged administration of trichloroethylene caused no fall in arterial pH or in mean blood pressure.

The mode of action of trichloroethylene and halothane on cerebral blood flow.

In an earlier study, using the same technique, halothane was shown to decrease cerebral cortical flow by 46 per cent (McDowall, Harper and Jacobson, 1963). As the cerebral cortical oxygen uptake was reduced by 49 per cent, it was considered that the flow reduction was due to this decrease in oxygen consumption, mediated by an autoregulatory mechanism functioning to maintain a constant cortical tissue Pco_2. As Sokoloff (1959) has said, "Any influence they [the general anaesthetics] may have is possibly chiefly secondary to their effects on blood pressure, cerebral metabolic rate and the respiratory gas tensions in the blood."

These results with trichloroethylene do not support this statement, since flow remained unaltered despite a 20 per cent reduction in cerebral metabolic rate (without any change of blood pressure or respiratory gas tensions). This finding could be explained by either of the following hypotheses:

(1) Anaesthesia interferes with the local control of the cerebral vessels so that they are unable to respond to the usual regulatory mechanisms.

(2) The unchanged flow with trichloroethylene is due to a balancing of a vasoconstrictive stimulus due to lowered oxygen consumption against a direct vasodilatory action of the drug on the vessel wall.

Hypothesis (1) receives some support from the work of Schieve and Wilson (1953), for they reported that the response of the cerebral vessels to added carbon dioxide was depressed by barbiturate anaesthesia. However, the results in table IV show that trichloroethylene does not impair the flow response to either increases or decreases in arterial Pco_2. In addition, Jacobson, Harper and McDowall (1963) have shown that during trichloroethylene anaesthesia, inhalation of 100 per cent oxygen produces a reduction in flow of 12 per cent; this is very close to the 13 per cent reduction found in conscious volunteers by Kety and Schmidt (1948). As, therefore, the cerebrovascular response to changes in arterial gas tensions is not impaired by trichloroethylene it is likely that the response to local changes in Po_2 and Pco_2 is also normal.

Some support for hypothesis (2) comes for the observation in two animals of an initial increase in flow in the early minutes of administration. This could be due to a direct vasodilator action of trichloroethylene increasing flow before the drug had produced depression of cerebral oxygen uptake. This was, however, not a consistent response and, even in the two dogs in which it was noted, a closer scrutiny of the results shows that depression of oxygen uptake had already occurred.

It would, therefore, appear that the effects of anaesthetic agents on cerebral blood flow cannot be related solely to the depression of cerebral oxygen uptake that they produce. Either their effects are due entirely to individual direct action on the vessel walls—in which case halothane is a potent local constrictor and trichloroethylene has no effect —or they are due to a combination of direct action and response to local metabolic requirements, when halothane would be without direct action and trichloroethylene would cause direct dilatation of a degree equal to the constrictive stimulus of a 20 per cent reduction in the oxygen requirements. It is proposed to investigate further the relationship between cerebral blood flow and depression of oxygen uptake and the connection, if any, between vasomotor effects and particular chemical structures, by studying a range of volatile anaesthetic agents.

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CIRCULATION SANGUINE CÉRÉBRALE PENDANT L'ANESTHÉSIE AU TRICHLORO-ÉTHYLÈNE — COMPARAISON DES EFFETS AVEC CEUX DE L'HALOTHANE

SOMMAIRE

L'irrigation sanguine du cerveau fut mesurée chez le chien par la méthode d'Ingvar et Lassen (1962), et l'emploi du calcul à partir du taux de clearance de 85 krypton dans le cortex cérébral, le krypton ayant été injecté au préalable dans la carotide. Les auteurs constatèrent que l'administration de 0.4 à 0.9% de trichloréthylène mélangé à l'habituelle préparation de protoxyde d'azote et d'oxygène ne provoqua aucune altération significative de la circulation sanguine du cerveau. Par contre le trichloréthylène reduisit la consommation d'oxygène du cortex cérébral de 20%. Après comparaison de ces constatations avec celle des effets de l'halothane — dont les auteurs ont parlé auparavant — ils discutent les différences surprenantes du mode de réaction des vaisseaux cérébraux sanguins aux deux substances.

CEREBRALE DURCHBLUTUNG WÄHREND DER TRICHLORÄTHYLEN-ANÄSTHESIE: EIN VERGLEICH MIT HALOTHANE

ZUSAMMENFASSUNG

Nach der Methode von Ingvar und Lassen (1962), bei der der Durchfluß aus der Clearance-Rate von Krypton 85 an der freigelegten Gehirnrinde nach einer Injektion in die Carotisarterie errechnet wird, wurde die Durchblutung des Gehirnes an Hunden gemessen. Es wurde festgestellt, daß der Zusatz von Trichloräthylen in Konzentrationen von 0.4–0.9 % zu einem Anästhesiegemisch von Lachgas und Sauerstoff die cerebrale Durchblutung nicht wesentlich veränderte. Trichloräthylen reduzierte jedoch den Sauerstoffverbrauch der Gehirnrinde um 20 %. Diese Befunde werden mit den kürzlich berichteten Wirkungen des Halothane verglichen. Die augenfälligen Unterschiede in bezug auf die Reaktion der cerebralen Blutgefäße auf die zwei Substanzen werden besprochen.

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CEREBRAL BLOOD FLOW DURING HALOTHANE ANAESTHESIA

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BY

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SUMMARY

Cerebral blood flow has been measured in dogs using the method of Lassen and Ingvar (1961), and Ingvar and Lassen (1962), which involves measurement of the rate of clearance of krypton 85 from an area of exposed cerebral cortex after injection into the internal carotid artery. In every measurement during halothane anaesthesia there was a considerable reduction in cerebral blood flow compared with the flows obtained with nitrous oxide and oxygen. The average reduction in flow was 46 per cent and this was accompanied by an average increase in cerebrovascular resistance of 50 per cent. Measurements were also made of the cerebral oxygen uptake ($CMRO_2$) and halothane produced an average decrease in uptake of 49 per cent. Possible mechanisms for the observed results are discussed.

Despite the very widespread use of halothane in anaesthesia today, there seems to be little knowledge of its action on cerebral blood flow (Graham, 1959). It seemed to us that the evaluation of the effects of this drug on cerebral haemodynamics and oxygen consumption would be of interest.

METHOD

The blood flow through the brain cortex was measured by the method of Lassen and Ingvar (1961), and Ingvar and Lassen (1962). This is an inert gas clearance method with the following rationale: krypton 85 (an inert, beta-emitting radioactive gas) is dissolved in dextran and injected over several minutes into the carotid artery. The gas diffuses almost equally into the blood and the brain tissue. On cessation of the injection the krypton diffuses back into the blood and the rate at which it is cleared from the brain tissue will depend on the quantity of blood perfusing the brain. There is no significant arterial recirculation of the gas as it is almost completely excreted in the lungs. The rate of clearance from the brain is measured by a Geiger counter mounted over the exposed brain cortex. As krypton 85 emits mainly beta particles, measurements of blood flow will be from the cerebral cortex alone.

Forty-six measurements of blood flow through the cerebral cortex were made on five unselected mongrel dogs. Anaesthesia was induced with thiopentone. A cuffed endotracheal tube was inserted and a 4:1 mixture of nitrous oxide and oxygen administered by a Starling respiratory pump, the stroke volume of the pump being adjusted to give an arterial carbon dioxide tension of 30 to 40 mm Hg. Suxamethonium chloride was given by intermittent injection to facilitate controlled ventilation. The Starling pump provided a non-rebreathing circuit which was essential to prevent recirculation of the krypton 85. Cannulae were inserted into a femoral vein and into the aorta via a femoral artery, the latter being connected to a three-way tap for the withdrawal of arterial blood samples and to a mercury manometer for the measurement of mean arterial blood pressure. The thyroid branch of the carotid artery was cannulated centripetally, the tip of the cannula lying in the carotid artery. The sagittal sinus was cannulated in its posterior third. The brain was exposed through a trephine hole made in the parietal bone and a segment of dura 1 cm in diameter excised. A thin polyethylene membrane was placed over the exposed brain cortex. Measurements of blood flow were made by injecting over 2 to 3 minutes about 0.5 mc of krypton 85 dissolved in dextran into the carotid artery. The clearance of krypton 85 was measured by a Geiger counter mounted 1 mm above the brain cortex and connected to a ratemeter and

direct writing recorder. Blood flow was calculated from the formula:

$$\text{Flow in ml/gm/min} = \frac{\lambda \log e\, 2 \times 60}{T\frac{1}{2}}$$

where λ = blood : brain cortex partition coefficient for krypton 85

and $T\frac{1}{2}$ = the duration in seconds for the decrease to one-half the initial value of a straight line fitted to a semilogarithmic plot of the initial part of the clearance curve (Ingvar and Lassen, 1962).

One minute after each measurement of blood flow through the cerebral cortex simultaneous blood samples were taken from the aorta and the sagittal sinus. The arterial blood samples were analyzed for pH and Pco_2 on the Micro-Astrup apparatus (Andersen et al., 1960) and both arterial and venous blood samples for oxygen saturation on a Kipp haemoreflector.

Throughout each experiment the level of anaesthesia was monitored by an Offner electroencephalograph, using stainless steel electrodes. Bipolar, bifrontal and right fronto-occipital recordings were taken during each blood-flow measurement.

For the flow measurements under halothane anaesthesia, halothane was administered from a Fluotec Mark II vaporizer, the drug being vaporized either in air or oxygen. The setting of the vaporizer was varied to maintain a constant level of anaesthesia by reference to the blood pressure and the electrocardiographic tracing, in any one dog and a reasonably constant level between dogs. The concentration used was that at which there was a reduction in mean blood pressure of about 20 per cent and at which the e.e.g. showed low voltage fast activity superimposed on slow waves of moderate voltage, i.e. pattern 2 of the classification described by Gain and Paletz (1957). The vaporizer settings used to obtain these conditions were either 0.5 per cent or slightly lower concentrations obtained by setting the control to positions between "off" and 0.5 per cent.

The first four experiments were divided into four parts: the animal was anaesthetized with

(1) 80 per cent nitrous oxide and 20 per cent oxygen.
(2) 0.5 per cent or less than 0.5 per cent halothane in air.
(3) 0.5 per cent or less than 0.5 per cent halothane in oxygen.
(4) 80 per cent nitrous oxide and 20 per cent oxygen.

In one experiment only, anaesthesia was progressively deepened by administering halothane in

TABLE I

Details of results obtained for cerebral blood flow, cerebral oxygen uptake and cerebrovascular resistance (c.v.r.) in anaesthesia with nitrous oxide and oxygen, and halothane in air or oxygen.

Exp. No.	Nitrous oxide and oxygen			Halothane and air			Halothane and oxygen		Nitrous oxide and oxygen		
	Blood flow (ml/g/min)	Oxygen uptake (ml/g/min)	c.v.r.	Blood flow (ml/g/min)	Oxygen uptake (ml/g/min)	c.v.r.	Blood flow (ml/g/min)	c.v.r.	Blood flow (ml/g/min)	Oxygen uptake (ml/g/min)	c.v.r.
1	0·63	0·054	2·38	0·51	0·035	2·23	0·46	2·93	0·65	0·036	2·43
	0·80	0·062	1·94	0·48	0·039	2·92	0·52	2·60	0·70	0·053	2·21
	0·74	0·052	2·10	—	—	—	—	—	—	—	—
2	0·94	—	1·68	—	—	—	0·42	2·62	0·60	—	2·50
	0·88	—	1·84	—	—	—	0·44	2·50	0·63	—	2·38
	0·81	—	1·98	—	—	—	0·39	2·95	—	—	—
3	0·53	0·034	3·40	0·38	0·019	4·08	0·36	4·30	0·48	0·034	3·75
	0·54	0·031	3·33	0·41	0·023	3·78	0·36	4·17	—	—	—
	0·56	0·029	3·21	0·34	0·020	4·56	—	—	—	—	—
4	0·77	0·067	2·60	0·26	0·023	5·96	0·26	5·19	0·61	0·065	2·79
	0·79	0·059	2·53	0·25	0·024	5·54	0·25	5·80	0·59	0·057	3·05
	0·73	0·048	2·67	0·25	0·020	4·14	0·25	5·60	0·57	0·065	3·25
Mean	0·73	0·048	2·47	0·36	0·025	4·15	0·37	3·87	0·60	0·052	2·80

concentrations varying from less than 0.5 per cent to 3 per cent and measurements of cerebral flow were made at each increase in gas concentration.

RESULTS

The results of the first four experiments are shown in table I. The mean values for blood flow, oxygen uptake and cerebrovascular resistance (c.v.r.) are given in table II. In each experiment halothane caused a fall in blood flow from 32 to 60 per cent of the flow during nitrous oxide anaesthesia. The cerebrovascular resistance rose on an average by 50 per cent and the cerebral oxygen uptake fell by 49 per cent. There was no significant difference in the results obtained under halothane and air compared with halothane and 100 per cent oxygen.

TABLE II

Means of the results obtained for cerebral blood flow, cerebral oxygen uptake and cerebrovascular resistance in experiments one to four.

Grand means	Nitrous oxide	Halothane
Blood flow ml/g/min	0·68	0·37*
Oxygen uptake ml/g/min	0·050	0·025*
Cerebrovascular resistance	2·60	3·99*

*Statistically significant difference ($P < 0.01$)

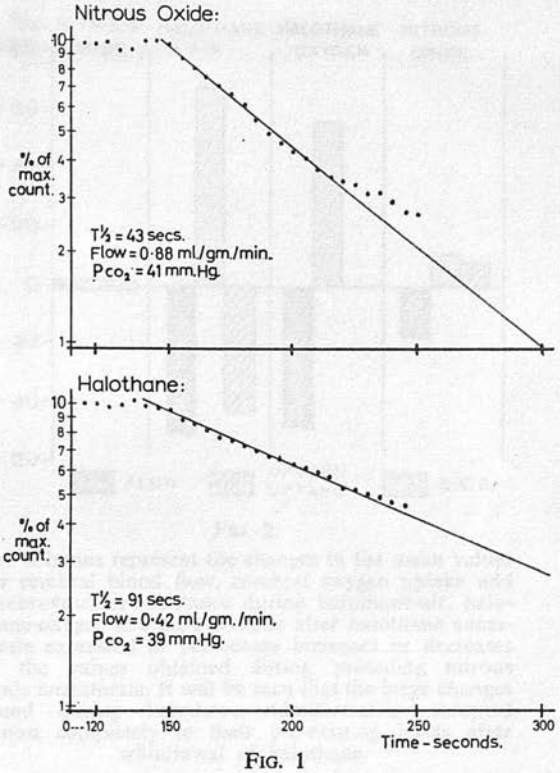

FIG. 1

Semilogarithmic plots of two clearance curves obtained from experiment 2.

TABLE III

Values for blood pressure, arterial pH, Pco_2 and oxygen saturation and cerebral venous oxygen saturation during each measurement of cerebral blood flow.

Exp. No.	Nitrous oxide and oxygen					Halothane and air					Halothane and oxygen					Nitrous oxide and oxygen				
	BP (mm Hg)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.	BP (mm Hg)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.	BP (mm Hg)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.	BP (mm Hg)	pH	Pco_2 (mm Hg)	Ao_2 % sat.	Vo_2 % sat.
1	150	7·38	33	95	52	140	7·36	36	89	54	135	7·35	36	100	58	160	7·32	41	87	59
	155	7·35	36	94	55	140	7·35	36	93	51	135	7·35	33	100	61	155	7·34	35	92	53
	155	7·34	36	89	53	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	158	7·29	39	100	85	—	—	—	—	—	110	7·27	39	—	—	150	7·37	40	99	51
	162	7·28	41	100	85	—	—	—	—	—	110	7·31	34	—	—	150	7·46	27	98	49
	160	7·28	38	98	76	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3	180	7·31	40	99	69	155	—	—	96	71	155	7·32	39	100	79	180	7·33	33	98	63
	180	7·29	40	97	69	155	7·28	46	94	67	150	7·29	37	100	81	—	—	—	—	—
	180	7·28	41	97	71	155	7·28	46	96	67	—	—	—	—	—	—	—	—	—	—
4	200	7·38	36	99	55	155	7·43	32	98	54	135	7·39	37	100	70	170	7·34	44	99	45
	200	7·38	36	99	61	155	7·39	38	96	52	145	7·39	36	100	61	180	7·36	43	91	42
	195	7·40	28	99	65	145	7·34	45	96	71	140	7·37	43	100	65	185	7·36	45	98	40
Mean	173	7·33	37	97	66	150	7·35	40	95	61	135	7·34	37	100	68	166	7·36	39	95	50

Semilogarithmic plots of two clearance curves obtained from experiment 2 are shown in figure 1. The other parameters measured are shown in tables III and IV. Figure 2 is a histogram to show the effects of halothane on flow, oxygen uptake and cerebrovascular resistance, expressed as percentage increases or decreases of the values obtained during preceding nitrous oxide anaesthesia.

Halothane anaesthesia caused an average fall of 18 per cent in mean arterial blood pressure from the values obtained under nitrous oxide (range 10 to 32.5 per cent). The lowest mean blood pressure during any flow measurement was 110 mm Hg. There was no significant difference in the arterial carbon dioxide tensions, the arterial oxygen saturations or the cerebral venous oxygen saturations between nitrous oxide and halothane.

TABLE IV

Means of values of blood pressure, arterial pH, Pco_2, oxygen saturation and cerebral venous oxygen saturation in experiments 1 to 4.

Grand means	Nitrous oxide	Halothane
Blood pressure (mm Hg)	170	142*
Arterial pH	7·34	7·34
Arterial Pco_2 (mm Hg)	37·6	38·3
Arterial oxygen saturation (% sat.)	96·4	97·2
Venous oxygen saturation (% sat.)†	59·9	64·1

*0·2>P>0·1

†Venous blood from superior sagittal sinus.

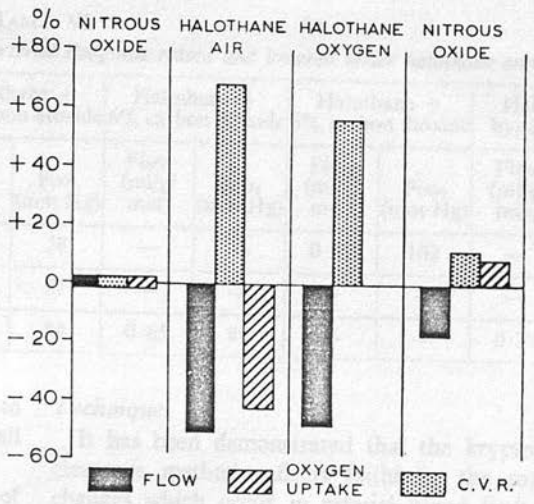

FIG. 2

The columns represent the changes in the mean values for cerebral blood flow, cerebral oxygen uptake and cerebrovascular resistance during halothane-air, halothane-oxygen and nitrous oxide after halothane anaesthesia expressed as percentage increases or decreases of the values obtained during preceding nitrous oxide anaesthesia. It will be seen that the large changes found during halothane administration returned almost completely to their pre-existing levels after withdrawal of halothane.

Table V shows the effect of different levels of halothane anaesthesia on the blood flow and cerebrovascular resistance. There is no significant alteration in blood flow at inspired concentrations of halothane ranging from less than 0.5 per cent to 3 per cent. With 3 per cent halothane there is,

TABLE V

The results obtained from dog (5) exposed to progressively increasing concentrations of halothane.

Percentage halothane in oxygen	Blood pressure (mm Hg)	pH	Pco_2 (mm Hg)	Flow (ml/g/min)	Cerebrovascular resistance
Less than 0·5	130	7·35	46	0·46	2·82
	130	7·35	46	0·38	3·42
0·5	120	7·34	48	0·41	2·93
	120	7·38	42	0·41	2·93
1·0	110	7·39	40	0·35	3·14
1·5	100	7·38	42	0·42	2·32
2·0	100	7·40	38	0·34	2·94
3·0	75	7·38	34	0·38	1·98

TABLE VI

The results for cerebral blood flow obtained when the arterial Pco_2 was raised and lowered under halothane anaesthesia.

Exp. No.	Nitrous oxide		Halothane		Halothane + 4% carbon dioxide		Halothane + 6% carbon dioxide		Halothane + 8% carbon dioxide		Halothane + hyperventilation	
	Flow (ml/g/min)	Pco_2 (mm Hg)	Flow (ml/g/min)	Pco_2 (mm Hg)	Flow (ml/g/min)	Pco_2 (mm Hg)	Flow (ml/g/min)	Pco_2 (mm Hg)	Flow (ml/g/min)	Pco_2 (mm Hg)	Flow (ml/g/min)	Pco_2 (mm Hg)
1	0·70	36	0·47	35	0·80	58	—	—	0·92	102	—	—
2	0·76	37	0·42	37	0·65	61	—	—	—	—	—	—
3	0·68	39	0·28	39	0·48	54	0·65	81	—	—	0·27	22

however, a fall in cerebrovascular resistance due to compensatory vasodilatation associated with a fall in mean arterial blood pressure.

Table VI shows the effect of the inhalation of varying concentrations of carbon dioxide and of hyperventilation on the cerebral blood flow under halothane anaesthesia. Inspired concentrations of carbon dioxide of 4 to 6 per cent were found to restore the cerebral blood flow to control levels. Hyperventilation did not produce any significant further decrease in blood flow.

DISCUSSION

Background.

Among the general anaesthetic drugs, only thiopentone (Pierce et al., 1962) and ether (Schmidt and Hendrix, 1937) have been carefully investigated with regard to their effects on cerebral haemodynamics. Thiopentone has been shown to be associated with cerebral vasoconstriction while vasodilatation occurs with ether. There seem to have been no measurements made of the cerebral vascular effects of halothane. In the absence of direct measurements there has been a tendency to assume that halothane is a cerebral vasodilator (Wylie and Churchill-Davidson, 1960). Clinically, however, anaesthetists and surgeons have noted the good operating conditions produced by halothane in neurosurgery and have ascribed these to reduced brain size and lower brain tension.

In this study we have found a reduction in the cerebral blood flow of approximately 46 per cent, an increase in cerebrovascular resistance of 50 per cent and a decrease in cerebral oxygen uptake ($CMRO_2$) of 49 per cent, all these results being statistically significant.

Technique.

It has been demonstrated that the krypton 85 clearance method reflects faithfully the marked changes which occur in arterial blood flow with alterations in arterial carbon dioxide tension (Ingvar and Lassen, 1962; Harper, Glass and Glover, 1961). In our experiments the fall in blood flow under halothane anaesthesia was of the same order as that which accompanies prolonged hyperventilation. However, halothane anaesthesia causes reduction in two other variables which might influence the cerebral blood flow, namely blood pressure and cardiac output. In discussing the possible influence of these variables on our results, constant reference will be made to the importance we attach to the demonstration of the raised cerebrovascular resistance under halothane anaesthesia. The cerebrovascular resistance is defined as the ratio of the cerebral blood pressure gradient (arterial minus venous blood pressure) to the blood flow. In these experiments we have ignored the venous pressure as its value, compared with the arterial pressure, is extremely low. With a constant arterial blood pressure and an increase in cerebral blood flow, the cerebrovascular resistance will fall, indicating vasodilatation of the cerebral blood vessels. Similarly with a constant blood pressure, but a decrease in blood flow, the cerebrovascular resistance will rise, indicating vasoconstriction. Again if both blood pressure and blood flow decrease, but the latter proportionately more than the former, the cerebrovascular resistance will again rise indicating vasoconstriction. The cerebrovascular resistance can only be expressed quantitatively in mm Hg if the pressure in the artery immediately proximal to the organ or tissue where flow is being measured is known. Our blood pressure measurements were

made in the aorta but we have shown that this pressure is identical with that in the carotid artery and are sure that it bears a constant relationship to that in the artery supplying the area of cortex under view.

Hypotension.

Halothane causes a fall in arterial pressure and the dog seems to be at least as sensitive to this action of the drug as man. The average mean blood pressure in these dogs dropped from 173 to 141 mm Hg on changing from nitrous oxide to halothane, an average drop of about 18 per cent. Could this degree of blood pressure reduction account for any part of the lowered flow demonstrated?

Stone, MacKrell and Wechsler (1955) showed that during controlled hypotension with hexamethonium bromide producing an average reduction of 44 per cent in mean arterial pressure (i.e. more than twice the average reduction in blood pressure on these dogs), the cerebral blood flow remained at prehypotensive levels, due to compensatory cerebral vasodilatation. Similarly, Crumpton and Murphy (1952) found no decrease in cerebral flow with hypotension, which they ascribed to a compensatory reduction in cerebrovascular resistance. In dogs, using the technique described in this paper, Harper and Bell (1963) found that the mean arterial blood pressure could be lowered from 150 to 90 mm Hg without causing any reduction in cortical blood flow. The lowest mean pressure during any flow measurement in this series was 110 mm Hg. The results of Morris et al. (1953) are at variance with the above, for they found a decrease in cerebral blood flow of 30 per cent following a reduction in mean arterial pressure of 39 per cent. What all these authors do agree on, however, is that there is a decrease in cerebrovascular resistance with hypotension, which either completely or partially maintains normal cerebral blood flow. Indeed Lassen (1959) states: "Within a wide pressure range, the cerebral blood flow is independent of changes of the arterial blood pressure". In the results presented here, halothane caused a much smaller blood-pressure drop, i.e. 18 per cent, a much greater drop in cerebral blood flow (46 per cent) and a large rise in cerebrovascular resistance (50 per cent). We can, therefore, assume that this degree of hypotension contributed little, if anything, to the reduced cerebral flow found.

It is interesting that in the dog subjected to deep halothane anaesthesia there was, at an inspired concentration of 3 per cent, a reduction in cerebrovascular resistance of approximately 30 per cent compared with the level at 2 per cent and this was associated with a marked drop in blood pressure. This suggests that although cerebral blood flow is lowered by halothane, the ability to maintain this reduced flow in the face of serious hypotension is preserved.

Cardiac output.

The reduction in cardiac output, which may occur during halothane anaesthesia (McGregor et al., 1958; Severinghaus and Cullen, 1958; Wyant et al., 1958), must be considered in evaluating these results. Stirling et al. (1960) have shown that all concentrations of halothane impair right ventricular function but that the impairment is not severe below an inspired concentration of 1.5 per cent. McGregor et al. (1958) found a reduction in cardiac output of 16.4 per cent at an inspired concentration of 1 per cent, while Severinghaus and Cullen (1958) found a reduction of 31 per cent using positive pressure ventilation but with an inspired concentration of 1.5 per cent. It therefore seems improbable that the reduction in cardiac output produced by the concentration of halothane used (0.5 per cent or less) could account for the observed reduction in cerebral flow.

Possible Mechanisms of the Cerebral Vasoconstrictive Effect of Halothane Anaesthesia

The effects of carbon dioxide.

A lowering of the arterial carbon dioxide tension is well known to produce vasoconstriction of the cerebral blood vessels (Kety and Schmidt, 1946); indeed hypocapnia is usually considered to be the most potent constrictor of the cerebral vascular tree known and yet a similar degree of constriction was repeatedly produced in these dogs by light halothane anaesthesia, in the presence of a carefully controlled normal Pco_2. When hyperventilation was added to the halothane anaesthesia, a lowering of the arterial Pco_2 to a level of 22 mm Hg did not produce further constriction. We were able to show that in order to reverse the vasoconstrictive action of halothane it was necessary to raise the Pco_2 to a level between 50 and 80 mm Hg.

The effects of oxygen.

A high arterial Po_2 causes cerebral vasoconstriction leading to a reduction in cerebral blood flow of about 12–15 per cent (Sokoloff, 1959). In our results there was no difference between the flow during halothane-oxygen as compared with halothane-air anaesthesia, possibly because halothane has produced near maximal constriction.

It might be suggested that our flow comparisons with nitrous oxide anaesthesia were fallacious because of hypoxic cerebral vasodilatation during anaesthesia with this agent. However, measurements of arterial saturation during each flow measurement ruled out this possibility.

Direct action on the vessel wall.

Halothane might produce constriction of cerebral arteries and arterioles by a direct action on the vessel wall. Burn and Epstein (1959), demonstrated by cross-perfusion experiments that the direct action of halothane on the arteries of the dog's hind limb is vasodilatation. However, it is probably a mistake to extend observations made on other parts of the vascular tree to the cerebral circulation, which is unique in many of its physiological and pharmacological responses (Sokoloff, 1959). Wyant and colleagues (1958) showed an increase in pulmonary vascular resistance during halothane anaesthesia, a part of which was ascribed to active pulmonary vasoconstriction, so that the cerebral circulation would not be quite unique if it responded in this way.

Autonomic vascular control.

Halothane might produce vasoconstriction by sympathetic stimulation, by sensitization of the vessel walls to tonic sympathetic impulses, by increasing the level of circulating catechol amines or increasing the vessel sensitivity to these amines or by inhibition of parasympathetic vasodilatory impulses.

Sympathetic stimulation could not account for the large decrease in cerebral blood flow found, for it is widely agreed that sympathetic vasoconstriction of cerebral vessels is weak (Sokoloff, 1959). Blockade of the stellate ganglia in man produces no increase in cerebral flow (Harmel et al., 1949), so that potentiation of tonic sympathetic impulses by halothane is improbable.

Measurements of catechol amines during halothane anaesthesia indicate no increase in their concentrations in the blood (Price et al., 1959; Hamelberg et al., 1960; Black and McArdle, 1962).

Vasodilator fibres supplying the cerebral vasculature have been demonstrated to travel in the facial nerve and then in the greater superficial petrosal nerve to reach the internal carotid plexus (Chorobski and Penfield, 1932). The effects of halothane on the parasympathetic ganglia are in dispute; on one hand it is argued that the observed bradycardia signifies lack of block (Stephen et al., 1958), while on the other, the depression of salivation is considered as evidence of such blockade. In any case, Sokoloff feels that there is no convincing evidence of significant resting vasodilatory tone, so that halothane blockade, if it occurred, would have little effect.

Lowered tissue Pco_2.

In face of these unlikely alternative explanations, we consider that the decrease in cerebral blood flow is due to the reduction in the cerebral metabolic consumption of oxygen which Pierce et al. (1962) found with thiopentone, and we have found with halothane. This leads to a decrease in carbon dioxide production by the cells so tending to lower the cerebral intracellular Pco_2, and this causes vasoconstriction of the vessels supplying these cells, either by a local axon reflex or by a direct action of the lowered Pco_2 on the vessel walls.

Far from disproving this hypothesis, the demonstration by Pierce and his colleagues of an unchanged jugular venous Pco_2 surely argues strongly for the efficiency of this homeostatic mechanism. The adjustment of flow to metabolic demand in this way is, of course, merely an extension of the method of local control of cerebral blood flow which operates under normal physiological conditions.

The observations, admittedly only in one dog, that the reduction in blood flow and oxygen consumption did not increase with deepening anaesthesia are intriguing. Firstly, this lends further support to the suggestion that the cerebral flow reduction observed in light halothane anaesthesia is not dependent on hypotension or lowered cardiac output, for, if it were, the flow reduction would have been progressive with deepening anaesthesia. Secondly, the compensatory responses to serious hypotension are not blocked by halothane.

Cerebral oxygen uptake.

The evaluation of the effects of halothane on cerebral metabolic requirements for oxygen is, of course, of great significance in the presence of the 46 per cent reduction in blood supply. We have found that oxygen requirements are reduced pari passu with the reduction in blood flow. The decrease in cerebral oxygen uptake is of the same order as that observed under thiopentone anaesthesia (Pierce et al., 1962). In no case was significant venous desaturation observed, so that tissue Po_2 was presumably within normal limits. These results, i.e. 46 per cent reduction in flow and a 49 per cent reduction in oxygen uptake, give added support to the mechanism suggested for the vasoconstriction found.

CONCLUDING REMARKS

In view of this evidence and that quoted for thiopentone, and remembering the normal mechanism for cerebral blood flow control we feel that it is possible that all potent general anaesthetic agents, intravenous and inhalational, will prove to be constrictors of the cerebral vasculature and that this action will be shown to be secondary to the reduction in cerebral oxygen consumption which these agents probably produce. The only possible exceptions to this hypothesis will, we think, be agents like ether with a pronounced local dilatating effect.

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CIRCULATION SANGUINE CÉRÉBRALE PENDANT L'ANESTHÉSIE AU HALOTHANE

SOMMAIRE

La circulation sanguine cérébrale a été mesurée par les auteurs sur le chien selon la méthode de Lassen et Ingvar (1961) et d'Ingvar et Lassen (1962) utilisant la mesure de la rapidité d'élimination de 85 krypton d'une région du cortex cérébral dégagée après injection du Kr dans l'artère carotide interne. Chaque mesure prise pendant l'anesthésie à l'halothane montra une réduction considérable de la circulation sanguine du cerveau comparativement à celle maintenue par l'oxyde nitreux et par l'oxygène: La réduction moyenne était de 46%, s'accompagnant d'une augmentation de 50% de la résistance cérébro-vasculaire. Les auteurs ont mesuré également l'absorption de l'oxygène ($CMRO_2$) et ils ont alors constaté que l'halothane diminua ce dernier également de 49%. Ils discutent le mécanisme possible des résultats observés.

DIE ZEREBRALE BLUTZIRKULATION WÄHREND DER HALOTHAN-NARKOSE

ZUSAMMENFASSUNG

Die zerebrale Blutzirkulation wurde bei Hunden nach der Methode von Lassen und Ingvar (1961), Ingvar und Lassen (1962). wobei die Clearance-Rate von Krypton 85 von einem freigelegten Bezirk der Gehirnrinde nach Injektion in die Arteria carotis interna bestimmt wird, gemessen. Bei jeder Messung während einer Halothan-Narkose fand sich eine beträchtliche Abnahme der Blutzirkulation im Gehirn im Vergleich mit den Werten bei Lachgas und Sauerstoff. Die durchschnittliche Abnahme der Zirkulation betrug 46%, und diese wurde von einer durchschnittlichen Steigerung im zerebro-vaskulären Widerstand um 50% begleitet. Es wurden ebenfalls Messungen der Sauerstoffaufnahme des Gehirns ($CMRO_2$) vorgenommen, Halothan rief eine durchschittliche Abnahme der Sauerstoffaufnahme um 49% hervor. Die möglichen Mechanismen für die beobachteten Untersuchungsergebnisse werden besprochen.