C E R E B R A L B L O O D F L O W

AN EXPERIMENTAL AND CLINICAL STUDY OF THE BLOOD FLOW THROUGH THE CEREBRAL CORTEX.

by

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INTRODUCTION

> For, as the ſubſtance of the brain, like that of the other ſolids of our body, is nearly incompreſſible, the quantity of blood within the head muſt be the ſame, or very nearly the ſame, at all times, whether in health or diſeaſe, in life or after death, thoſe caſes only excepted, in which water or other matter is effuſed or ſecreted from the blood-veſſels; for in theſe, a quantity of blood, equal in bulk to the effuſed matter, will be preſſed out of the cranium.

wrote Alexander Monro in 1783. This postulate, subsequently reaffirmed by Kellie (1824) and thereafter known as the Monro-Kellie doctrine, became widely accepted. However, it seems that too literal an interpretation of Monro's statement may have delayed subsequent study of the cerebral circulation as it led to the generally held assumption that the cerebral blood vessels are passive and incapable of any change in calibre. The feelings of the fairly recent past are summed up in an extensive survey of the physiology and pathology of the cerebral circulation by Leonard Hill (1896) who stated ".... the whole circulatory system of the brain will have assimilated itself into a scheme of rigid tubes" (page 68) and "In every experimental conditio

the cerebral circulation passively follows the change in the general arterial and venous pressures" (page 76). Hill's reasoning was founded on measurements of cerebral arterial and venous pressures and cerebro-spinal fluid pressure in the experimental animal - a technique totall unsuited to yield information on blood flow - and it is perhaps unfortunate that he dismissed the earlier observations of Donders (1850) and Roy and Sherrington (1890). The former worker observed that the blood vessels of the pia mater were capable of change in size (they were observed to dilate during asphyxia) but Hill brushed aside this important observation with the curiou argument that "if the capillaries are expanded the veins may be proportionately compressed" and that there was nc alteration in blood flow.

Roy and Sherrington (1890), although using a technique for measuring changes in the vertical diameter in the brain which admittedly was open to serious criticism, were the first to suggest that ".... the chemical products of cerebral metabolism contained in the lymph which bathes the walls of the arterioles of the brain can cause variations of the calibre of the cerebral vessels: that in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with

local variations of functional activity." (Roy and Sherrington, 1890).

However, this study did not find general acceptance, and Hill's conclusion that the cerebral blood flow was solely dependent on the arterial and venous blood pressures was generally accepted for many years.

In 1928 Forbes refined the technique used earlier by Donders (1850) for observing changes in the diameter of the pial blood vessels and began to question the validity of Hill's conclusions. During the 1930's many papers by such workers as Forbes & Wolff in the United States and Fog in Copenhagen, pointed out that the cerebral blood vessels were capable of change in calibre under certain experimental conditions - for instance alteration in the blood content of carbon dioxide and oxygen.

However, there were still no reliable quantitative estimates of cerebral blood flow. Although studies with heated thermocouples (Schmidt 1936) and flowmeters in the carotid artery (Dumke and Schmidt, 1943) suggested that there was an "intrinsic" control of the cerebral blood flow, the results were inconsistent and often conflicting.

It was not until 1945 that Kety & Schmidt described a method, brilliant in its simplicity, for the indirect measurement of cerebral blood flow. This technique, based on the Fick principle, paved the way for a wide variety of studies of the cerebral blood flow in man under physiological conditions and in disease, and the importance of the blood gases in the regulation of the cerebral circulation was finally established (Kety and Schmidt, 1948).

However, Kety and Schmidt's method had the serious disadvantage that it permitted the estimation of only average intracranial blood flow over ten to fifteen minutes and was not suitable for detecting rapid changes in blood flow; nor could measurements be repeated frequently in any one subject.

In 1960 I was searching for a method which would permit rapid and easily repeatable measurements of cerebral blood flow in the experimental animal in order to study the changes in blood flow which might take place in certain experimental conditions - particularly in haemorrhagic shock, during heart-lung bypass and in other conditions which might have a subsequent application in clinical surgery. During a visit to the laboratory of Neils Lassen in Copenhagen,

it was demonstrated to me that Kety's method could be adapted to give values for blood flow through local areas of the brain in the experimental animal; the only physical measurement necessary being the recording of the rate of clearance from the exposed brain cortex of an inert radioactive gas following its injection into the arterial blood supply to the brain.

As this method appeared promising for use in the experimental laboratory, it was tested and perfected in a series of experiments in dogs. As the animal experiments appeared to be successful, and to give accurate and reproducible results, it was decided, with the collaboration of a physicist colleague, Mr. H.I. Glass, to adapt the technique devised by Lassen to the measurement of blood flow through the cerebral cortex in man.

The study undertaken and here presented had, therefore, three main objects:

1) To assess the value and test the validity of the inert gas clearance method described by Lassen and Ingvar (1961) for the measurement of blood flow through the cerebral cortex in the experimental animal and to produce a physiologically stable preparation for

subsequent studies of blood flow under varying experimental conditions.

2) To study some of the factors which influence cerebral blood flow and, in particular, to determine the effect of changes in the arterial carbon dioxide tension and in the systemic blood pressure on the blood flow through the cerebral cortex. Also to determine the inter-relationship between the arterial carbon dioxide tension and blood pressure in the control of blood flow through the cerebral cortex.

3) To apply the inert gas clearance method to the study of blood flow through the cerebral cortex in man and to determine whether the method is sufficiently sensitive to detect, on altering certain conditions in physiological environment, changes in blood flow which might have been expected on the basis of the animal experiments.

PART 1.

DETERMINATION OF BLOOD FLOW THROUGH THE CEREBRAL CORTEX BY MEASUREMENT OF THE CLEARANCE OF KRYPTON 85.

THEORY & PROCEDURE.

NORMAL VALUES IN THE DOG.

EVOLUTION OF THE INERT GAS CLEARANCE METHOD FROM THE FICK PRINCIPLE

The well-known Fick principle states that the quantity of a substance taken up by an organ in a specific time is equal to the product of the blood flow and the arterio-venous difference for that substance. Alternatively, this can be expressed as

$$\text{Flow in time } t = \frac{Q_t}{Ca-Cv}$$

where Q_t = quantity of substance taken up in time t.

Ca = concentration of substance in arterial blood.

Cv = concentration of substance in venous blood drawing the oxygen.

Kety realised that the Fick principle could be applied to the study of cerebral blood flow. In his own words, "Unfortunately, the brain, unlike the kidney, does not specifically and selectively remove foreign substances from the blood and excrete them for accurate measuremen Furthermore, although it does consume large quantities oxygen, that consumption cannot independently be measur

or even assumed to be constant since it would be expected to vary with activity and disease. The brain does, however, absorb by physical solution an inert gas such as nitrous oxide, which reaches it by way of the arterial blood. It was hoped that the quantity of this gas absorbed by the brain would be independent of the state of mental activity and susceptible of measurement on the basis of physical solubility alone. If this were found to be the case, then the numerator of a Fick equation applied to the brain could be derived." (Kety 1965).

Kety and Schmidt published the first account of their method in 1945. Briefly, their subjects inhaled a low concentration of nitrous oxide over a period of ten minutes. During the period of inhalation a series of samples of blood were taken from an artery and from the internal jugular vein and analysed for nitrous oxide content. At the end of ten minutes, the arterial blood, brain tissue and cerebral venous blood were approximately in equilibrium for nitrous oxide and contained approximately equal concentrations of the gas. The numerator of the Fick equation then became Cvt or the cerebral venous concentration of nitrous oxide at time t (in this case 10 minutes). As the arterio-venous

difference for nitrous oxide was continuously changing, the denominator of the Fick equation became the sum of all the arterio-venous differences over the period of inhalation.

If one reverts to the original Fick equation:

$$\text{Flow} = \frac{Q_t}{Ca-Cv}$$

but $Q_t = W \times C_B$

where W = weight of brain

and C_B = concentration of nitrous oxide in brain

$\therefore \quad Q_t = W \times Cvt \quad (\text{as } C_B \simeq Cv \text{ at time } t)$

$$\text{and } Ca-Cv = \int_0^t (Ca-Cv)\, dt$$

$$\therefore \quad \text{Flow} = \frac{WCvt}{\int_0^t (Ca-Cv)\, dt}$$

$$\text{or Flow per unit weight} = \frac{Cvt}{\int_0^t (Ca-Cv)\, dt}$$

Therefore, in order to calculate blood flow through the brain, one has to measure the arterial and cerebral venou concentrations of nitrous oxide at intervals during a 10-minute period of inhalation and to assume that, at the end of 10 minutes, the brain tissue and the cerebral venous blood are in equilibrium for the gas.

This method has proved successful over many years for measuring average cerebral blood flow over the 10-minute period of inhalation. The substitution of the inert radioactive gas Krypton 85 as a tracer in place of nitrous oxide (Lassen and Munck, 1955) simplified the analysis of the gas content of the blood samples but the method remained essentially unchanged.

However, in 1955 Lewis and his associates adapted the technique to allow continuous measurements of cerebral blood flow by substituting the gamma-ray-emitting inert gas Krypton 79. If the subject inhaled Krypton 79 and the amount of radioactivity in the brain was measured with external detectors, the numerator of the Fick equation (Qt) could be derived at any one instant, the denominator being calculated in the usual fashion from the arterio-venous difference for the gas at that instant. However, this method proved to be technically very difficult and the results were influenced by contamination of the extracerebral tissues with the isotope.

A further modification of the Fick principle was reported by Kety and his co-workers (1955) to permit estimations of blood flow through local areas of the brain in the experimental animal. In this instance

I^{131} - tagged trifluoroiodomethane was injected intra-arterially as an indicator and the numerator of the Fick equation (Qt) derived from the content of radio-activity in brain slices which were obtained after decapitating the animal and freezing the brain in liquid nitrogen. Obviously, however, only one value for each area of the brain could be obtained in any one animal and the method was therefore severely limited in its applications.

In 1961 Lassen and Ingvar substituted, for the unacceptably traumatic technique of tissue sampling, the recording of the beta emissions of the inert gas Krypton 85 from the exposed brain cortex; the isotope being administered by injection into the carotid artery. With this method blood flow through the cerebral cortex can be calculated in quantitative terms, the only measurement necessary being the rate at which Krypton 85 is "cleared" from the cerebral cortex after its injection.

A full description of the theory and procedure of this inert gas clearance method for the measurement of cortical blood flow is given in the succeeding pages.

THEORY OF THE KRYPTON 85 CLEARANCE METHOD

Krypton 85 is an inert radioactive gas with a half life of approximately 11 years. The predominant decay (99.6%) is beta emission with peak energy of 0.67 MeV. Two important physical properties must be mentioned:

(1) The solubility of Krypton 85 in air is some twenty times greater than for blood or tissue (Lawrence, Loomis, Tobias & Turpin (1946). This means that if it enters into physical solution with the venous blood a high proportion of it will, on reaching the pulmonary capillaries, escape into the alveolar air and be excreted by the lungs (Chidsey, Fritts, Hardewig, Richards & Cournand, 1959).

(2) As Krypton 85 is an inert gas, its entry into tissue will depend solely on diffusion and solubility, and following its introduction into the arterial blood supply of an organ, it will diffuse very rapidly across the capillary walls and reach equilibrium betweer

blood and tissue. It has been shown that in a typical case 95% equilibrium should be reached within one second (Kety 1951).

Fig. 1 (page 14) illustrates how these properties of Krypton 85 can be used to measure blood flow through tissue. The left side of the diagram illustrates Krypton (dissolved in saline) being injected into the arterial blood supply to an organ. On reaching the capillaries, the gas will diffuse very rapidly between the blood and tissue. Krypton carried away in the venous blood will be excreted in the lungs.

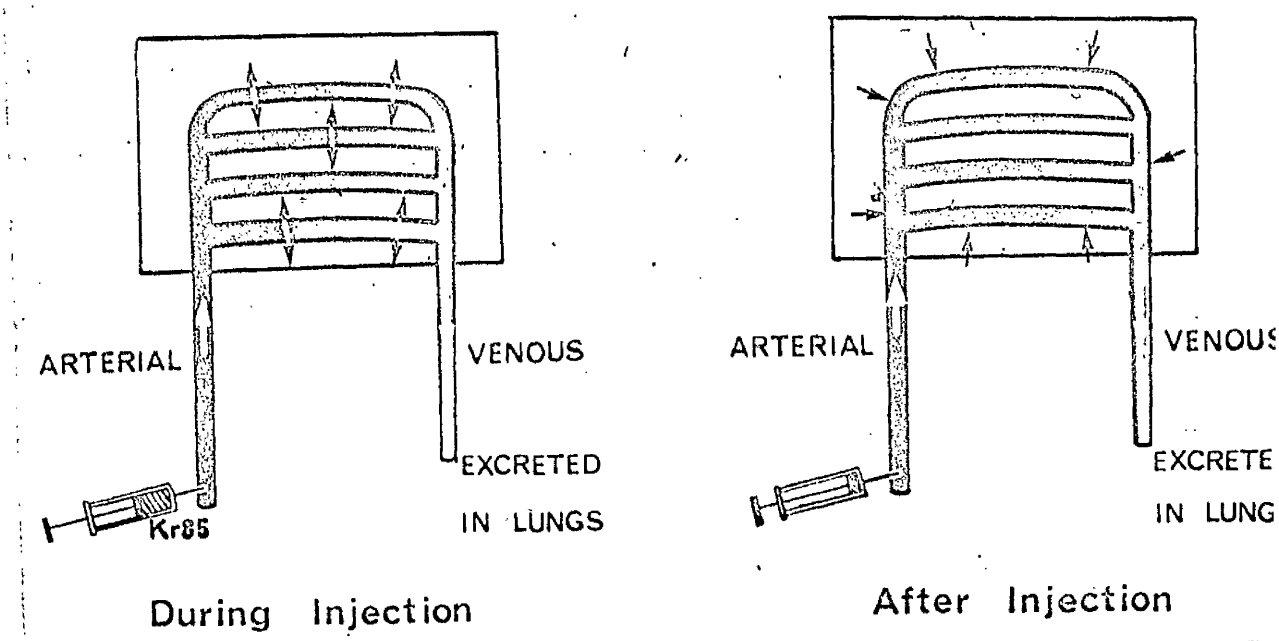

Fig.1 - See text.

On the right side of Fig.1 the injection has been completed. As the concentration of Krypton in the arterial blood is now negligible, the gas will diffuse back from the tissue into the capillary and hence the venous blood. The rate at which the isotope disappears from the tissue will then depend on the blood flow. The more rapid the blood flow the more rapidly will the Krypton be cleared from the tissue and vice versa.

The rate of clearance of Krypton 85 from the cerebral cortex can be calculated by measuring the beta radiation over the cerebral cortex with a Geiger-Müller tube. As the beta rays of Krypton 85 have a maximum range in tissue of 2.6 mm and an average range of 0.7 mm (Glass, Harper & Glover, 1961), such a procedure should allow the calculation of average blood flow through approximately the first millimetre in thickness of the cerebral cortex.

The mathematical analysis necessary to define blood flow in quantitative terms is presented.

Mathematical Proof of Clearance Method.

The following is an expanded version of the proof presented by Glass, Harper and Glover (1961) and derived from the work of Lassen and Ingvar (1961) and Ingvar and Lassen (1962).

Assuming a single homogeneous tissue, the Fick principle states that the quantity of Krypton lost by the tissue is equal to the quantity carried to it by arterial blood less the quantity removed by venous blood (there is no loss by metabolism). After injectio has ceased, the arterial blood will contain no Krypton and the Fick equation can be written:

$$dQi = -Fi\ Cv\ dt \quad \ldots\ldots\ldots\ldots (1)$$

where dQi = change in quantity of krypton in the tissue.

dt = time in which this change occurs.

Fi = blood flow in ml/min.

Cv = venous concentration of inert gas per ml. of blood.

But $Qi = Ci\ Wi$

where Wi = weight of tissue in gms.

and Ci = tissue concentration of krypton per gm. of tissue.

$$\therefore \frac{dCi}{dt} = \frac{-Fi}{Wi}\ Cv \quad \ldots\ldots\ldots\ldots (2)$$

Let λi be the tissue - blood partition coefficient for krypton at body temperature (i.e. the ratio of the solubility of krypton in brain and blood). If we assume that the partial pressure of krypton in the

venous blood is the same as in the tissues, then

$$Cv = \frac{Ci}{\lambda i}$$

and equation (2) becomes $$\frac{dCi}{dt} = \frac{-Fi}{Wi} \frac{Ci}{\lambda} \quad \ldots\ldots\ldots\ldots\ldots (3)$$

The solution of this differential equation is:

$$Ci = Coi\ e^{-kit} \quad \ldots\ldots\ldots\ldots\ldots (4)$$

where Coi = initial concentration of krypton in the tissue

and $$ki = \frac{Fi}{Wi}\ \lambda i$$

This is a simple mono-exponential curve and when the concentration is plotted against time on a semi-logarithmic paper, the result is a straight line. The time for the concentration to reach one half of its initial value ($T\frac{1}{2}$ minutes) is expressed as $\log_e 2\ \frac{Wi\ \lambda i}{Fi}$.

Thus, in these circumstances, the flow is determined by $$\frac{Fi}{Wi} = \frac{\log_e 2\ \lambda i}{T\frac{1}{2}} = \frac{0.693\ \lambda i}{T\frac{1}{2}}$$

i.e. flow (ml/gm/minute) = $\frac{0.693\ \lambda i}{T\frac{1}{2}}$

When more than one type of tissue is viewed by the detector the situation is slightly more complex.

Let W_1, W_2, ----- Wi be the weights of the different types of tissue seen with equal efficiency by the detector.

Then Total Weight (W) of all of these tissues is given by -

$$W = W_1 + W_2 + W_3 \text{ ------ } W_n = \sum Wi$$

The total quantity (Q) of Krypton present is given by -

$$Q = C_1W_1 + C_2W_2 + \text{------} C_nW_n = \sum CiWi$$

Then the mean concentration in the tissues (C) is given by -

$$C = \frac{Q}{W}$$

$$\text{i.e. } C = \frac{\Sigma CiWi}{W}$$

If we assume that, initially, the arterial concentration of Krypton is zero and that the partial pressure of Krypton in each type of tissue is the same as in the venous blood draining from it, then the clearance is given by -

$$C = \Sigma Coi \frac{Wi}{W} e^{-kit} \quad \text{..... (5)}$$

where, as before, $ki = \frac{Fi}{\lambda i\ Wi}$

If we assume that (a) the initial concentration (Coi) in each tissue is the same and that (b) the partition coefficient (λi) is the same for each tissue then -

$$C = \frac{Coi}{W} \sum e^{-kit} \qquad \text{..... (6)}$$

$$\text{where } ki = \frac{Fi}{\lambda Wi}$$

Clearly the average rate of flow will be determined by the rate of decrease of average concentration when the concentration in all the tissues is the same, and clearly this information can be obtained only from the early part of the clearance curve.

If the clearance is plotted as before on semi-logarithmic paper the curve will not generally be a straight line but the slope will decrease as time goes on. This is because the Krypton will be very quickly cleared from rapidly perfused tissues and only the more slowly perfused tissues will retain radioactivity. Therefore the "tail end" of the curve will reflect only blood flow in slowly perfused tissues. To calculate mean flow one must concentrate on the early part of the clearance curve.

In practice the procedure is to plot the clearance curve on semi-logarithmic paper and to draw a tangent to the early part of the curve. The time for this straight line to reach half of its initial value ($T\frac{1}{2}$ mins.) allows the mean flow to be calculated as before:

$$\text{flow (ml/gm/min.)} = \frac{\lambda \log_e 2}{T_{\frac{1}{2}} \text{ (initial slope)}}$$

where $T_{\frac{1}{2}}$ is expressed in minutes.

Before discussing the validity of the assumptions made in this proof, the experimental procedure used in determining cortical blood flow in dogs will be described.

EXPERIMENTAL PREPARATION AND PROCEDURE.

All the animal experiments described in this thesis were performed on the same standard type of experimental preparation, and used the same basic procedure for measuring cortical blood flow. This will be described before giving an account of experiments designed to test the validity of the Krypton 85 clearance method.

Material.

The experiments were carried out on mongrel dogs ranging in weight from 10 to 30 Kg. They were unselected with the exception that obviously aged or ailing animals were excluded.

Anaesthesia.

Anaesthesia was induced with thiopentone (20 mg/Kg body weight) administered intravenously. A cuffed tube was inserted into the trachea and connected to the outflow of a Starling respiratory pump. A Boyle's anaesthetic machine was connected to the inflow of the pump and a 4:1 mixture of nitrous oxide and oxygen delivered to the

animal. During the operative surgery supplementary doses of thiopentone (5 mg/Kg) were given when necessary. Following completion of surgery, a muscle relaxant, succinylcholine chloride (5 mg), was administered. Repeated doses of 1 to 2 mg were given every 20 minutes throughout the rest of the experiment, anaesthesia being maintained with nitrous oxide.

Cannulation of Vessels.

A femoral vein and femoral artery were exposed in the groin. A polythene catheter was introduced into the femoral vein and advanced until its tip lay in the inferior vena cava. This catheter was used for the administration of succinylcholine chloride. A polythene catheter was introduced into the femoral artery and advanced until its tip lay in the iliac artery. The distal end of the catheter was connected via a three-way tap to a mercury manometer for the measurement of arterial blood pressure. Arterial blood samples were withdrawn at intervals through the tap for the measurement of blood pH and blood tensions of oxygen and carbon dioxide.

The right common carotid artery was exposed in the neck and the superior thyroid branch isolated. The

superior thyroid artery was ligated distally and a fine polythene catheter introduced into its lumen. The catheter was advanced until its tip lay at the junction of the thyroid artery with the common carotid artery. This catheter was used for the injection of Krypton 85 into the carotid artery.

Exposure of the cerebral cortex.

With diathermy a cruciate incision was made over the scalp and the right temporal muscle excised to the extent shown in Fig.2 (page 24). A trephine hole 2.3 cm in diameter was made in the parietal bone. Any bleeding from the diploic veins was arrested with bone wax.

Any meningeal vessels running over the surface of the exposed dura mater were carefully coagulated with diathermy. A cruciate incision was made in the dura and the cut edges reflected. The area of cortex exposed (about 1 cm in diameter) was covered with a thin transparent polyester film (Melinex, I.C.I.) 0.006 mm in thickness. The purposes of the film were (a) to prevent dessication and cooling of the cerebral cortex, and (b) to prevent diffusion of the molecules of Krypton 85 from the cortex into the atmospheric air while still permittin passage of its beta emissions.

The bone surrounding the trephine hole was covered with a thin lead shield, which can be seen in Fig.2 (page 24). Following completion of the surgery, the preparation was left undisturbed for one hour before commencing measurements of cortical blood flow.

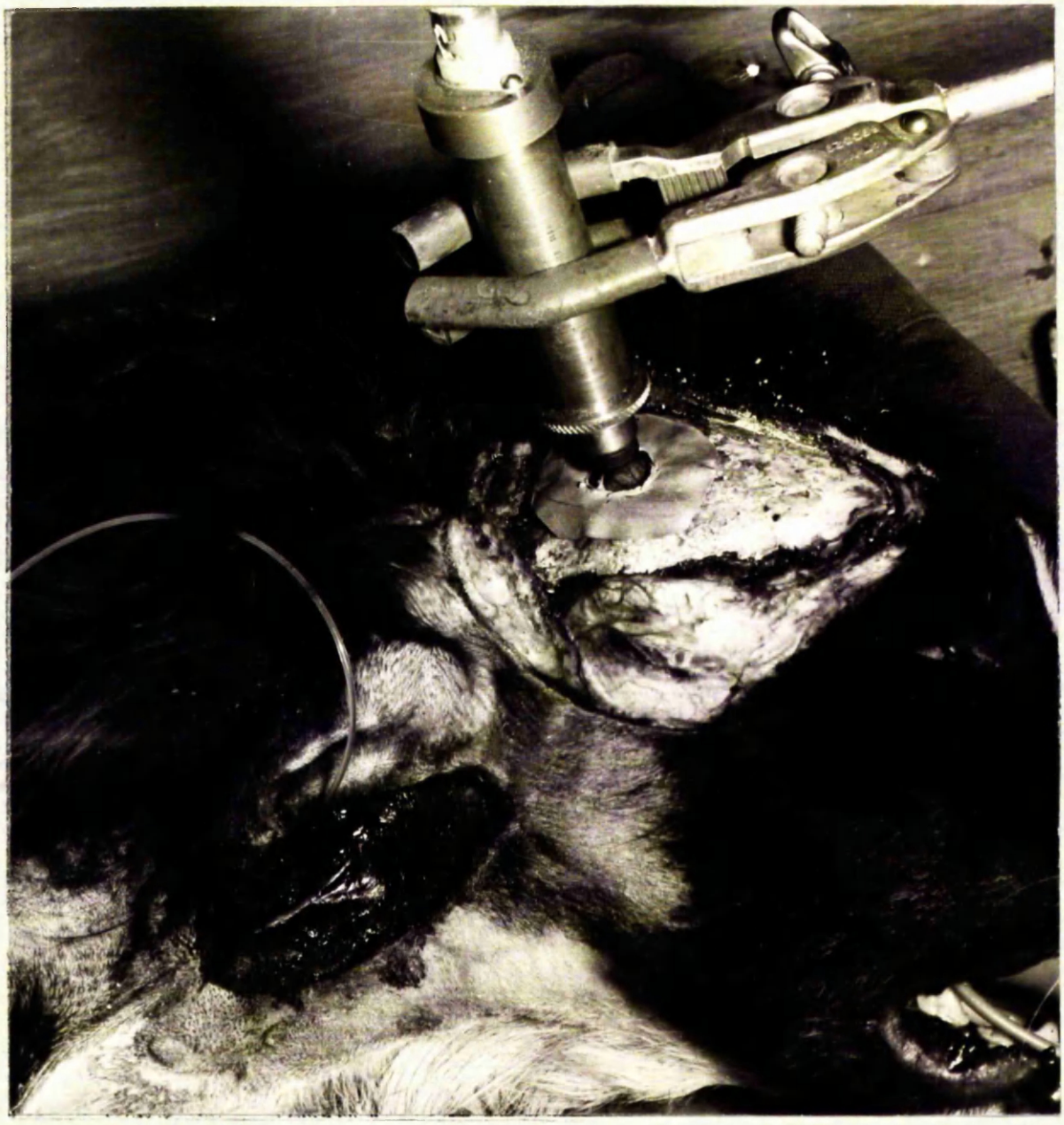

Fig.2 - Preparation used for the measurement of cortical blood flow. The Geiger-Müller tube can be seen mounted above the cortex. On the left a catheter leads into the thyroid branch of the carotid artery.

Maintenance of body temperature.

In each experiment the body temperature (measured by a mercury thermometer placed in the pharynx) was maintained between 37 and 40°C by means of an infra-red heating lamp. If the body temperature fell below 37°C no measurements of blood flow were made until it had been restored to 37°C.

Control of pulmonary ventilation and blood gas content.

At the onset of each experiment the respiratory pump rate was set at 26 per minute and the stroke volume adjusted to give an arterial carbon dioxide tension of between 30 and 40 mm.Hg. The oxygen saturation of the arterial blood was measured at intervals during each experiment on a Kipp haemoreflector. The oxygen saturation of the arterial blood was maintained above 90 per cent at all times. No measurements of cerebral blood flow were made if the oxygen saturation was found to be below 90%.

Following each measurement of cortical blood flow, a 1 ml. sample of arterial blood was removed anaerobically and the pH and PCO_2 measured on an Astrup apparatus (see Appendix).

Measurement of blood pressure.

The catheter in the femoral artery was joined to a mercury manometer for the measurement of arterial blood pressure. The catheter led into the top of a reservoir, 2 inches in diameter, which was filled with saline in the top three-quarters and mercury in the bottom quarter. A U-tube led from the mercury to a scale graduated in millimetres. The reservoir functioned as a "damper" of the systolic-diastolic fluctuations in pressure and allowed the effective mean pressure to be read on the scale. The system could be perfused with saline through a three-way tap placed proximally to the reservoir.

Preparation of Krypton 85.

Krypton 85 was received in sealed glass ampoules (capacity 20 cc) containing 1 curie of radioactivity from the Radioisotope Centre at Amersham. It was dispensed in the following manner:

A brass, lead shielded, container of 1000 cc capacity was evacuated by a vacuum pump to 0.25 mm pressure. The ampoule of Krypton 85 was connected to a side arm of the container and the seal broken by a

rod fixed to the inside of the connecting tube. The Krypton was sucked into the container. Through another side arm Dextran (Plasma substitute) was introduced into the container and filled the rest of the vacuum.

The container was now vigorously shaken to dissolve Krypton in the Dextran. A 20 cc luerlock syringe was fitted to the side arm of the box and the desired quantity of Dextran withdrawn - this being immediately replaced with fresh Dextran.

Measurement of cortical blood flow.

An end window Geiger-Müller tube (Mullard-MX113) with a diameter of 1 cm was mounted above the exposed cerebral cortex. The edge of the window of the GM tube rested on the edge of the centre hole in the lead shield shown in Fig.2 (page 24).

The G.M. tube was connected to a ratemeter (IDL 1750) and a direct writing recorder (Honeywell). The experimental set-up is illustrated diagrammatically in Fig.3 (page 28).

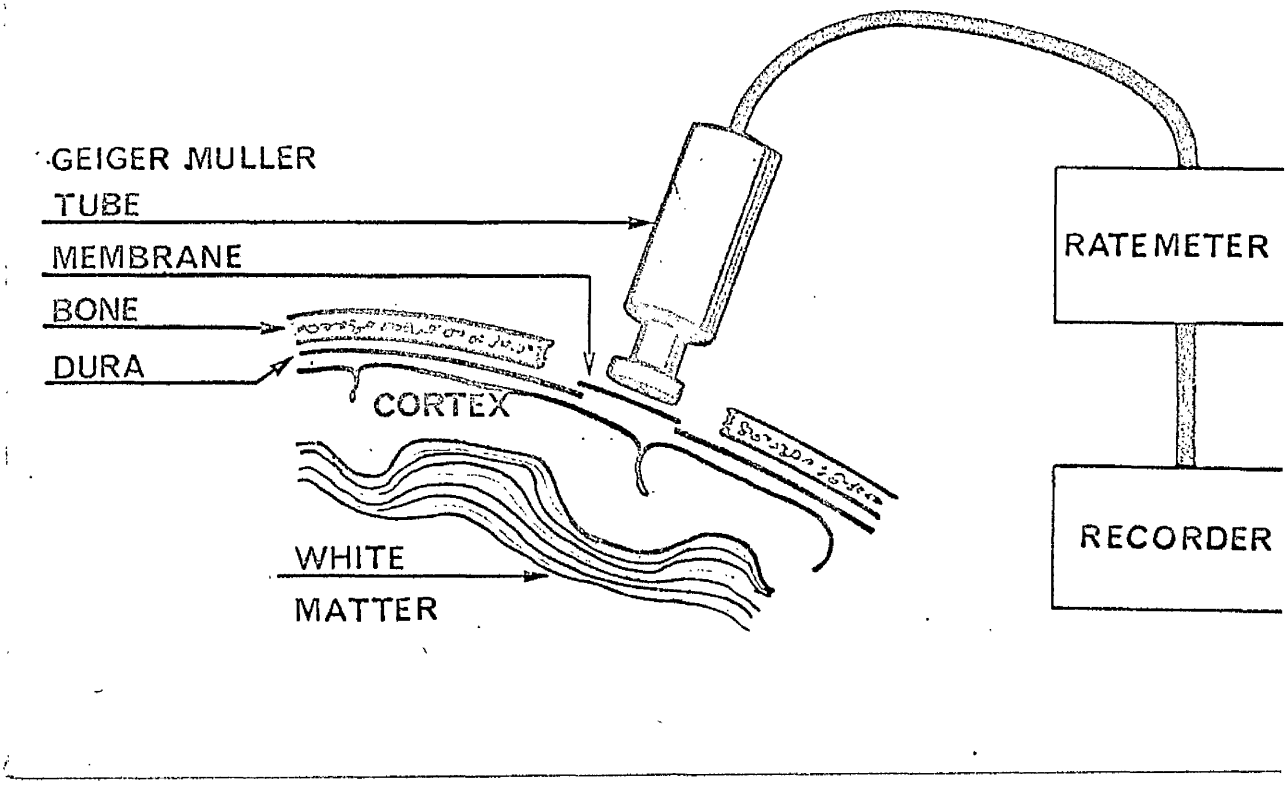

Fig.3 - Diagram of G.M. tube in position above brain cortex.

The time constant of the ratemeter was set at 1 second or 5 seconds (the former used for fast clearance rates).

The range was set at a maximum deflection of either 100 or 300 counts per second.

A syringe containing Krypton 85 dissolved in Dextra plasma substitute was connected to the catheter inserted into the thyroid branch of the common carotid artery.

Krypton 85 was injected fairly rapidly to produce

an initial rise of radioactivity in the cortex to 90% of maximum on the ratemeter range. The injection was then slowed to maintain this level of activity over the next 100 to 150 seconds. When the injection was stopped a clearance curve was recorded. The rate of injection never exceeded 3 ml/minute in large dogs and was less in smaller animals.

Three tracings illustrating the uptake and clearanc of Krypton 85 from the cerebral cortex in one experiment are shown in Figs.4(a), 5(a) and 6(a) - pages 31, 32 and 33. The cortical blood flow was purposely varied either by administering CO_2 or by hyperventilation (see page 64 The tracings (reading from right to left) show the initial rapid rise in radioactivity, the plateau effect obtained as the rate of injection is slowed, and the final clearance of the radioactivity after the injection Fig.4(a) shows the pattern under "normal" conditions. Fig.5(a) shows a more rapid fall off of radioactivity, indicating a more rapid cortical blood flow, and Fig.6(a shows a slower clearance rate, indicating a slower blood flow.

These clearance curves have been plotted on a semi-logarithmic scale on Figs.4(b), 5(b) and 6(b) - pages 31 32 and 33. Zero time has been taken at approximately 5 seconds after the end of the injection of Krypton. A

straight line has been fitted to the initial part of the clearance curve and the time taken for the radioactivity to fall to one half of its initial value ($T\frac{1}{2}$) on this line has been estimated in seconds. Blood flow has then been calculated from the formula -

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

When λ(brain:blood partition coefficient for Krypton 85) is taken as 0.91 (Ingvar & Lassen, 1961: Glass & Harper, 1962) this formula becomes -

$$\text{Flow (ml/gm/min)} = \frac{37.8}{T\frac{1}{2} \text{ (secs)}}$$

[Note - as $T\frac{1}{2}$ is measured in seconds, the factor 60 is introduced into the top line of the equation to give flow per minute.]

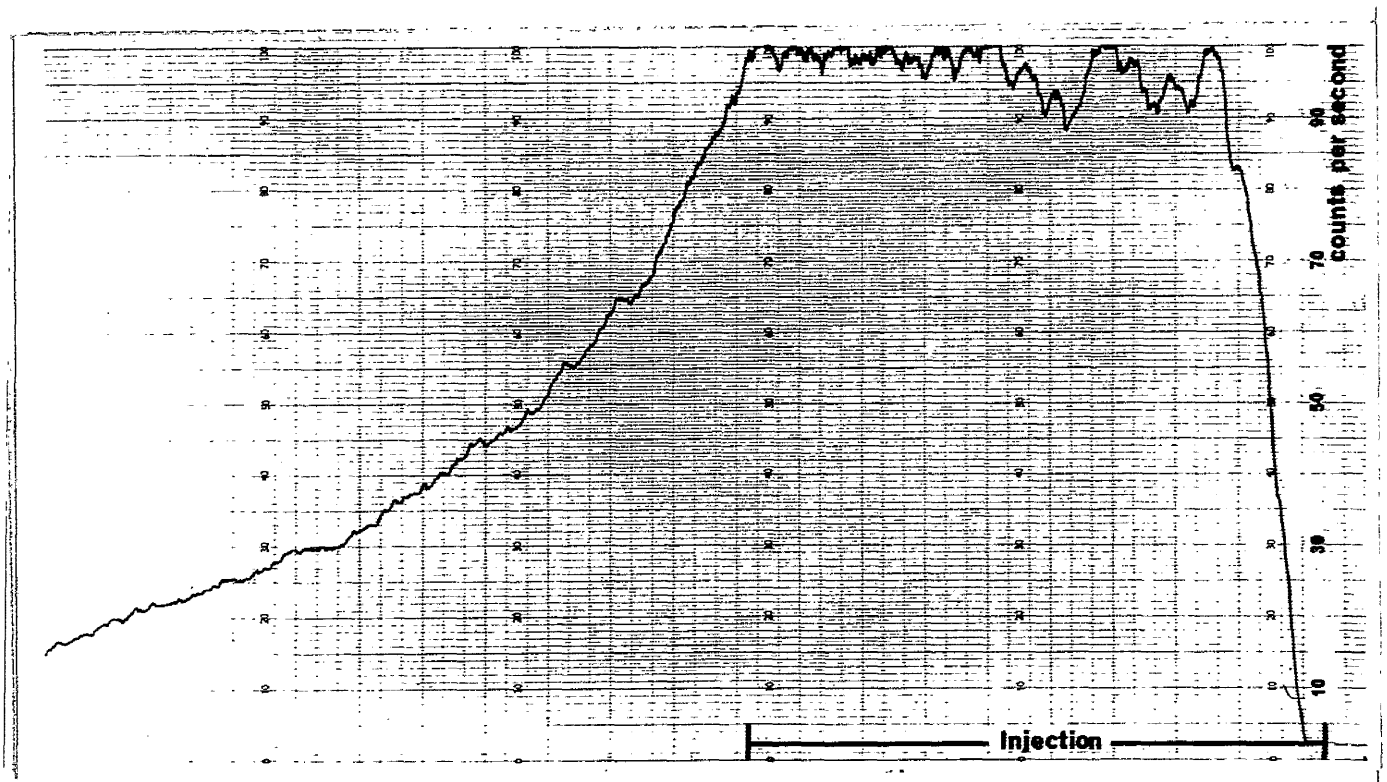

Fig.4(a) - Uptake and clearance of Krypton 85 from the cerebral cortex under "normal" conditions with an arterial PCO_2 of 36 mm.Hg.

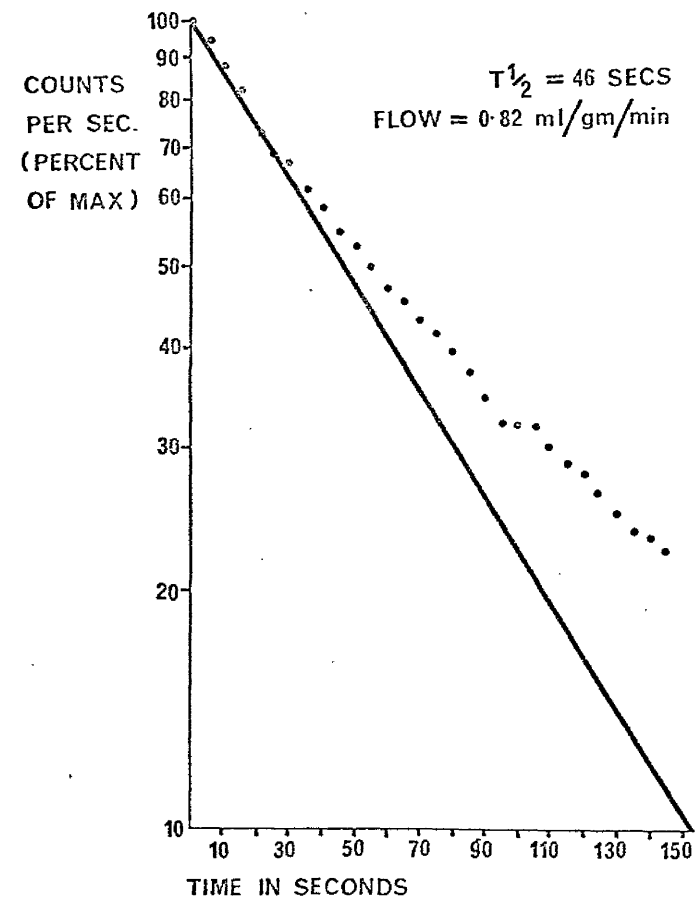

Fig.4(b) Semi-log plot of clearance curve.

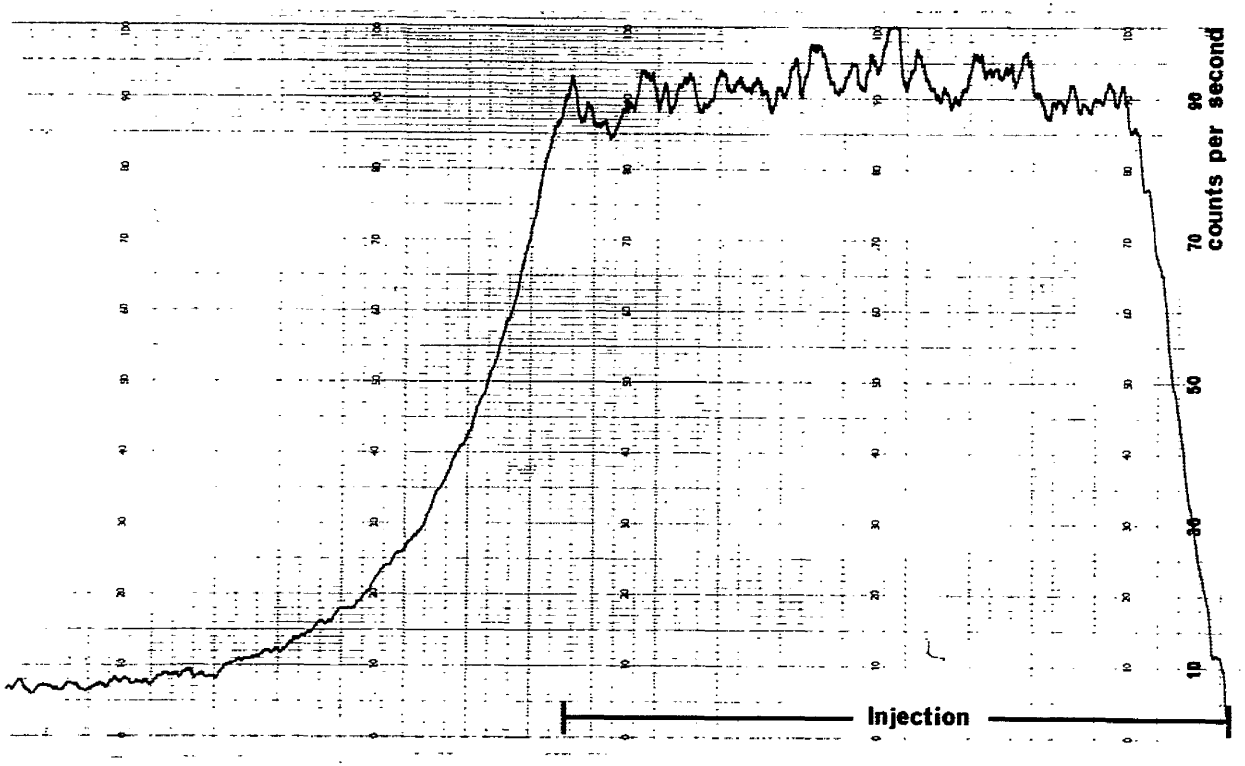

Fig.5(a) - Uptake and clearance of Krypton 85 from the cerebral cortex during the administration of CO_2 to the anaesthetic mixture (arterial PCO_2 80 mm.Hg).

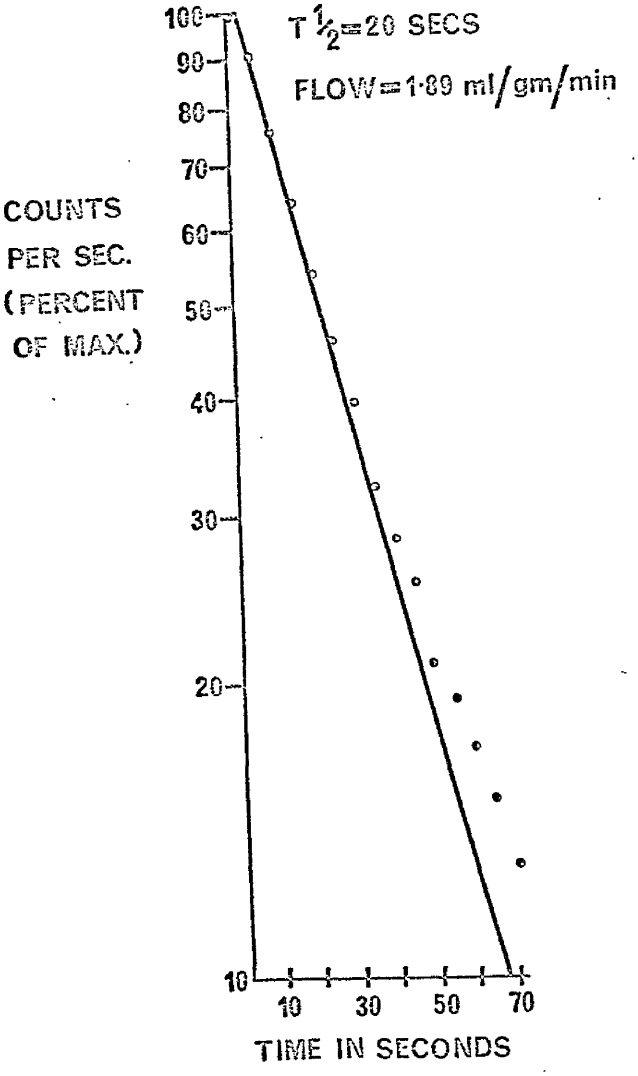

Fig.5(b) Semi-log plot of clearance curve.

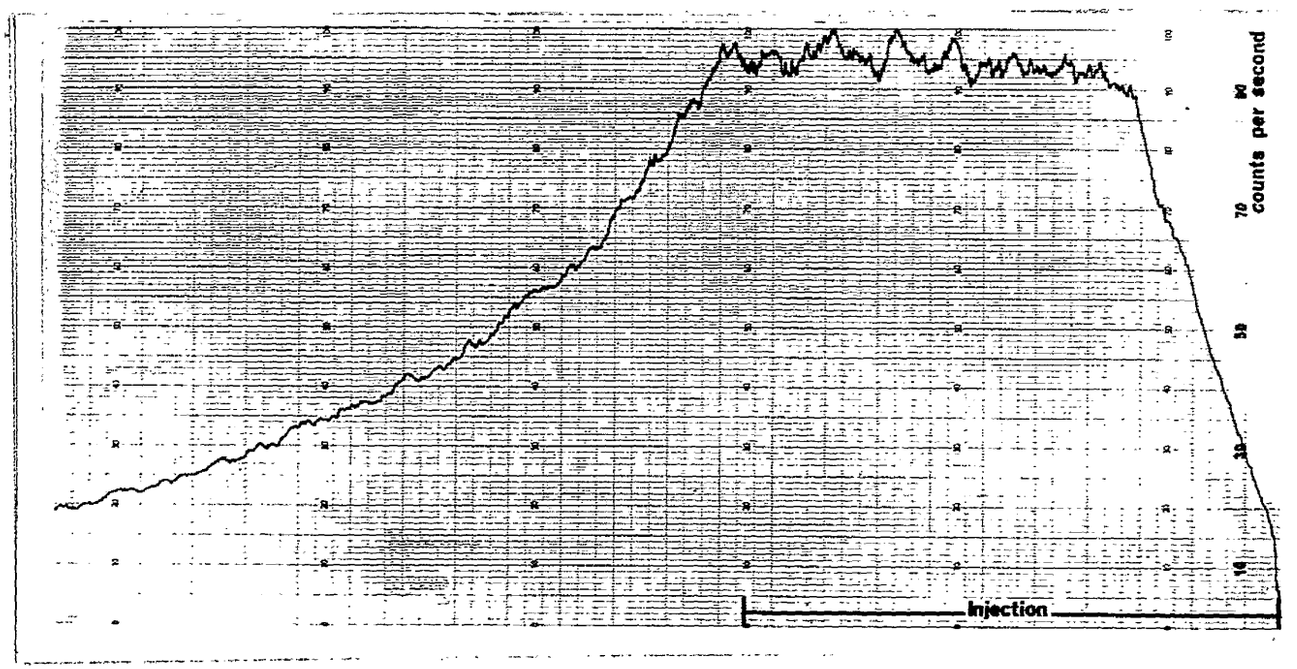

Fig.6(a) - Uptake and clearance of Krypton 85 from the cerebral cortex during moderate hyperventilation (arterial PCO_2 29 mm.Hg).

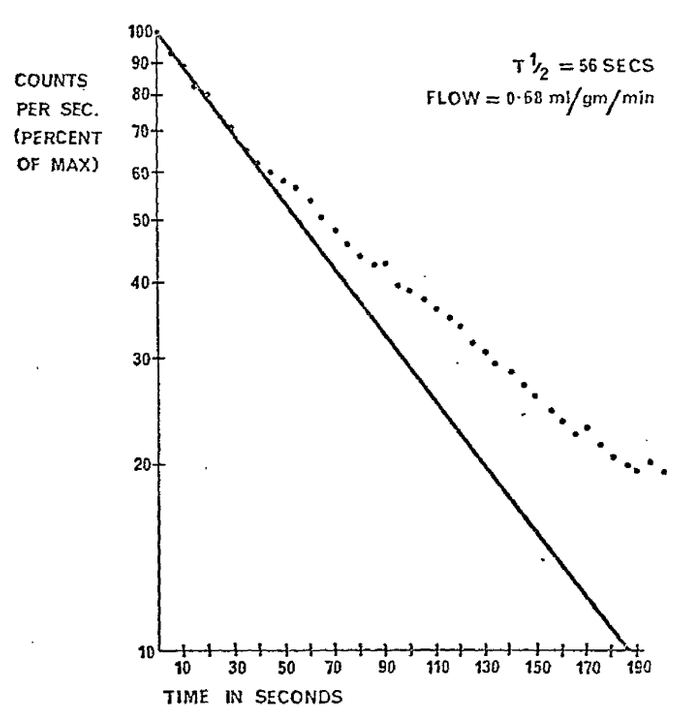

Fig.6(b) Semi-log plot of clearance curve.

THE VALIDITY OF THE KRYPTON 85 CLEARANCE METHOD

In the mathematical proof presented on page16 several basic assumptions were made. These were that the arterial concentration of Krypton 85 at the beginning of the clearance curve was zero, and that the tissue components of the cerebral cortex contained equal concentrations of Krypton at the start of the clearance curve, and had equal partition coefficients for Krypton. The validity of these assumptions will be discussed as well as other factors which could have influenced the blood flow results.

1) Is there significant arterial recirculation of Krypton?

Chidsey, Fritts, Hardewig, Richards & Cournand (1959) found that when Krypton 85 was injected rapidly into a vein only 3% (average value) reached the arterial blood, the rest being excreted in a single cycle through the lungs. If the injection was prolonged over two minutes, 6% reached the systemic circulation.

However, recirculation following on intra carotid injection can be expected to be much lower than this as

the blood returning from the head is diluted with that from the rest of the body. Ingvar and Lassen (1962) estimate the effective arterial recirculation to be 1%. They tested this by recording the count rate from the cortex, following an intravenous injection of Krypton 85 and found only a negligible increase in background activity.

This experiment was repeated by injecting into the femoral vein the same quantity of Krypton 85 that was required to give a count rate of 300 cps from the cortex with an intracarotid injection. Following the intravenous injection the maximal activity recorded from the cortex was only 1.5% of that recorded following an intracarotid injection. This recirculation was found to have no measurable effect on the initial slope of the clearance curve.

2) <u>Are there equal concentrations of Krypton 85 in the various tissue components of the cortex at the commencement of the clearance curve</u>?

In a multi-component system such as the brain cortex, the initial slope of the Krypton 85 clearance curve will be a valid index of blood flow only if all the tissue components contain equal concentrations of the isotope at the start of clearance. Ingvar and Lassen (1962) assumed that the cortex consisted of two

main components, one being perfused with blood at a fast rate and the other at a slow rate. They tried to achieve equal concentrations of Krypton by injecting rapidly for 30 seconds and then continuing at one fifth of the previous rate for about 3 minutes.

The technique employed in the present series of experiments was slightly different. This consisted of injecting rapidly at first, and then more slowly to maintain a "plateau" effect (Fig.4a - page 31) over the next two minutes or so. Essentially what happens is that, after the initial rapid injection, the concentration of Krypton in the more rapidly perfused components will reach a much higher level than in the more slowly perfused components. In the plateau region the concentration in the former will fall and the concentration in the latter will rise - the total quantity in the tissues being held constant by varying the rate of injection. The injection time necessary to reach equilibrium for Krypton between the various tissue components of the cortex was calculated experimentally.

The results of an experiment to test the effect of varying the injection times are shown in Table 1 (page 38 It can be summarised as follows. Injection times of

between 5 and 75 seconds gave a mean flow of 1.32 ml/gm/min. (standard deviation $\pm$ 0.47). If the injection time was raised to 100 seconds, the mean blood flow was 0.75 ml/gm/min. ($\pm$ 0.037). Injection times of between 200 and 500 seconds gave a similar value of 0.74 ml/gm/min. ($\pm$ 0.041).

As expected, therefore, a short injection gave a falsely fast clearance rate - due to Krypton being unequally distributed in favour of the rapidly perfused component.

Injection times of between 100 and 500 seconds gave approximately the same flow value (within the experimental error of the method - see page 47). It can be assumed that if, at 100 seconds, the various tissue components did not contain equal concentrations of Krypton, injections of over 100 seconds would result in a slower calculated blood flow. That this did not happen appears to indicate that, when the injection is continued for 100 seconds or longer, equilibrium for Krypton is reached between the various tissue components of the cerebral cortex.

Sequence of injections	M.A.B.P. (mm.Hg)	Time of injection. (secs.)	PCO_2 (mm.Hg)	Flow (ml/gm/min)
1.	175.0	5.0	41.0	1.88
2.	175.0	25.0	40.5	1.76
5.	165.0	40.0	-	1.09
10.	145.0	55.0	40.5	0.79
3.	175.0	75.0	40.5	1.08
4.	175.0	100.0	40.0	0.74
7.	155.0	100.0	-	0.71
9.	130.0	100.0	-	0.74
12.	160.0	100.0	-	0.80
8.	145.0	200.0	39.5	0.74
6.	155.0	300.0	39.0	0.79
11.	140.0	500.0	40.5	0.71

Table 1 - Effect of varying injection times on calculation of cortical blood flow.

3) Are the partition coefficients for Krypton 85 the same for each tissue component within the cortex?

As the tissue components which give rise to the multi-exponential clearance of Krypton 85 from the cortex have not yet been identified, this is a difficult question to answer. However, Ingvar & Lassen (1962) have examined autoradiographs of the cerebral cortex

taken from cats which had inhaled Krypton 85 for 1 hour. As the autoradiographs of the cortex had a uniform density this was "taken to indicate approximately the same Krypton 85 solubility within the different layers of the cerebral cortex" (Ingvar and Lassen 1962).

4) Is the clearance of Krypton 85 from the cortex dependent only on the blood flow or is there diffusion into the atmosphere or into other tissues?

This was tested by suddenly arresting the circulation during a clearance measurement. Fig.7 (page 40) shows an experiment in which Krypton was injected into the carotid artery - the injection being sustained for two minutes. When the injection was stopped the isotope cleared in the usual manner. During the clearance the aorta was cross-clamped just distal to the aortic valve. Following the arrest of the circulation there was little further decrease in the level of radioactivity recorded from the cerebral cortex, with the exception of a very slight fall just after the clamp had been applied, which could be attributed to a reduction in volume of the brain with a consequent change in counting geometry. When the clamp was released and the circulation restored, the clearance of Krypton from the cortex was again obvious

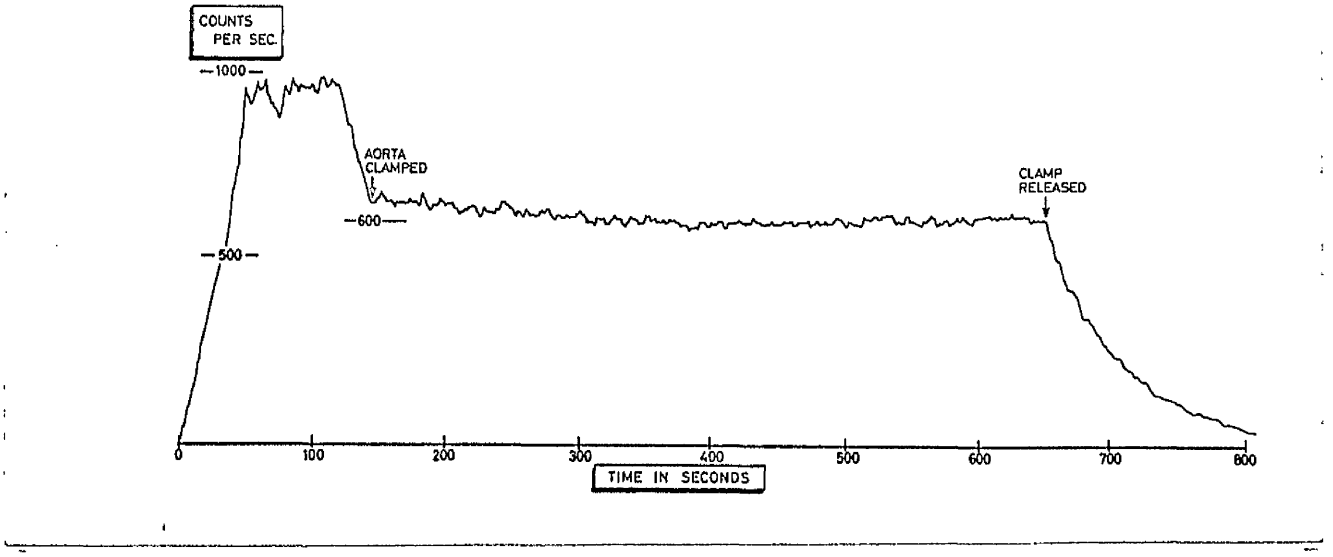

Fig.7 - Effect of complete circulatory arrest of clearance of Krypton 85 from the cerebral cortex.

This experiment would appear to indicate that (with a polyester membrane covering the cortical surface) there is no diffusion of Krypton 85 from the cortex into either the atmosphere or the underlying tissues of the brain which could produce a significant artefact on clearance curves recorded from the cerebral cortex.

5) Do different areas of the cerebral cortex have different flow rates?

Although the flow measurements presented in this thesis were all taken from the parietal region (sensory-

motor cortex), it was decided to compare blood flow measurements in the frontal, parietal and occipital cortex. The results are shown in Table 2 (page 42). As there were variations in the arterial carbon dioxide tension between each estimation, the flow results have been corrected (using Fig.12 - page 64) to the flow results which would have been expected had the PCO_2 been 40 mm.Hg during each measurement. When this correction factor had been applied, there was no significant difference in the values obtained from the 3 areas of the cortex. This is in agreement with studies by Landau, Freygang, Roland, Sokoloff and Kety (1955) who measured blood flow through various areas of the brain in cats, using the decapitation technique referred to on page 10. They quote "... whereas local blood flow varied significantly among the various cortical areas in the conscious cat, thiopental anaesthesia reduced them all to a relatively uniform level". McDowall (1966) has also measured the blood flow through different areas of the cerebral cortex in dogs anaesthetised with fluothane. Using the Krypton 85 clearance technique, he could detect no difference in blood flow through frontal, parietal and occipital cortex.

Position of counter.	M.A.B.P. (mm.Hg)	Arterial PCO_2 (mm.Hg).	Flow (ml/gm/min)	Flow (standardised to PCO_2 of 40 mm.Hg).
Occipital cortex.	170	46	1.45	1.20
Frontal cortex.	175	43	1.28	1.18
Parietal cortex.	180	47	1.45	1.16

Table 2. - Blood flow through different areas of the cerebral cortex.

6) Could the surgery necessary to expose the cerebral cortex affect the blood flow?

Meticulous care was taken in carrying out the surgery necessary to expose the area of cerebral cortex. If there was the slightest suspicion of damage to the surface of the cortex after the dura mater had been opened, or if there was any persistent contamination of the surface of the cortex with blood, the experiment was abandoned and no measurements of blood flow were made. The dura mater was replaced with a thin polyester membrane and a layer of cerebro-spinal fluid prevented actual contact between the membrane and the surface of the cortex. As an additional precaution, the preparation

was allowed to stabilize for 60 minutes after completion of the surgery.

During the exposure of the cortex, when the dura mater was opened, there was a spillage of cerebro-spinal fluid and therefore a drop in cerebro-spinal fluid pressure. It could be argued that this change in cerebro-spinal fluid pressure might affect the blood flow. This argument is difficult to refute absolutely, as there are no reliable quantitative estimations of cortical blood flow in the dog with an intact skull, with which to compare the results. However, work by Kety, Shenkin and Schmidt (1948) has shown that the cerebro-spinal fluid pressure in man could be raised to as high as 45 cm. H_2O without affecting the cerebral blood flow. Therefore, while it is difficult to deny that a drop in cerebro-spinal fluid pressure might cause an alteration in cortical blood flow in the dog, I think that it is unlikely that this would be of any magnitude.

7) Did the anaesthetic influence the cortical blood flow?

The anaesthetics and drugs given were thiopentone, nitrous oxide, and oxygen during the operative surgery, and nitrous oxide with oxygen and intravenous succinylcholine chloride during the measurements of blood flow.

(i) Thiopentone has been shown by Pierce, Lambertsen, Deutsch, Chase, Linde, Dripps & Price (1962) to reduce cerebral blood flow in man. In the experiments reported in this thesis an initial dose of thiopentone (20-30 mg/Kg) was given to induce anaesthesia and a further supplementary dose (5-7 mg/Kg) given after approximately 30 minutes. It was not usually necessary to give any further supplements of thiopentone as the surgery was, in most cases, completed within one hour. Following completion of the surgery, the animal was left undisturbed for a further hour, breathing nitrous oxide and oxygen, before measurements of blood flow were commenced. There was therefore a period of one and a half hours after the administration of thiopentone, before blood flow was measured.

That this period of time was sufficient to overcome the anaesthetic effect of thiopentone is shown by the following sequence of events in a control experiment. A dog weighing 13.5 Kg was given approximately 30 mg/Kg of thiopentone. Thirty minutes later an additional dose of 7 mg/Kg was given. Thirty minutes after this the animal was semiconscious, and 1 hour later was fully conscious.

Therefore it would appear that, in the experiments

reported in this thesis, the time which elapsed between the last dose of thiopentone and the measurement of blood flow was sufficient to ensure that the effects of thiopentone on the central nervous system had worn off.

(ii) Nitrous Oxide - It is difficult to determine the influence of nitrous oxide on the cortical blood flow in the dog, as it was not possible to make control measurements in the conscious animal. However, Wollman and his co-workers (1965) have shown, in man, that nitrous oxide is almost unique among anaesthetics in producing no significant change in cerebral blood when compared with values obtained in the conscious state.

If, however, nitrous oxide did have an effect on the blood flow through the cerebral cortex in the dog, this was likely to be constant as the animals had been inhaling nitrous oxide for at least 2 hours before measurements of blood flow were made - a time sufficient to ensure saturation of the brain with the gas.

(iii) Succinylcholine chloride - Measurements of cortical blood flow before and after the administration of succinylcholine chloride in the experiments reported in this thesis, did not reveal any significant change in blood flow.

8) Could the injection of Krypton 85 dissolved in dextran into the carotid artery influence the blood flow through the cerebral cortex?

Dextran containing Krypton 85 was injected into the common carotid artery via a catheter inserted into the superior thyroid branch. The maximal rate of injection was 3 ml/min. Using an electromagnetic flowmeter, I have found the blood flow through the common carotid artery in average sized dogs (15-25 Kg), under nitrous oxide anaesthesia, to be 80-120 ml/min. Relative to this flow, I consider it unlikely that small injections of dextran (less than 3 ml/min.) could have influenced cortical blood flow. However, experimental evidence to support this has recently been furnished by McDowall & Betz (1966), who measured the effects of injecting various quantities of saline into the common carotid artery on the cortical blood flow in dogs. Measuring qualitative changes in blood flow by means of a heated thermocouple placed on the cortex, they found that saline injected into the carotid artery at rates up to 3 ml/min. did not influence blood flow. It was only with extremely rapid injections, for instance 1 ml in 2 secs, that transient changes in blood flow were observed.

ACCURACY AND REPEATABILITY OF THE KRYPTON 85 CLEARANCE METHOD.

In 6 dogs repeated estimations of cortical blood flow were made under constant experimental conditions in order to determine the accuracy and repeatability of the method. The results are summarised in Table 3 and given in full in Table 4 (page 133).

Exp. No.	No. of Ests.	Time between first & last est. (mins.)	Mean & S.D. B.P.	Mean & S.D. PCO_2	Mean & S.D. Flow	Coeff. of Variation for Flow.
1.	7	215	156 ± 6	38.4 ± 1.5	0.97 ± 0.09	9.3 %
3.	6	220	162 ±	40.3 ± 1.04	0.99 ± 0.10	10.1 %
4.	7	155	150 ± 7	38.4 ± 1.9	1.15 ± 0.24	20.9 %
5.	10	275	168 ± 6	42.1 ± 1.9	0.85 ± 0.10	11.8 %
8.	9	160	151 ± 6	37.0 ± 1.5	0.96 ± 0.05	5.2 %
16.	7	70	151 ± 15	40.0 ± 0.8	0.75 ± 0.04	5.3 %

Table 3. - Mean values for repeated estimations of cortical blood flow under constant experimental conditions.

The number of estimations in each dog ranged from 6 to 10 and the time between the first and last estimations, from 70 minutes to over four and a half hours. The blood pressure and arterial carbon dioxide tension were kept within fairly narrow limits in each animal. The mean flow values ranged from 0.75 to 1.15 ml/gm/min. and the coefficient of variation (standard deviation expressed as a percentage) from 5.2 to 20.9%.

The final weighted mean for blood flow from all six dogs was 0.94 ml/gm/min. at a mean PCO_2 of 39.4 mm.Hg. The average coefficient of variation was 10.4%.

The mean value for cortical blood flow calculated from the initial control measurements made in 40 dogs from Tables 4, 5, 7, 8 and 13 was 0.87 ml/gm/min ($\pm$ 18% S.D.) at a mean arterial PCO_2 of 36.7 mm.Hg. This is equivalent to a flow value of 0.93 ml/gm/min. at a $PaCO_2$ of 40 mm.Hg (correction factor from blood flow/PCO_2 response curve (Fig.12 - page 64)).

Discussion.

Table 3 (page 47) shows that with a stable preparation, there was no significant change in blood flow with time, even up to 4½ hours after the beginning of measurements, and that the accuracy of the method was

approximately plus or minus 10% (standard deviation) for repeated results under constant experimental conditions.

It is difficult to compare the values reported here with other studies. For instance, Landau and his co-workers (1955), using the decapitation technique in cats, reported a blood flow of 0.65 ml/gm/min. through the sensory-motor cortex under thiopentone anaesthesia, but unfortunately did not report the arterial carbon dioxide tension (which is of paramount importance in determining cerebral blood flow). In addition, thiopentone is known to depress cerebral blood flow (see page 44). In dogs anaesthetised with Nembutal an average blood flow of 0.65 ml/gm/min. was found in the sensory-motor cortex using a similar Krypton 85 clearance technique to that described in this thesis (Gleichmann, Ingvar, Lassen, Lübbers, Siesjö and Thews (1962). However, the authors themselves admit that their figure "represents different depths of anaesthesia and different states of functional activity." In addition, the values for arterial carbon dioxide tension which they report, have a very wide range of from 14 to 52 mm.Hg.

In the work reported here great care was taken to ensure "steady state" conditions in each experiment,

especially with regard to ventilation and anaesthesia. Under these conditions the blood flow through the cerebral cortex at an arterial $PaCO_2$ of 40 mm.Hg averaged 0.93 ml/gm/min. The standard deviation for values calculated from 40 different dogs was 18%. The standard deviation in any one dog for repeated estimations under constant conditions averaged 10%. These values can therefore be regarded as giving an accurate estimate of blood flow through the cerebral cortex under light nitrous oxide anaesthesia; differences from the values reported by Landau et al. and Gleichmann et al. are probably due to differences in the technique of anaesthesia and control of respiration.

Summary of Part 1.

The development of the Krypton 85 clearance method from the Fick principle is traced and a mathematical "proof" of the method is presented.

A laboratory preparation for the measurement of blood flow through the cerebral cortex in dogs has been developed and experiments carried out to test the validity of the method.

The mean value for cortical blood flow in 40 dogs under control conditions was estimated at 0.93 ml/gm/min. with a standard deviation of 18%. The standard deviation of repeated estimations in any one animal under constant experimental conditions averaged 10%.

It is proposed that the method establishes the possibility of making rapid and frequently repeatable estimations of blood flow through the cerebral cortex with a fairly high degree of accuracy.

PART 2

THE PHYSIOLOGY OF CEREBRAL BLOOD FLOW

A STUDY OF SOME OF THE FACTORS THOUGHT TO BE OF IMPORTANCE IN THE CONTROL OF THE FLOW OF BLOOD THROUGH THE CEREBRAL CORTEX.

THE INFLUENCE OF CHANGES IN THE pH OF ARTERIAL BLOOD ON THE BLOOD FLOW THROUGH THE CEREBRAL CORTEX.

Object

The experiments reported in this part of the thesis were designed primarily to study the effects on the blood flow through the cerebral cortex of alterations in the arterial carbon dioxide tension and arterial blood pressure, with special emphasis on the inter-relationship of these two variables in the control of cortical blood flow.

However, as alterations in arterial carbon dioxide tension are known to produce concomitant changes in blood pH, it was decided to make a preliminary study of the effects of a change in blood pH by itself on the blood flow to the cerebral cortex.

Experiments were designed so as to test the effect on the cortical blood flow of altering the pH of the arterial blood while maintaining arterial PCO_2 at a steady constant value.

Method.

The experimental preparation has been described on pages 21 to 30.

At the start of each experiment the output from the respiratory pump was adjusted to produce an arterial PCO_2 of between 30 and 40 mm.Hg as described previously. In five dogs acidosis was induced by the infusion of a 2% solution of lactic acid in normal saline. In another five dogs alkalosis was induced by the infusion of sodium bicarbonate in saline (50 mEq. in 100 ml.). The arterial carbon dioxide tension was held constant by altering the respiratory pump output when necessary.

RESULTS

The results from each experiment are given in Table 5 (pages 135 and 136) and summarised in Table 6 (page 56). The arterial PCO_2 was kept nearly constant in each experiment. The maximal standard deviation (in dog P5) was $\pm$ 2.8 mm.Hg from a mean of 38.1 mm.Hg. There were slight changes in mean arterial blood pressure in individual experiments but the deviations were inconstant and were not considered significant. The mean blood pressure from all the experiments was 161.5 mm.Hg and the mean $PaCO_2$ from all experiments was 36.7 mm.Hg.

In the experiments the lowest pH recorded was 6.74 and the highest 7.80. Even at these extreme levels there was no noticeable alteration in blood flow. In none of the experiments was the correlation coefficient for blood flow against pH significant.

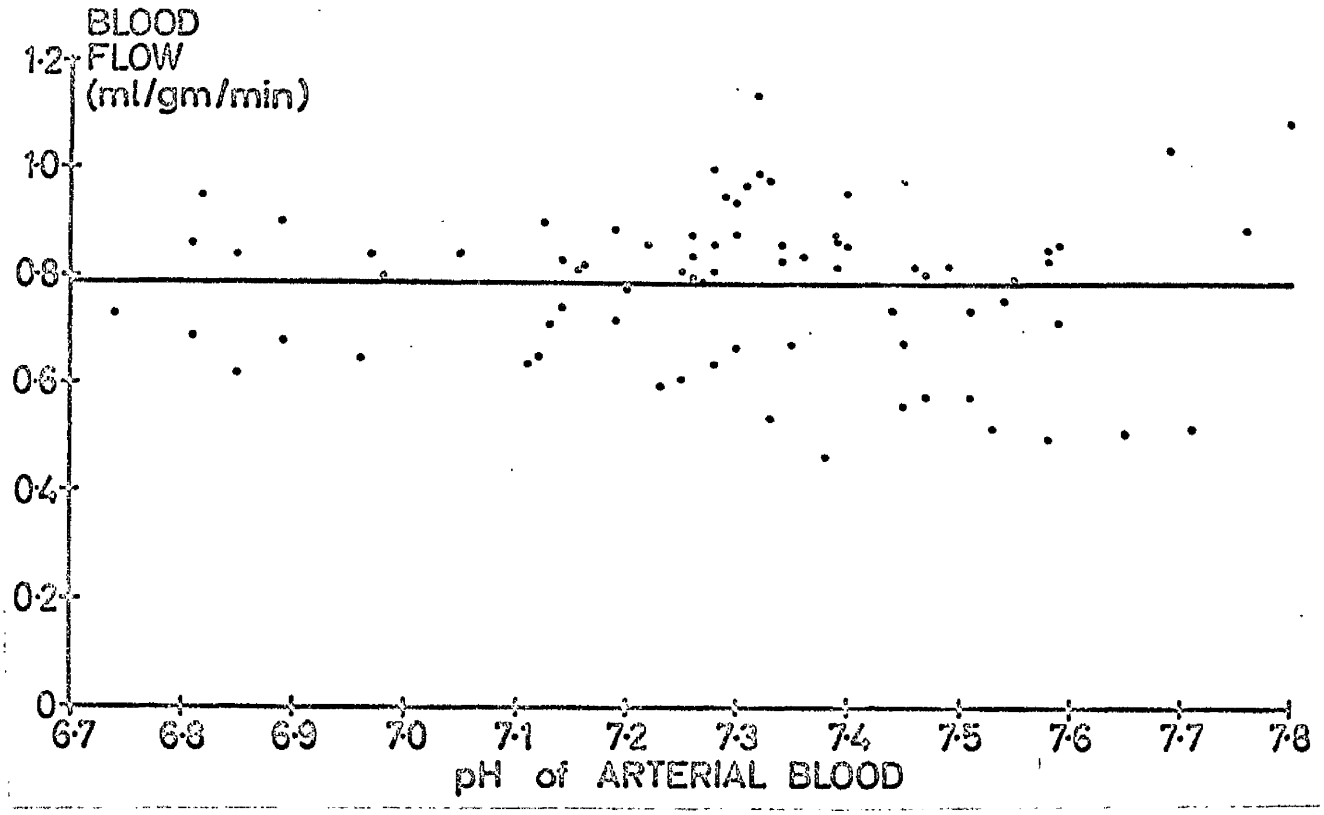

Fig.8 - The blood flow through the cerebral cortex plotted against blood pH from all 10 experiments. The calculated linear regression line has the formula $y = 0.02x + 0.773$.

In Fig.8 the blood flow estimations from all the experiments have been plotted against the blood pH. The calculated linear regression line was found to be horizontal.

TABLE 6

Exp. No.	No. of Estimations	pH Range	Mean and S.D. of PCO_2 (mm.Hg.)	Mean and S.D. Mean Arterial Blood Pressure (mm.Hg.)	Mean and S.D. Blood Flow (ml./g./min.)	Correlation Coefficient of Blood Flow against pH
ACIDOSIS						
P.1	6	6.97-7.36	36.1 ± 1.8	148 ± 8	0.86 ± 0.03	0.16
P.2	10	6.81-7.34	37.7 ± 1.4	152 ± 10	0.83 ± 0.09	0.24
P.3	10	6.81-7.39	32.8 ± 0.8	181 ± 7	0.73 ± 0.08	0.16
P.4	8	6.74-7.32	36.2 ± 1.5	208 ± 14	0.74 ± 0.12	0.39
P.5	7	6.82-7.25	38.1 ± 2.8	157 ± 9	0.85 ± 0.05	0.36
ALKALOSIS						
P.6	10	7.29-7.59	38.0 ± 1.6	184 ± 12	0.85 ± 0.07	0.56
P.7	5	7.28-7.69	40.2 ± 1.8	140 ± 6	0.81 ± 0.18	0.36
P.8	10	7.23-7.71	37.4 ± 1.0	130 ± 7	0.54 ± 0.04	0.55
P.9	7	7.28-7.59	34.9 ± 1.4	158 ± 13	0.86 ± 0.12	0.63
P.10	6	7.32-7.80	34.5 ± 1.9	157 ± 4	0.94 ± 0.14	0.01

Discussion

Various workers on cerebral circulation have reported vasodilatation occurring with acidosis and constriction with alkalosis, but these changes have not been marked. In the perfused dog brain Schmidt (1928) reported dilatation by acid and constriction by alkali. In the perfused cat brain Geiger and Magnes (1947) reported that only extreme changes in pH produced any effect. Using a cranial window technique, Wolff and Lennox (1930) reported transient dilatation of the pial arteries in the cat following an intravenous injection of lactic acid. However, Schmidt and Pierson (1934) found that the changes produced by acidosis on the blood flow through the medulla were uncertain, and Bronk and Gesell (1927) reported that alkalosis increased the blood flow through the carotid artery.

Kety and his colleagues (1948) found a convincing increase in cerebral blood flow in patients with a metabolic acidosis due to diabetic coma, even although the arterial PCO_2 was low. Schieve and Wilson (1953) have questioned whether this increase in cerebral blood flow is due to some factor other than acidosis. They infused ammonium chloride into patients to produce a

slight acidosis and found a decrease in blood flow as measured by Kety's nitrous oxide method. They also found an increase in cerebral blood flow when metabolic alkalosis was produced by infusion of sodium bicarbonate. In the latter studies, however, no figures were given for PCO_2.

In these experiments I have tried to achieve constant physiological conditions in order that the principal variable was the blood pH. The arterial carbon dioxide tension and blood pressure were successfully kept within narrow limits. There is no evidence that there were any variations in the depth of anaesthesia which could have influenced the results: the same concentrations of anaesthetic gas were given throughout each experiment. Under these "steady state" conditions there was no marked alteration in the cortical blood flow in either metabolic acidosis or alkalosis.

However, as noted on page 48, repeated estimations in any one animal under constant conditions of arterial PCO_2, pH, and blood pressure show a coefficient of variation of 10%. It is possible therefore that changes in blood flow of this order might not be revealed in these results. However, changes in blood flow of more than 10% would almost certainly be noticed as it will be

shown that the method records faithfully the changes which occur in the blood flow on raising and lowering the arterial carbon dioxide tension under the same experimental conditions (page 65).

Sokoloff (1959) has stated that "a final evaluation of the direct action of acids and alkalies on the cerebral circulation is difficult because of the usual association of secondary extraneous influences, particularly changes in blood PCO_2." I believe this study to be the first in which the arterial PCO_2 was carefully controlled and only the pH allowed to vary. Under these circumstances changes in blood pH did not produce significant changes in the blood flow through the cerebral cortex.

THE INFLUENCE OF THE ARTERIAL CARBON DIOXIDE TENSION ON THE BLOOD FLOW THROUGH THE CEREBRAL CORTEX

Object

Although it has long been known that asphyxia causes dilatation of the cerebral blood vessels (Roy and Sherrington, 1890), Wolff and Lennox (1930) were the first to show that a change in the blood content of carbon dioxide could, by itself, affect the cerebral circulation. They demonstrated that the inhalation of CO_2 in the presence of a normal arterial oxygen content, caused dilatation of the blood vessels of the pia mater. Since then quantitative studies in man (Kety and Schmidt, 1948), (Fazekas, Alman and Bessman 1952), (Hafkenschiel and Friedland 1952), (Novack, Shenkin, Bortin, Goluboff and Soffe 1953), (Patterson, Heyman, Battey and Ferguson 1955), (Fieschi, Agnoli and Galbo 1963), (Alexander, Wollman, Cohen, Chase and Behar 1964) have confirmed that an increase in the arterial carbon dioxide tension results in a rise in cerebral blood flow, and a decrease in carbon dioxide tension a fall in cerebral blood flow.

However, the exact relationship between blood flow and PCO_2 over a wide range of PCO_2 values is still not clear, and it has not been firmly established whether there are upper and lower limits of arterial PCO_2 beyond which the cerebral blood vessels cease to respond.

In addition, there is no information on the response of the cerebral blood flow to alterations in arterial PCO_2 in hypotensive states - information which could be of considerable importance if one were contemplating the administration of CO_2 in an endeavour to restore cerebral blood flow in conditions of shock.

The experiments reported in this section were designed to investigate the relationship of the blood flow through the cerebral cortex to the arterial carbon dioxide tension, both under "steady state" conditions and during haemorrhagic shock.

Method.

The experimental preparation has been described on page 21. The experiments were divided into three groups:

Group 1 - Carbon dioxide tension variations during normal arterial blood pressure.

The $PaCO_2$ was gradually raised in 10 dogs by adding increasing quantities of carbon dioxide to the anaesthetic mixture,

and lowered in 9 dogs by increasing the volume delivered by the respiratory pump. When carbon dioxide was added to the anaesthetic mixture the quantity of nitrous oxide was reduced by the same amount, the oxygen content being kept constant.

Group 2 - Carbon dioxide variations during moderate arterial hypotension.

The mean arterial blood pressure was lowered and maintained at 100 mm.Hg by bleeding the animals from a cannula in the femoral artery into a reservoir flask held at this pressure. The $PaCO_2$ was raised in 7 dogs and lowered in 5 dogs.

Group 3 - Carbon dioxide variations during marked arterial hypotension.

The mean arterial blood pressure was maintained at 40-60 mm.Hg. The $PaCO_2$ was raised in 5 dogs and lowered in 5 dogs.

Analysis of results.

As there was considerable variation in the initial control values for each experiment, the blood flow was plotted against the $PaCO_2$ individually for each dog. Lines giving the best fit for individual experiments

were drawn by hand and each dog's flow results expressed as a percentage of its blood flow at an arterial carbon dioxide tension of 40 mm.Hg as estimated from the individual graph (Figs.9 and 10 - page 149). This enabled the results in each experiment to be expressed as a percentage change in blood flow from that occurring at a $PaCO_2$ of 40 mm.Hg. The results were then plotted on one graph and the Deuce digital computer at the University of Glasgow was used to calculate the best fit for a polynomial curve (Fig.12 - page 64).

Results.

Group 1 (Carbon dioxide tension variations during normal arterial blood pressure).

The results are given in Tables 7 and 8 (pages 137 and 139). Graphs of the blood flow/$PaCO_2$ relationship in each dog are shown on Figs.9 and 10 (page 149) A "blanket" graph of all the results (unstandardised) is shown on Fig.11 (page 150).

The standardised results are shown in Fig.12 (page 64).

In the dogs subjected to hypercapnia there was a marked rise in blood flow as the $PaCO_2$ increased. The rise in $PaCO_2$ was accompanied by a fall in pH.

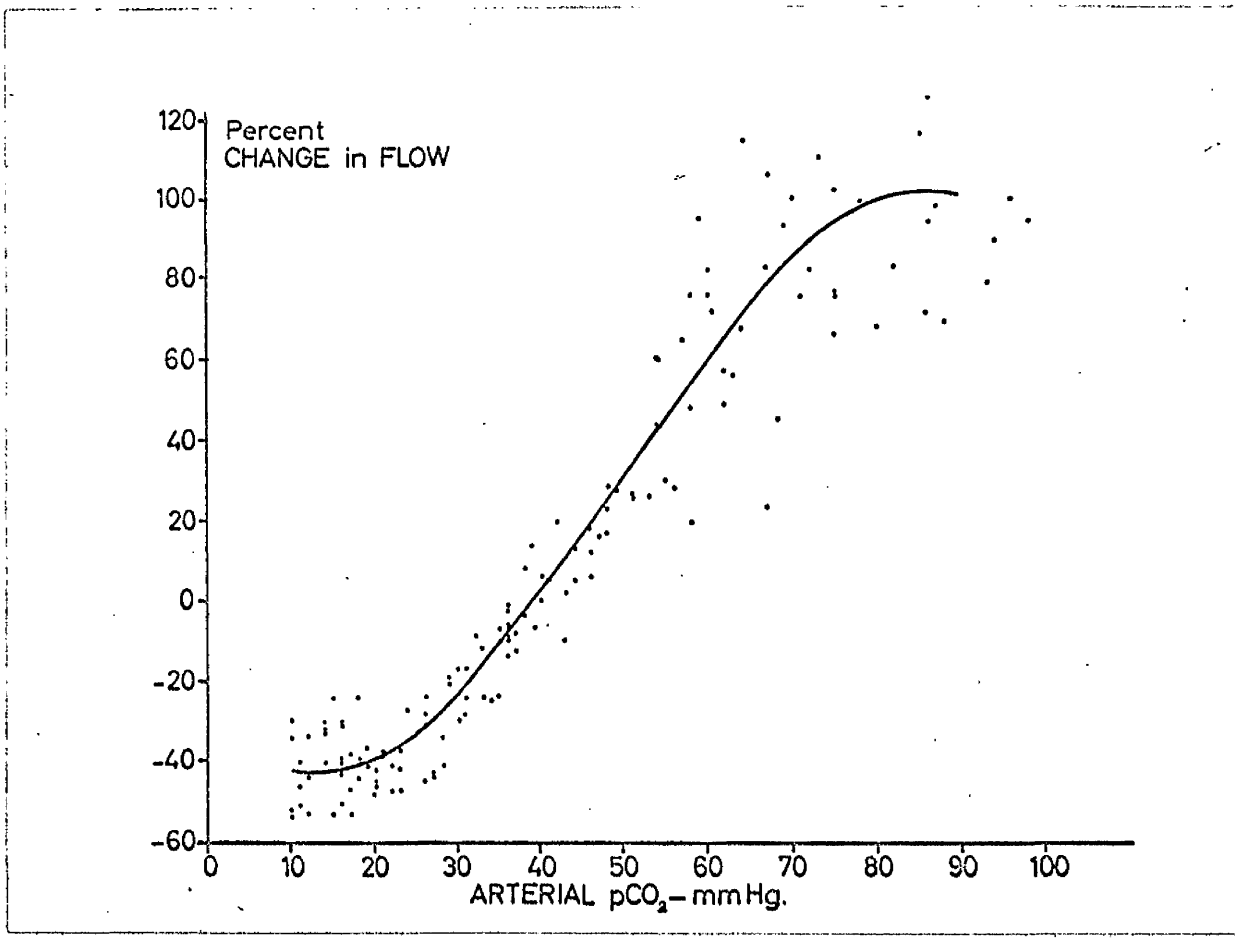

Fig.12 - The effect of alterations in $PaCO_2$ in normotensive animals on the cortical blood flow. Zero reference line for blood flow is at $PaCO_2$ of 40 mm.Hg.

In hypocapnia the blood flow decreased on lowering the $PaCO_2$.

The mean value for blood pressure in this group was 152 mm.Hg. The standard deviations for blood pressure in individual animals ranged from 1.7 to 9.0% with an average of 3.5%. There were no consistent increases or decreases in blood pressure in either hypercapnia or hypocapnia.

A cubic curve was found to give the best fit to the standardised blood flow results (Fig.12 - page 64). From this graph it can be seen that raising the $PaCO_2$ from 40 to 80 mm.Hg caused approximately a 100% increase in blood flow. Lowering the $PaCO_2$ from 40 to 20 mm.Hg caused a 40% decrease in blood flow. There was no further obvious decrease in blood flow when the $PaCO_2$ fell below 20 mm.Hg.

Group 2 (Carbon dioxide variations during moderate arterial hypotension - M.A.B.P. 100 mm.Hg).

The results are given in Tables 9 and 10 (pages 141 and 143). Graphs of the blood flow/$PaCO_2$ relationship in each dog are shown on Figs.13 and 14 (page 151). A "blanket" graph of all the results (unstandardised) is shown on Fig.15 (page 152).

The standardised results are shown on Fig.16 (page 66).

The change in blood flow on altering the $PaCO_2$ is similar to, but less pronounced than, in Group 1. It can be seen from Fig.16 that the percentage increase in blood flow when the $PaCO_2$ is raised from 40 to 80 mm.Hg is only 50% (compared with 100% increase in Group 1). Similarly, the reduction in

flow when the $PaCO_2$ was lowered from 40 to 20 mm.Hg was only 25% (compared with a 40% decrease in Group 1).

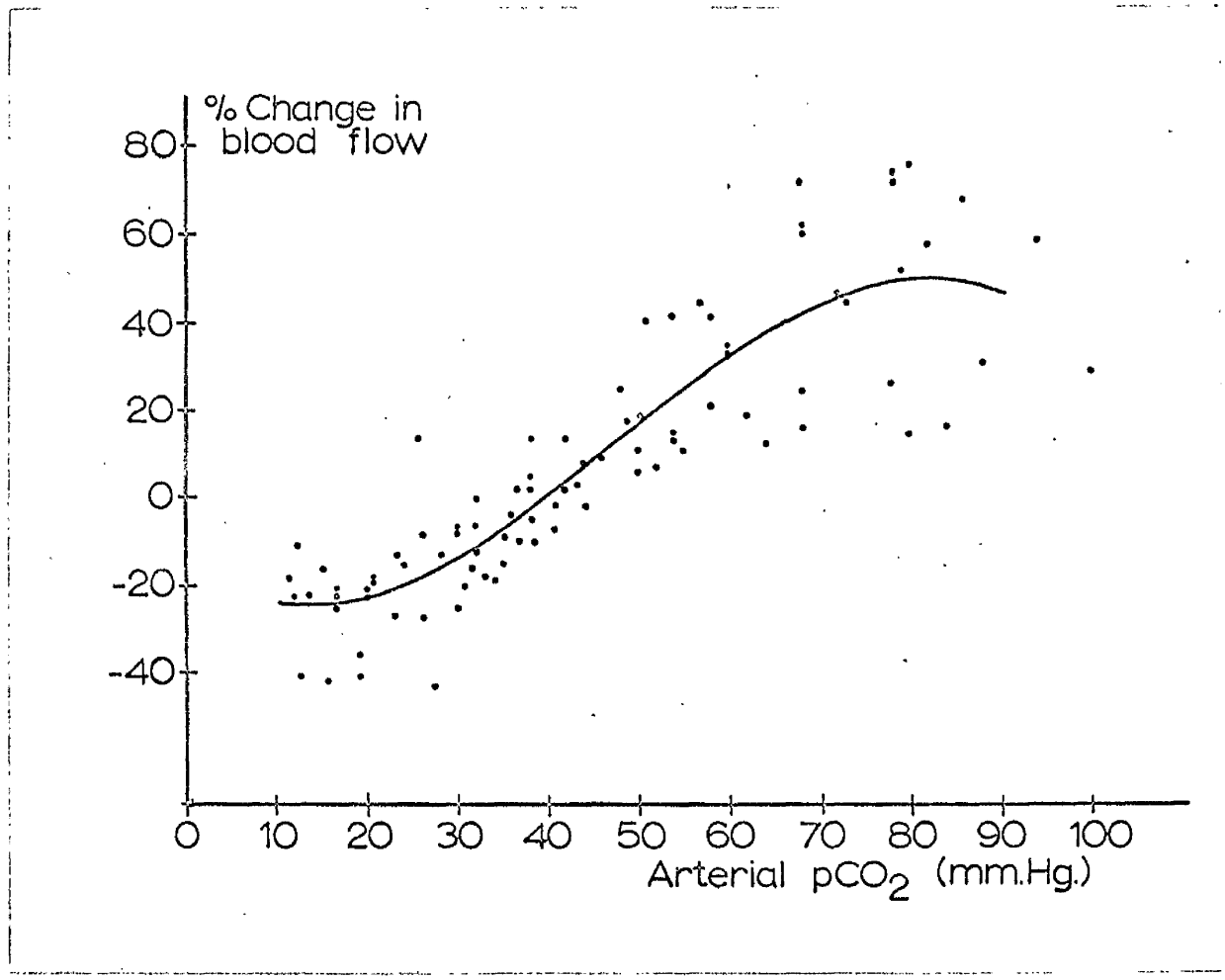

Fig.16 - The effect of alteration in $PaCO_2$ in hypotensive animals (M.A.B.P.100 mm. Hg) on cortical blood. Zero reference line for blood flow is at $PaCO_2$ of 40 mm.Hg.

Group 3 (Carbon dioxide tension variations during severe arterial hypotension - M.A.B.P. 40 to 60 mm.Hg).

The results are given in Tables 11 and 12 (pages 144 and 145). Graphs of the blood flow/$PaCO_2$

relationship in each dog are shown on Figs.17 and 18 (page 153). A "blanket" graph of all the results (unstandardised) is shown on Fig.19 (page 154).

The standardised results are shown on Fig.20.

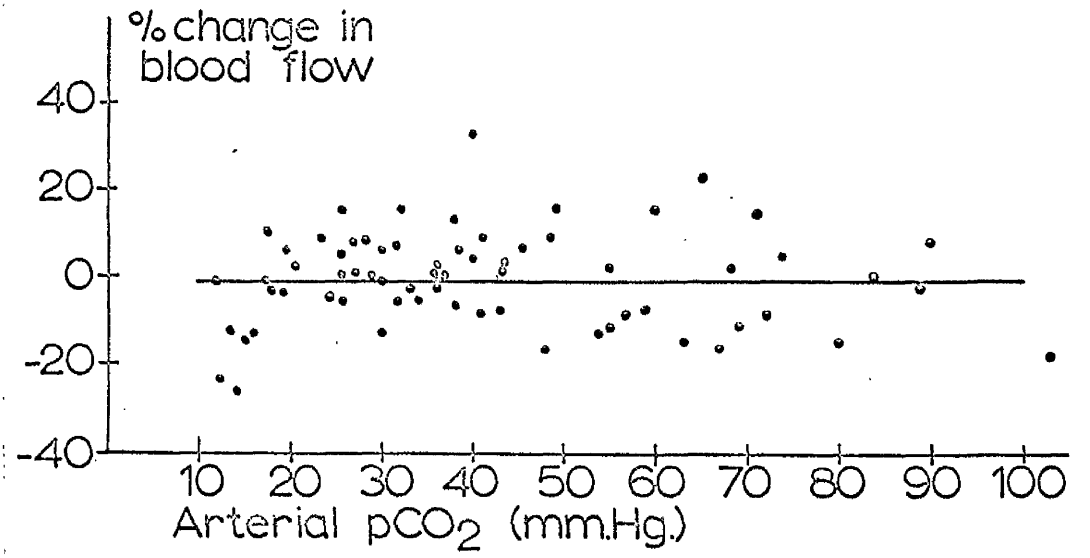

Fig.20 - The effect of alterations in $PaCO_2$ in hypotensive animals (M.A.B.P. 40-60 mm.Hg) on cortical blood flow. Zero reference line for blood flow is at $PaCO_2$ of 40 mm.Hg.

It can be seen from Fig.20 that neither raising nor lowering the $PaCO_2$ had any significant effect on the cortical blood flow.

Discussion.

In the experiments in which the arterial carbon dioxide tension was altered in normotensive animals

vasodilatation was observed during hypercapnia and vasoconstriction during hypocapnia. Until recently there has been insufficient data on the shape of the $PaCO_2$/blood flow response curve with which to compare these results. However, after the experiments reported here had been completed, a paper was published by Reivich (1964) in which the cerebral blood flow (measured with thermistor flowmeters in the internal jugular veins) was calculated for numerous values of $PaCO_2$ in anaesthetised monkeys.

The results obtained by Reivich are shown on Fig.21 (page 69) and show a remarkable similarity to the results for cortical blood flow in the dog (Fig.12 - page 64).

The following comparisons may be made between the two studies:

(1) Both studies show approximately a 100% increase in blood flow on raising the $PaCO_2$ from 40 to 80 mm.Hg.

(2) Both studies show approximately a 40 to 50% decrease in blood flow on lowering the $PaCO_2$ from 40 to 20 mm.Hg.

(3) In Reivich's graph there is a "levelling out" of the blood flow at $PaCO_2$ greater than 100-120 mm.Hg. In the dog experiments, however, this upper limit of increase was observed at about 80-100 mm.Hg.

However, too much reliance cannot be placed on the extreme upper end of the dog curve (Fig.12 - page 64) as the data are rather scanty and the values show considerable scatter.

(4) At $PaCO_2$ of less than 20 mm.Hg both studies show no further significant decrease in blood flow.

In spite of the differences in method in the two studies, there is a striking similarity between the response to changes in $PaCO_2$ of cortical blood flow in dogs on the one hand and average total cerebral blood flow in monkeys on the other.

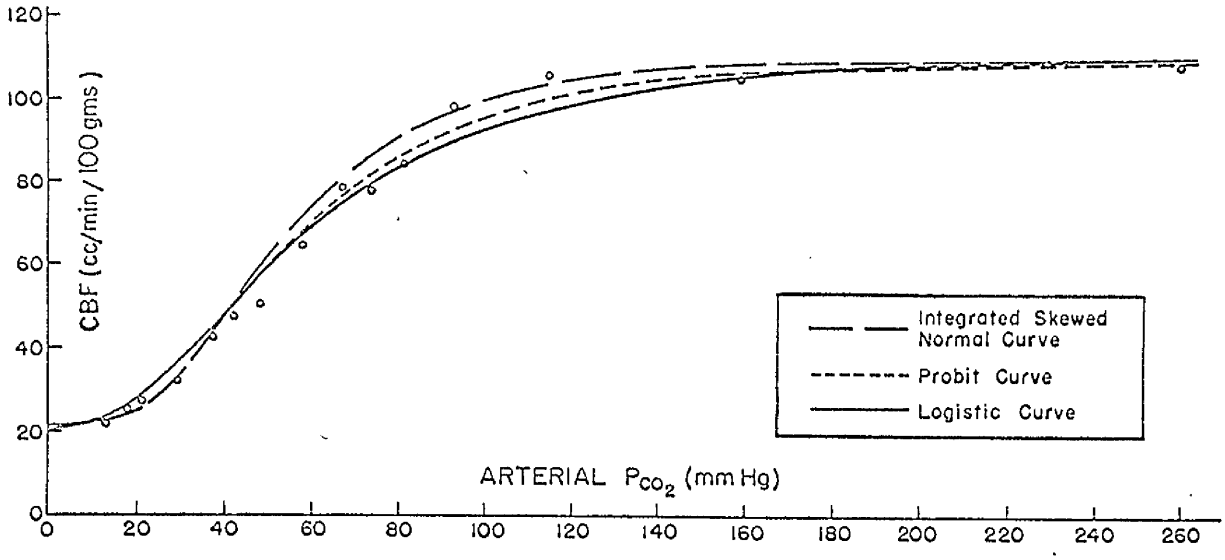

Fig.21 - Comparison of three different types of asymmetric sigmoid curves fitted to the cerebral blood flow versus arterial PCO_2 data. o = Values of running averages of ten data points from all eight monkeys. There is not a significantly different fit among the three curves. (Reivich, 1964, Am.J.Physiol).

Comparison with results in man.

In normal man, the responses of the total cerebral blood flow (measured by the nitrous oxide technique of Kety and Schmidt 1945) to changes in the $PaCO_2$ have been variously reported as an increase of 75% when the $PaCO_2$ was raised from 43 to 52 mm.Hg (Kety and Schmidt 1948), an increase of 40% when the $PaCO_2$ was raised from 43 to 50 mm.Hg (Novack, Shenkin, Bortin, Goluboff and Soffe 1953), an increase of 10% when the $PaCO_2$ was raised from 39 to 45 mm.Hg (Patterson, Heyman, Battey and Ferguson 1955), and a decrease of 35% when the $PaCO_2$ was lowered from 45 to 26 mm.Hg (Kety and Schmidt 1948). Thus the percentage change in blood flow for every millimetre change in $PaCO_2$ over the range 26 to 52 mm.Hg from these studies was 8.3%, 5.7%, 1.7% and 1.8% respectively - a very considerable variation. In the animal experiments reported in this section the change in blood flow through the cerebral cortex was approximately 2.5% per mm. change in $PaCO_2$ over the range 30-50 mm.Hg.

Physiological limits of response to variations in $PaCO_2$.

The experiments presented here suggest that there is a lower limit of $PaCO_2$ beyond which the cerebral

vessels do not constrict further. In Fig.12 (page 64) there appears to be no further significant decrease in blood flow below a $PaCO_2$ of 20 mm.Hg. This finding is in agreement with the work of Noel and Schneider (1944), who reported no further decrease in blood flow estimated from the arterio-venous oxygen difference below a $PaCO_2$ of 20 mm.Hg.

Patterson and his co-workers (1955) have suggested that the response of the cerebral blood flow to hypercapnia is a threshold phenomenon and only occurs when the $PaCO_2$ has risen by more than 4 mm.Hg from the normal of 40 mm.Hg. This phenomenon was not noticed in the experiments reported in this thesis. From Fig.12 (page 64) there appears to be a continuous change in blood flow when the $PaCO_2$ is varied. However, the experimental error of the N_2O method used by Patterson is not precisely known and it is possible that a change in blood flow of about 8 - 10% (which might be expected for a $PaCO_2$ rise of 4 mm.Hg) could remain undetected.

Mechanism of Action.

It has been suggested that the purpose of the marked sensitivity of the cerebral blood vessels to carbon dioxide is to maintain homeostasis for tissue

PCO_2 (Lassen 1959). Any increase in cerebral neuronal activity will increase metabolism and produce more carbon dioxide. This will cause an increase in cerebral blood flow until tissue PCO_2 returns to normal levels. Similarly, a reduction in cerebral metabolism will cause a fall in tissue PCO_2 with resultant vasoconstriction. CO_2 will accumulate again until tissue PCO_2 returns to normal.

Although the inhalation of carbon dioxide is sometimes followed by a rise in arterial pressure, this is not a constant phenomenon and cannot explain the increase in cerebral blood flow. It has also been shown that the fall in arterial pH which accompanies a rise in $PaCO_2$ is not responsible for the increase in cerebral blood flow (Schieve and Wilson, 1953; Lambertsen et al, 1961).

As the response of the cerebral vessels to carbon dioxide is not affected by spinal transection, decerebration or cervical sympathectomy (Wolff, 1936), it is probable that carbon dioxide acts directly on the smooth muscle of the vessel wall (Sokoloff 1959).

Response to CO_2 in hypotensive states.

In Fig.16 (page 66) where the mean arterial blood

pressure was reduced to and maintained at 100 mm.Hg, the increase in blood flow on raising the $PaCO_2$ from 40 to 80 mm.Hg was only 50% compared with the 100% increase in the normotensive dogs. Similarly, there was considerably less reduction in flow with hypocapnia. This is even more strikingly shown in Fig.20 (page 67) where, at a mean arterial blood pressure of 50 mm.Hg, no change in flow occurred during either hypercapnia or hypocapnia. It has been shown directly and indirectly (Forbes, Nason & Wortman, 1937; Fog, 1938; Carlyle and Grayson, 1955; Rapela and Green, 1964; Harper, 1965) that the cerebral blood vessels dilate, possibly compensatorily, in response to a fall in arterial blood pressure. It seems reasonable to postulate that, in severe hypotensive states, the cerebral vessels, being already maximally relaxed, are unable to dilate further in response to increased $PaCO_2$.

The failure of the cerebral vessels to constrict when the $PaCO_2$ is lowered could indicate that in severe hypotension the maintenance of cerebral perfusion takes precendence biologically over the maintenance of a normal tissue PCO_2. This "over-ride" mechanism could be mediated through the tissue oxygen tension, which is

presumably low due to the inadequate blood flow, and could cancel the vasoconstrictive effect of hypocapnia.

Clinical applications of CO_2 response.

As cerebral blood vessels dilate when the $PaCO_2$ is increased, it might seem tempting to administer CO_2 in conditions where there is impairment of the cerebral blood flow - for instance, in haemorrhagic shock. However, it will be argued later (page 80) that it is only in severe hypotension that the cerebral blood flow becomes significantly reduced. Since it is precisely in those conditions of severe hypotension that CO_2 has no effect on the cerebral blood vessels (Fig.20 - page 67), it would appear that the administration of carbon dioxide in an attempt to increase cerebral blood flow in hypotensive shock is unlikely to be efficacious.

Similarly, in cases of focal ischaemia of the brain - caused for instance by thrombosis or embolism - one might consider the possibility of giving CO_2 in an attempt to produce vasodilatation. However, areas of focal ischaemia will already have a low perfusing blood pressure and a low tissue tension of oxygen * - both of

* (The effect of low PO_2 on cerebral blood flow is discussed on page 97).

which would have influenced the tone of the vessels in the ischaemic area. The administration of CO_2 would tend, therefore, to cause an increase in blood flow in the unaffected areas of the brain but offer little assistance to the ischaemic area, where the vessels will probably have undergone maximum vasodilatation in response to the stimuli of low blood pressure and low PO_2.

It appears then unlikely that CO_2 will be of much value in the therapy of local or general ischaemia of the brain. However, CO_2 has been reported to be of value in hastening the recovery from general anaesthesia (Sokoloff 1959). The increase in cerebral blood flow brought on by a rise in $PaCO_2$ is thought to help in "washing out" the anaesthetic from the cerebral tissues and also, by stimulating the respiratory centre, to assist in the pulmonary clearance of the anaesthetic.

CO_2 has also been used to delay the onset of unconsciousness following radial acceleration (positive g) (Van Middlesworth and Kline, 1948). However, it probably does this as much by its action on constricting peripheral blood vessels (Irving 1938), and thus preventing pooling of blood in the limbs, as by its effect on increasing cerebral blood flow.

The cerebral vasoconstriction which occurs on

lowering the $PaCO_2$ during overbreathing has an application in the field of neurosurgery. It has long been the practice of anaesthetists to hyperventilate their patients during neurosurgical operations in an endeavour either to minimise haemorrhage from the cut surface of the brain or to reduce the brain volume. However, the evidence presented here suggests that maximal cerebral vasoconstriction is achieved at a $PaCO_2$ of 20 mm.Hg and that it is probably unnecessary to reduce the $PaCO_2$ below this level.

Finally, the $PaCO_2$/blood flow response curves shown in Figs.12 and 16 (pages 64 and 66) do have one important application - in the field of experimental pharmacology.

In the past many reports on the effect of drugs (for instance anaesthetics or so-called cerebral vasodilators) on the cerebral circulation have been misleading and conflicting because of the failure of the investigators to realise the importance of the $PaCO_2$ on the cerebral circulation, and thus the difficulties in interpretation of cerebral blood flow values when the administration of a drug leads to changes in the $PaCO_2$. For instance, Himwich, Homburger, Maresca and Himwich (1947) claimed that barbiturates caused an

increase in blood flow. However, as McDowall (1965) has pointed out, the observed increase in blood flow is due to a rise in $PaCO_2$ secondary to respiratory depression, and that, if the $PaCO_2$ is kept constant, a decrease in cerebral blood flow follows the administration of barbiturates.

However, utilising CO_2/blood flow response curves at different blood pressures, it should be possible to correct or standardise blood flow values obtained under different $PaCO_2$ values to a predicted value occurring at a "normal" $PaCO_2$. An example of this can be seen in Table 2 (page 42) where flow results obtained at $PaCO_2$'s of 43, 46 and 47 mm.Hg have been standardised to the blood flow which would have been expected had the $PaCO_2$ been 40 mm.Hg. It was possible in this instance to compare the flow results between different areas of brain cortex under "standard" conditions and correct for the extraneous influence of slight differences in the $PaCO_2$.

THE INFLUENCE OF THE ARTERIAL BLOOD PRESSURE ON THE BLOOD FLOW THROUGH THE CEREBRAL CORTEX

Object:

Until fairly recently it "was believed that cerebral blood flow followed the mean arterial blood pressure more or less passively, and the stability of the cerebral circulation under physiological conditions reflected only the relative constancy of the arterial pressure maintained by the homeostatic pressor reflex mechanism" (Sokoloff 1959). That there might also be an intrinsic regulation of cerebrovascular tone was suggested by Fog (1934 and 1938) and by Forbes, Nason and Wortman (1937). These workers observed that the blood vessels of the pia mater constricted in response to a rise in arterial blood pressure and dilated in response to a fall in pressure.

Although more recent studies in man (summarised by Lassen 1959) seem to refute the idea of a passive pressure/flow relationship for the cerebral circulation, there is still disagreement regarding the precise rôle

of the arterial blood pressure in the control of the cerebral blood flow.

The experiments now reported were undertaken to measure the effect of gradual reduction of the mean arterial blood pressure on the blood flow through the cerebral cortex - under "normal" respiratory conditions (that is a $PaCO_2$ of 40 mm.Hg) and under conditions of hypercapnia (CO_2 being added to the respiratory mixture).

Method:

The experimental preparation has been described on pages 21 to 30.

The experiments were divided into two groups:

Group 1 - Blood pressure reduction during normocapnia.

The mean arterial blood pressure was gradually lowered in 8 dogs by bleeding the animals into a reservoir flask. The $PaCO_2$ was held between 30 and 40 mm.Hg by adjusting the respirator.

Group 2 - Blood pressure reduction during hypercapnia.

The $PaCO_2$ was raised to, and maintained at, 68-86 mm.Hg (mean values) by adding carbon dioxide to the anaesthetic mixture

in 4 dogs. The arterial blood pressure was then gradually lowered by bleeding into the reservoir flask.

Results:

Group 1 - Blood pressure reduction during normocapnia.

The results are given in Table 13 (page 146). Graphs of the blood pressure/blood flow relationship in each dog are shown on Fig.22 (page 155). A "blanket" graph of all the results in this group is shown on Fig.24 (page 81).

The $PaCO_2$ was held within fairly narrow limits for each dog. A metabolic acidosis developed in each animal as the blood pressure fell. The mean initial blood pressure from the experiments in this group was 155 mm.Hg. The mean $PaCO_2$ was 35.3 mm.Hg. Mean values of $PaCO_2$ for individual dogs ranged from 31.8 to 40.9 mm. Hg. The standard deviation of $PaCO_2$ for individual dogs ranged from 5.0 to 9.2% with an average of 6.6%.

From Fig.24 (page 81) it can be seen that the blood pressure could be lowered to approximately 90 mm.Hg without any marked change in blood flow. At lower blood

pressures, however, blood flow declined with blood pressure in a near-linear fashion.

Over a fairly wide range of blood pressure (from 90 to 180 mm.Hg) the blood flow remained relatively constant, despite a varying blood pressure. This phenomenon will hereafter be referred to as "autoregulation".

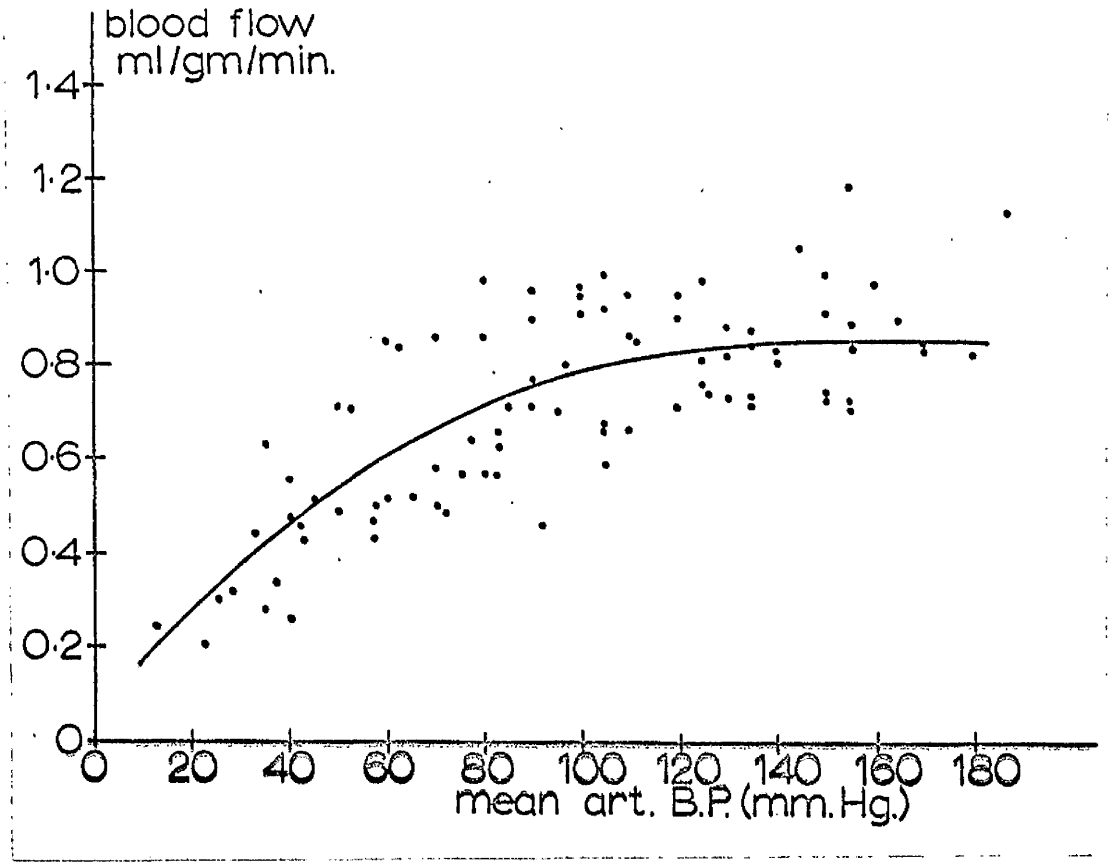

Fig.24 - Effect of alterations in systemic blood pressure on cortical blood flow in normocapnic dogs. Line is best polynomial fit calculated by digital computer - in this case a quadratic.

Group 2 - Blood pressure reduction during hypercapnia.

The results are given in Table 14 (page 148). Graphs of the blood flow/blood pressure relationship in each dog are shown on Fig.23 (page 155). A "blanket" graph of all the results in this group is shown on Fig.25.

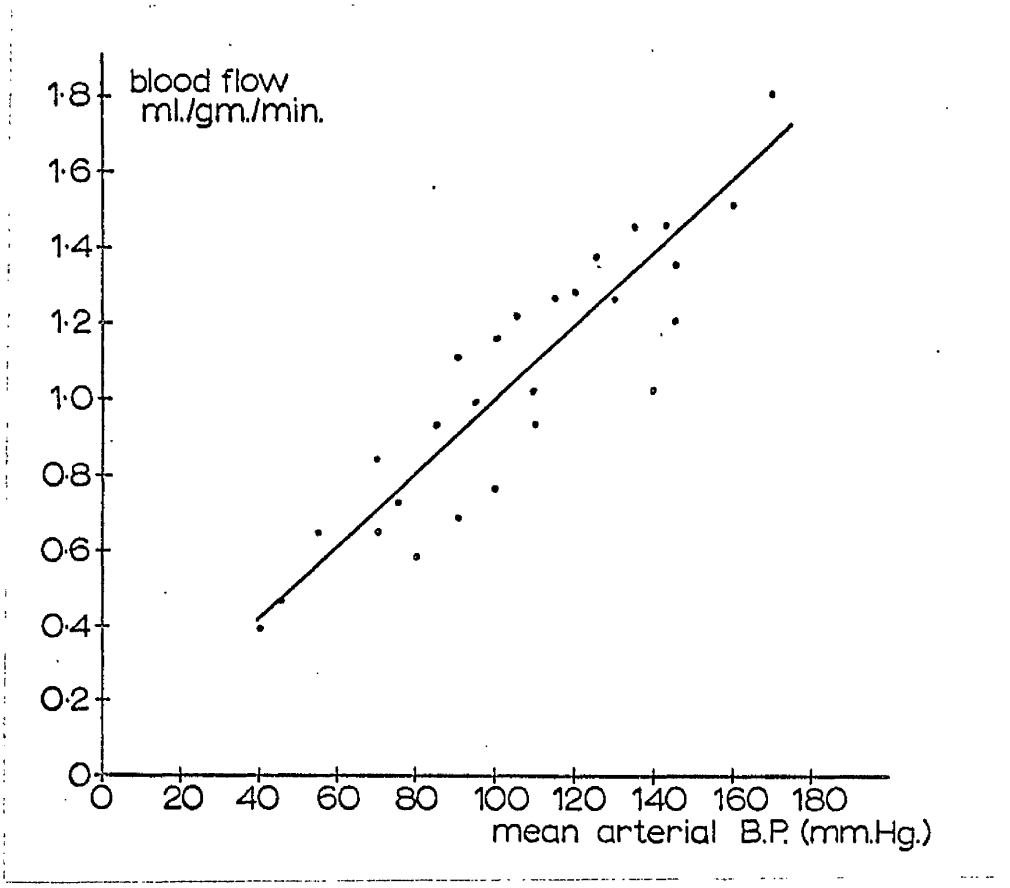

Fig.25 - Effect of alterations in systemic blood pressure on cortical blood flow in hypercapnic dogs. Line is calculated linear regression line.

The mean values for $PaCO_2$ for each of the 4 dogs in this group are 69, 83, 68 and 86 mm.Hg. (standard deviations 3.5%, 4.3%, 4.3% and 8.1%). From Fig.25 (page 82) it can be seen that blood flow declined linearly with blood pressure.

Discussion.

I would suggest that the experiments shown on Fig.24 (page 81) indicate the existence of a mechanism for "autoregulation" of blood flow in the face of moderate changes in the arterial blood pressure. This is in agreement with studies by Carlyle and Grayson (1955) who used a heat-clearance technique to obtain a qualitative index of the blood flow through the cerebral cortex in anaesthetised rabbits. These workers found that if the mean arterial blood pressure was lowered from the control level of approximately 90 mm.Hg to approximately 45 mm.Hg, there was no change in the heat clearance and, by inference, in the blood flow. More recently Rapela and Green (1964) estimated cerebral blood flow in dogs by measuring the venous outflow from the brain and found a marked autoregulatory response over the pressure range 90 - 50 mm.Hg. Unfortunately,

however, the authors do not report either the anaesthetic used or the $PaCO_2$ values obtained in their experiments.

However, other workers using isolated-head-perfusion techniques have denied the existence of autoregulation and have claimed that the cerebral blood flow is passively dependent on the perfusion pressure (Geiger and Magnes 1947, Sagawa and Guyton 1961). Factors which could have "masked" autoregulation in these studies must be considered.

Fig.25 (page 82) shows that autoregulation is abolished by hypercapnia. Presumably the explanation for this is that vessels already maximally or nearly maximally dilated by hypercapnia are unable to dilate further in response to a lowered blood pressure. A passive pressure/flow relationship will then be observed. In the papers cited above, very extensive surgical trauma was inflicted in isolating the cerebral circulation and fairly deep anaesthesia must have been required. In neither study was the $PaCO_2$ reported, but if it was elevated the resultant hypercapnic cerebral vasodilatation may have been sufficient to abolish or obscure autoregulation.

In the paper by Rapela and Green referred to on

page 83, autoregulation was observed in autoperfused isolated cerebral circulations but was not so apparent in artificially perfused preparations. The authors state that "The absence of (autoregulatory) response in some experiments may be explained by the vulnerability of blood vessel responses to traumatic, surgical or artificial perfusion procedures which appear to induce a near-maximal dilation."

It would appear then that, in the experimental animal, under "normal" physiological conditions, the calibre of the cerebral blood vessels tends to be adjusted to maintain a constant blood flow in the face of fairly wide fluctuations in the arterial blood pressure. However, under certain abnormal conditions, hypercapnia for instance, or probably any condition which produces near-maximal dilation, autoregulation is reduced or absent.

Mechanism of autoregulation.

In the studies of the pial blood vessels by * Fog (1938) in which vasoconstriction was demonstrated on raising the blood pressure and vasodilatation on lowering

* Fog's studies were first published in Danish ("Om piaarteriernes vasomotoriske reaktioner, Copenhagen, Munksgaard" 1934). I have preferred to quote from his later publications in the English language.

the blood pressure, the response was not affected by sectioning of the vagi, cervical sympathetic or the sinus and aortic nerves. This is beautifully demonstrated in Figs.26a and 26b (page 87) reproduced from Fog's paper.

It appears probable, therefore, that autoregulation is effected by some local intrinsic mechanism and not by nervous control from the sympathetic or parasympathetic nervous systems.

Lassen (1959) has suggested two possible mechanisms which could effect autoregulation of cerebral blood flow in response to changes in arterial blood pressure.

(1) The myogenic theory. Studies of segments of isolated arteries by Bayliss in 1902, suggested that alteration of intravascular pressure will produce an automatic response from the smooth muscle in the vessel wall - contraction in response to a rise in pressure and relaxation in response to a drop in pressure. As this property is seen in segments of vessel perfused in vitro, it appears to be independent of nervous mechanisms.

(2) The metabolic theory. Lassen suggested that alterations in vessel diameter following changes in blood pressure could be mediated secondarily through alterations in the tensions of oxygen and carbon dioxide in the blood and tissues.

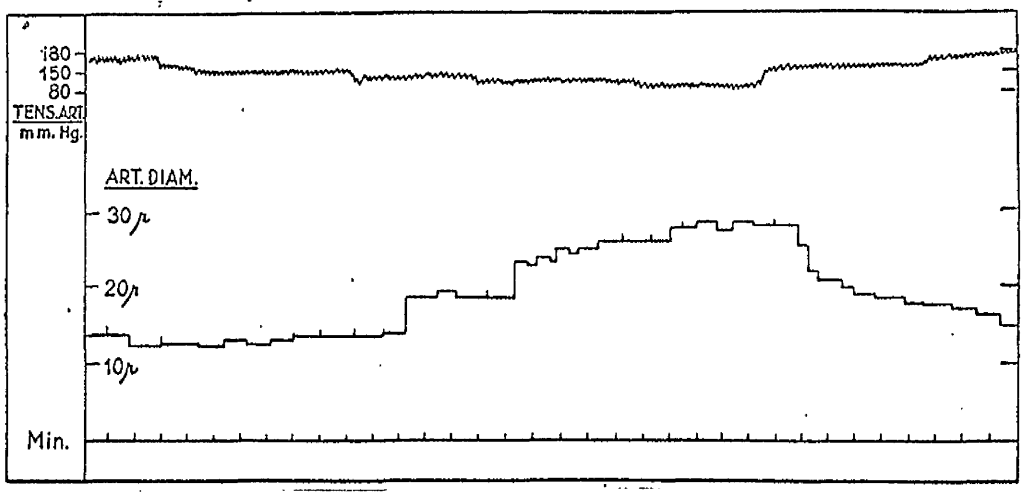

Fig.26(a) - Reactions of a pial precapillary arteriole during decrease and increase of blood pressure, induced by variation of circulating blood volume. The vagi, sinus, aortic nerves, and the cervical sympathetic trunk intact. (Fog 1938 - J.Neurol. Psychiat.)

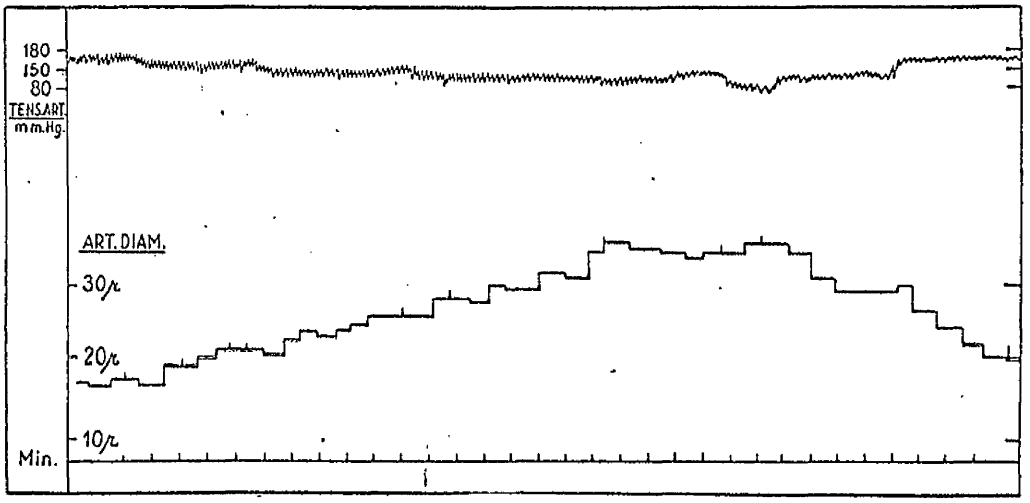

Fig.26(b) - Reactions of a pial precapillary arteriole during decrease and increase of blood pressure. The vagi, sinus and aortic nerves, and the cervical sympathetic trunk severed. (Fog 1938 - J. Neurol. Psychiat.)

One factor which might argue against the myogenic theory is the speed of response of the cerebral blood vessels to changes in blood pressure. Figs.26a and 26b (page 87) (Fog 1938) show that there is vasodilatation of the pial blood vessels following gradual reduction in the arterial blood pressure. However, Fog points out that following a sudden reduction in blood pressure, no vasodilatation is apparent for one or two minutes. Similarly, Schneider (1963) quotes Hirsch as demonstrating in the experimental animal that a sudden decrease in systemic blood pressure from 200 to 100 mm.Hg caused an immediate reduction in cerebral blood flow. More than two minutes later, however, the blood flow had almost returned to the control level. Rapela and Green (1964) have also reported a transient decrease in flow following a sudden drop in blood pressure, returning to control values, however, in only 30 seconds.

Now if the response of the cerebral blood vessels to a change in blood pressure was caused exclusively by a local myogenic reflex in the smooth muscle of the vessel wall, one might expect this to occur very rapidly and the response would be most unlikely to have a lag of some 30 seconds to 2 minutes.

On the other hand, a time lag might easily occur if

a metabolic factor were involved. The following sequence of events possibly offer a reasonable explanation of the phenomenon of autoregulation. A decrease in blood pressure is followed by a reduction in blood flow. Following this, the tension of oxygen in the tissues will fall progressively and the tension of carbon dioxide will rise. Both the low PO_2 and high PCO_2 will tend to cause cerebral vasodilatation with the eventual return of the blood flow to its initial value. Such a sequent of events could account for a slight time lag before the onset of autoregulation.

Unfortunately, there is little direct evidence on this question, for which an answer must await measurement of the tensions of O_2 and CO_2 in cerebral tissue during alterations in systemic blood pressure. However, studies by Carrier, Walker and Guyton (1964) have shown that there is a twofold increase in conductance in isolated strips of artery (0.5 - 1 mm. in diameter) perfused with blood, when the PO_2 of the perfusate was lowered from 100 to 30 mm.Hg - this response being relatively greater in the smaller than in the larger vessels. Similarly, it has been shown by in vitro experiments that CO_2 dissolved in Ringer solution dilates isolated strips of artery (Cow 1911).

If, then, one assumes that any decrease in blood flow which follows a sudden fall in pressure will result in a rise in tissue tension of CO_2 and a fall in tissue tension of O_2, and that this can have a local vasodilatory effect on cerebral arteries and arterioles, the metabolic theory of autoregulation becomes tenable and teleogically appropriate.

The absence of autoregulation in circumstances where there is pre-existing cerebral vasodilatation - e.g. during hypercapnia or hypoxia - does not negate this theory, but probably indicates that under these circumstances the vessels have reached their mechanical limit of dilation. As they can then respond no further to a reduction in blood pressure, a passive pressure/flow relationship is established.

Autoregulation in man.

Extensive studies of the response of the cerebral blood flow to changes in blood pressure have not been carried out in man due to ethical considerations and methodological difficulties. However, some studies on the effect of hypertension and drug induced hypotension have been reported. Lassen (1959) presented a graph of the pressure/flow relationship in man compiled from

seven different sources in the literature. This study showed that neither essential nor drug-induced hypertension (Moyer et al. 1953, Moyer and Morris 1954, Hafkenschiel et al. 1954, Moyer et al. 1954) nor hypertensive toxaemia of pregnancy, caused any significant difference in blood flow when compared with control groups of normal young men and normal pregnant women (Kety and Schmidt 1948, McCall 1953).

Similarly, moderate drug-induced hypotension was not associated with any significant change in blood flow (McCall 1953).

Lassen suggests that within a wide pressure range (approximately 60 to 170 mm.Hg) the calibre of the cerebral blood vessels can alter to compensate for changes in mean arterial blood pressure. It is only in severe hypotension - that is to approximately one-third of the normal level (Finnerty, Witkin and Fazekas, 1954) - that cerebral vasodilatation is insufficient to compensate for the low arterial blood pressure, and signs of cerebral ischaemia become apparent.

Additional studies in which measurements of cerebral blood flow were made with Kety's nitrous oxide technique before and after adrenalectomy, spinal sympathetic block, or the administration of hypotensive

drugs, have been reported, mainly in patients with pre-existing hypertension. These can be summarised as follows (pressures are mean arterial pressure):

1) Hafkenschiel et al. (1954) - Blood pressure lowered from 170 to 118 mm.Hg. No significant change in cerebral blood flow.
2) Bessman et al. (1952) - Blood pressure lowered from 133 to 87 mm.Hg. No significant change in cerebral blood flow.
3) Kleh and Fazekas (1956) - Blood pressure lowered from 158 to 98 mm.Hg. No significant change in cerebral blood flow.
4) Moyer et al. (1953) - Blood pressure lowered from 173 to 108 mm.Hg. No significant change in cerebral blood flow.
5) Stone et al. (1955) - Blood pressure lowered from 117 to 62 mm.Hg. No significant change in cerebral blood flow.

However, contradictory findings were reported by:

1) Crumpton et al. (1955) - Blood pressure lowered from 181 to 111 mm.Hg, accompanied by a 14% fall in cerebral blood flow.

2) Morris et al. (1953) - Blood pressure lowered from 104 to 63 mm.Hg, accompanied by a 30% fall in cerebral blood flow.

3) Kety et al. (1950) - Blood pressure lowered from 155 to 106 mm.Hg, accompanied by a 12% fall in cerebral blood flow.

In the last study the $PaCO_2$ fell by 5 mm.Hg, which could well account for the observed decrease in cerebral blood flow.

However, with the exception of the conflicting studies of Crumpton et al. (1955) and Morris et al. (1953) the weight of evidence seems to favour the existence of autoregulation in man. It appears that the mean arterial blood pressure can fall by at least one-third without affecting cerebral blood flow.

But before one assumes that the administration of hypotensive drugs or the use of hypotensive anaesthesia will not imperil cerebral blood flow, one important point must be considered. The animal experiments reported in this thesis demonstrate that, although the systemic blood pressure can be altered over a fairly wide range without affecting the cortical blood flow in <u>normocapnic</u> animals, there is a passive pressure/flow relationship in <u>hypercapnic</u> animals. Consider now a

patient who has relative ischaemia of a local area of brain. Within and around the local ischaemic area, the blood vessels will probably be dilated under the influenc of elevation of local cerebral tissue PCO_2 and reduction of tissue PO_2. This dilatation may well be sufficient to maintain a normal blood flow and the ischaemia will be "compensated". But if the pressure of the blood perfusing this area is now reduced, there will be a parallel reduction in local blood flow (there will be no autoregulation because of pre-existing vasodilatation) with the net result of an "uncompensated" ischaemia. This mechanism underlines the possible danger of administration of hypotensive drugs to cases with cerebral vascular disease.

DISCUSSION OF OTHER FACTORS WHICH HAVE BEEN IMPLICATED IN THE CONTROL OF CEREBRAL BLOOD FLOW

Although Part 2 of this thesis has been mainly concerned with the inter-relationship of arterial pH, $PaCO_2$ and blood pressure in the control of the cerebral circulation, it seems appropriate to discuss briefly the rôle of some other factors which have been thought to influence cerebral blood flow.

Neurogenic Control

The major cerebral arteries have an abundance of perivascular nerve fibres, both myelinated and unmyelinated. Sympathetic fibres, from the superior cervical and stellate ganglia, accompany the internal carotid and vertebral arteries into the skull (McNaughton, 1937). Forbes and Wolff (1928) have shown that stimulation of the cervical sympathetic causes slight constriction of the pial arteries. When the nerve is divided, however, the calibre of the vessels is not changed. On the other hand, neither stimulation nor extirpation of the stellate ganglion

had any effect on the pial vessels.

Studies in animals have indicated a slight reduction in blood flow in some but not all areas of the brain on stimulation of the cervical sympathetic (Schmidt, 1934, 1936); on the other hand, studies in the monkey,using a flowmeter on the carotid artery, have failed to confirm this (Dumke and Schmidt, 1943).

Unmyelinated fibres from the facial nerve have been shown to pass through the geniculate ganglion and form a plexus round the carotid artery (Chorobski and Penfield, 1932). Slight dilatation of the pial blood vessels has been noticed on stimulation of the fibres (Forbes, Nason and Wortman, 1937). Division of the nerve had no effect. The same workers noticed slight dilatation of the pial vessels following stimulation of the vagus, aortic and sinus nerves. However, this phenomenon may be due to a concomitant fall in arterial blood pressure (Lassen, 1959). Other studies (Schmidt, 1936) reported that there was no change in blood flow following stimulation of these nerves.

It would appear that although stimulation of the cervical sympathetic may cause slight cerebral vaso-constriction, and stimulation of the vagus slight dilatation, these nerves do not appear to exert a

significant effect on the overall control of the cerebral circulation. Whether or not the perivascular nerve fibres of the cerebral vessels play some rôle in the control of local blood flow, is as yet uncertain.

Oxygen.

The effect of hypoxia on cerebral blood flow is directly opposite to that of hypocapnia. A reduction of the inspired oxygen concentration to 10% increased the cerebral blood flow by 35 per cent in normal young men (Kety and Schmidt, 1948); in this study the $PaCO_2$ fell by 4 mm.Hg due to the associated overventilation. However, a further investigation in which $PaCO_2$ was held constant showed that the response of cerebral blood flow to the inhalation of 10 per cent oxygen remained the same (Turner, Lambertsen, Owen, Wendel and Chiodi, 1957).

It has been reported that elderly patients with cerebrovascular disease show a reduced response to hypoxia (Fazekas, Alman and Bessman, 1952). However, if the initially reduced blood flow is taken into account, the percentage increase in blood flow when the inspired oxygen concentration was reduced to 10% was approximately the same as in normal young men.

There appears to be a fairly high threshold for

the response of the cerebral blood flow to hypoxia. In dogs, Harper, McDowall and Jacobson (1966) report that no change in flow through the cerebral cortex is observed until the arterial oxygen saturation has fallen below 75 per cent (PaO_2 40 mm.Hg). Thereafter the blood flow increases as the saturation falls. At an arterial oxygen saturation of 35 per cent (PaO_2 20 mm.Hg) the blood flow is twice that of the control value. In man it has also been shown that cerebral blood flow is not affected by moderate variations in arterial oxygen content (Turner et al. 1957).

The rise in cerebral blood flow which accompanies hypoxia is an important homeostatic mechanism which permits the brain to tolerate moderate degrees of hypoxaemia. However, it has been shown in man that although the oxygen uptake of the brain is not altered on the inhalation of 10 per cent or 8 per cent oxygen, symptoms of mental disturbance were present (Kety and Schmidt, 1948b). The authors suggested that this was due to a reduction in mean arterial tissue PO_2 affecting some cerebral oxidation processes which were forced to operate at a lower oxygen tension, even though the total oxygen consumption of the brain was unchanged. Alternatively, only localized areas of the brain might

be affected by the reduction in PaO_2, while the total oxygen uptake apparently did not alter.

The effect of increased partial pressures of oxygen on cerebral blood flow is at present of considerable interest because of the increasing use of pressure chambers. The administration of 85-100 per cent oxygen at one atmosphere has been shown to cause a 13 per cent reduction in total cerebral blood flow in normal young men at a constant $PaCO_2$ (Kety and Schmidt, 1948b). Similarly, Lambertsen et al. (1953) found a 15 per cent drop in cerebral blood flow when breathing oxygen at 1 atmosphere. At 3.5 atmospheres of oxygen the same authors found a 25 per cent decrease in blood flow as compared with the control values when their patients were breathing air. However, there was a concomitant fall in the $PaCO_2$ of 5 mm.Hg and they suggested that the decrease in cerebral blood flow was due in part to the fall in $PaCO_2$. More recently, Jacobson, Harper and McDowall (1963b) measured the blood flow through the cerebral cortex in dogs at 1 and 2 atmospheres of oxygen, while maintaining a constant arterial PCO_2 by adjusting the ventilation. These workers found that at 1 atmosphere of oxygen the blood flow was reduced by 12 per cent and at 2 atmospheres by 21 per cent compared

with the control values on air. In these experiments there was no significant alteration in arterial pressure or $PaCO_2$.

It appears, then, fairly well established that increased partial pressures of oxygen result in cerebral vasoconstriction. This is possibly a further homeostatic mechanism which tends to maintain tissue PO_2 within normal limits, and so to mitigate possible harmful effects of high pressures of oxygen on the central nervous system.

However, in hypotensive states this mechanism does not appear to operate. A recent study has shown that in dogs rendered hypotensive by bleeding to an arterial blood pressure of 50 mm.Hg, the administration of oxygen at 2 atmospheres had no effect on blood flow through the cerebral cortex (Harper, McDowall and Ledingham, 1965). The oxygen uptake of the cortex, however, was restored to normal levels.

Venous Pressure.

As the cerebral venous pressure is comparatively low, it can be assumed to contribute little to the regulation of cerebral blood flow under normal circumstances. But when coughing or straining at stool,

there is considerable elevation in venous pressures, which might affect cerebral blood flow. Moyer, Miller and Snyder (1954), however, have raised the internal jugular venous pressure in man to 23 cm. H_2O without producing any significant alteration in cerebral blood flow. More recently, Jacobson, Harper and McDowall (1963a) have measured blood flow through the cerebral cortex in dogs before and during constriction of the superior vena cava. Following this procedure, the pressure in the sagittal sinus rose as high as 52 cm. H_2O in one experiment, and to 30 cm. H_2O on average. It was observed that in each experiment there was a slight increase in cortical blood flow following caval compression. The results showed a wide scatter and the experiments were difficult to interpret, but they suggested that there may be autoregulation of cerebral blood flow in response to fluctuations in venous pressure.

Intracranial Pressure.

It might be expected that alterations in cerebrospinal fluid pressure would affect the cerebral blood vessels - a rise in pressure producing constriction and a fall dilatation. However, the distending pressure of the cerebral arteries must depend on the counter-action

of the intravascular and extravascular pressures. Thus, when assuming the erect posture, the cerebrospinal fluid pressure will fall, but the arterial blood pressure will also be reduced, with the result that the distending pressure of the cerebral vessels and the cerebral blood flow are unchanged (Scheinberg and Stead, 1949).

It has been shown (Fog, 1934) that a rise in cerebrospinal fluid pressure can cause dilatation of the pial vessels - presumably an autoregulatory mechanism maintaining a constant blood flow. However, if the rise in cerebrospinal fluid pressure is accompanied by a simultaneous rise in arterial pressure, the diameter of the cerebral vessels and the blood flow will remain unaltered.

Kety, Shenkin and Schmidt (1948) have investigated the effect of increased cerebrospinal fluid pressure due to intracranial lesions on cerebral blood flow. They observed that at pressures up to 45 cm. H_2O there was no significant change in cerebral blood flow, but that the increase in cerebrospinal fluid pressure was accompanied by an increase in arterial pressure. Above the critical level of 45 cm. H_2O, however, marked reductions in blood flow were observed.

Temperature.

Cerebral blood flow falls with reduction in body temperature. Rosomoff (1956) has reported that the cerebral blood flow in dogs fell by 6-7 per cent per degree Centigrade fall in temperature. An approximate reduction of 50 per cent in cerebral blood flow when the body temperature is reduced to 28°C has been reported by other workers in animal studies (Kleinerman and Hopkins, 1955; Loughead and Kahn, 1955). Similar results have been obtained in man (Albert and Fazekas, 1956).

It could be argued that the fall in cerebral blood flow during hypothermia is due to an associated fall in arterial PCO_2 which accompanies the lowered metabolism of the body. However, in a recent animal study (Forrester, McDowall, Harper and Nisbet, 1964) the $PaCO_2$ was kept constant during cooling by adding carbon dioxide to the anaesthetic mixture. Even under these circumstances the cerebral blood flow fell appreciably and it appears possible that cold has a direct effect on the cerebral blood vessels.

Conclusion.

A study of the factors controlling the circulation through the brain suggests that the cerebral blood flow

is adapted to maintain a constant "milieu intérieur" for the brain tissue. There appears to be an intrinsic mechanism of control of the diameter of the cerebral blood vessels which maintains a constant blood flow in the face of fluctuations in arterial, cerebral venous, or cerebrospinal fluid pressures. It is only under conditions of fairly extreme change in pressure that the vessels fail to compensate, resulting in a fall in cerebral blood flow.

The blood gases exert a powerful influence on the cerebral circulation; hypercapnia and hypoxia cause an increase in cerebral blood flow, while there is a decrease with hypocapnia and hyperoxia. However, the normal effects of changes in concentration of the blood gases may be absent under certain physiopathological conditions - extreme hypotension for instance. The teleological significance of the response of the cerebral circulation to the blood gases would appear to be, firstly, the maintenance of a constant tissue environment of carbon dioxide and oxygen, and, secondly, an adjustment of blood flow to meet any increase in metabolic requirements - presumably mediated through the increase in tissue carbon dioxide production.

Summary of Part 2.

The principal object of Part 2 of this thesis was the study of the inter-relationship between the arterial carbon dioxide tension and blood pressure in the control of blood flow through the cerebral cortex. Using a standard experimental preparation, in which other variables such as arterial oxygen tension and body temperature were kept constant, the arterial PCO_2 was altered in dogs at normal and low arterial blood pressures, and the mean systemic blood pressure was altered in dogs at normal and elevated arterial tensions of carbon dioxide.

From these experiments the following conclusions were drawn:-

1) In normotensive animals a rise in arterial carbon dioxide tension resulted in an increase in cortical blood flow, and a fall in arterial carbon dioxide tension resulted in a decrease in blood flow. The $PaCO_2$/blood flow response curve was found to have a sigmoid shape and there appeared to be upper and lower limits of $PaCO_2$ beyond which the blood flow did not change.

2) In moderately hypotensive animals (hypotension induced by haemorrhage), changes in blood flow in response to changes in $PaCO_2$ were much less than those observed in normotensive animals. In severely hypotensive animals alteration in $PaCO_2$ had no effect on the cortical blood flow.

3) In normocapnic animals, autoregulation of cortical blood flow in response to a reduction in the mean systemic blood pressure was observed. The arterial blood pressure (as measured in the iliac artery) could be reduced from the mean control value of 155 mm.Hg to 90 mm.Hg without affecting the blood flow. At lower pressures, blood flow declined with blood pressure.

4) In hypercapnic animals there appeared to be a linear relationship between blood flow and blood pressure.

The significance of these observations in the interpretation of the values obtained for cerebral blood flow in various experimental and clinical situations has been discussed.

As the pH of the arterial blood was an uncontrolled

variable in the studies on the effects of changes in $PaCO_2$ and blood pressure on the cortical blood flow, experiments were designed to test the effect of changes in arterial pH on the blood flow. It was found that when the arterial blood pressure and carbon dioxide tension were kept relatively constant, changes in blood pH per se had no effect on cortical blood flow.

Mention is also made of other factors which could be of importance in controlling cerebral blood flow. These include the sympathetic and parasympathetic nerve supply, cerebral venous pressure and cerebrospinal fluid pressure, blood content of oxygen and body temperature.

PART 3.

ADAPTATION OF THE INERT GAS CLEARANCE METHOD TO THE MEASUREMENT OF BLOOD FLOW THROUGH THE CEREBRAL CORTEX IN MAN

APPLICATION OF THE INERT GAS CLEARANCE METHOD TO MAN.

Introduction.

The technique for the measurement of blood flow through the cerebral cortex described in Section 1, depended on the measurement of the beta emissions of Krypton 85 from the exposed cortex. The method is therefore unsuitable for clinical use, except in the operating theatre. In 1963 the author of this thesis, in collaboration with Mr. H.I. Glass of the Western Regional Physics Department, reported what I believe to be the first measurement of blood flow in the cerebral cortex through the intact skull in man (Glass and Harper 1963). The isotope used was the inert radioactive gas Xenon 133. The principle of the method is the same as described for the measurement of blood flow in the exposed cerebral cortex (page 7). Xenon 133 dissolved in saline was injected into the internal carotid artery in anaesthetised patients and the level of radio-activity in the brain measured by counting the gamma radiation through the intact skull with a scintillation crystal.

The mathematical proof of the inert gas clearance

method (page 15) depended on the presence of equal concentrations of the isotope and equal partition coefficients in the various tissue components of the cortex. Evidence was presented that this was true for Krypton 85 when only beta radiations were recorded from the cerebral cortex.

However, if gamma emissions are detected, radioactivity will be recorded from both cortex and the white matter lying beneath it. Not only do grey and white matter have different partition coefficients for both Krypton (Lassen and Munck 1955) and Xenon (Veall and Mallet 1965) but as the blood flow ratio of grey to white matter is approximately 5:1 (Kety et al. 1955), it would also be extremely difficult to ensure uniform distribution of the isotope between grey and white matter. As a non-uniform distribution of the gas in the brain would introduce errors into the calculation of blood flow from the initial slope of the clearance curve, an attempt was made to localize the counting area to cerebral cortex by means of a depth-focusing collimator.

Choice of isotope.

Although Krypton 85 emits 0.5% of gamma radiations which can be used to record cerebral radioactivity with

external counting (Lassen and co-workers 1963), the comparatively high energy of the gamma rays (510 KeV) make it unsuitable for localising in depth.

However, the inert radioactive gas Xenon 133 (half life 5.2 days) emits low energy gamma rays of only 81KeV which are more readily absorbed by tissue. It was thought that this property of Xenon 133 could be utilised in order to record radioactivity mainly from the outer layers of the brain and thus permit calculation of blood flow through the cerebral cortex.

Detection of radioactivity.

The level of radioactivity in an area of the cerebral cortex was detected by means of a scintillation crystal, in front of which was mounted a depth-focusing collimator. A cross-section of a very simple collimator is shown diagrammatically in Fig.27 (page 112). It consists of a lead disc $\frac{1}{2}$ in. thick in which a circular tapered channel has been cut. Radioactive emissions can reach the crystal only through this channel. The maximum efficiency of counting comes from the area of cortex completely enclosed by the dotted lines. Outside the radiating lines some radioactivity will be recorded on a more limited area of the crystal but its effect will be reduced by distance and by

absorption in tissue.

The collimator used in patients was designed by Mr. H.I. Glass and has been fully described elsewhere (Glass 1964). It was similar in principle to that shown in Fig.27 but had twin channels consisting of two segmented tapered circular annuli cut in a ½ inch lead disc. This was mounted in front of a sodium iodide scintillation crystal 5 inches in diameter and ¼ inch thick. The exposed area of the crystal was equivalent to the unobstructed area of an 0.85 inch diameter crystal An end view of the collimator is shown in Fig.28 (page 113).

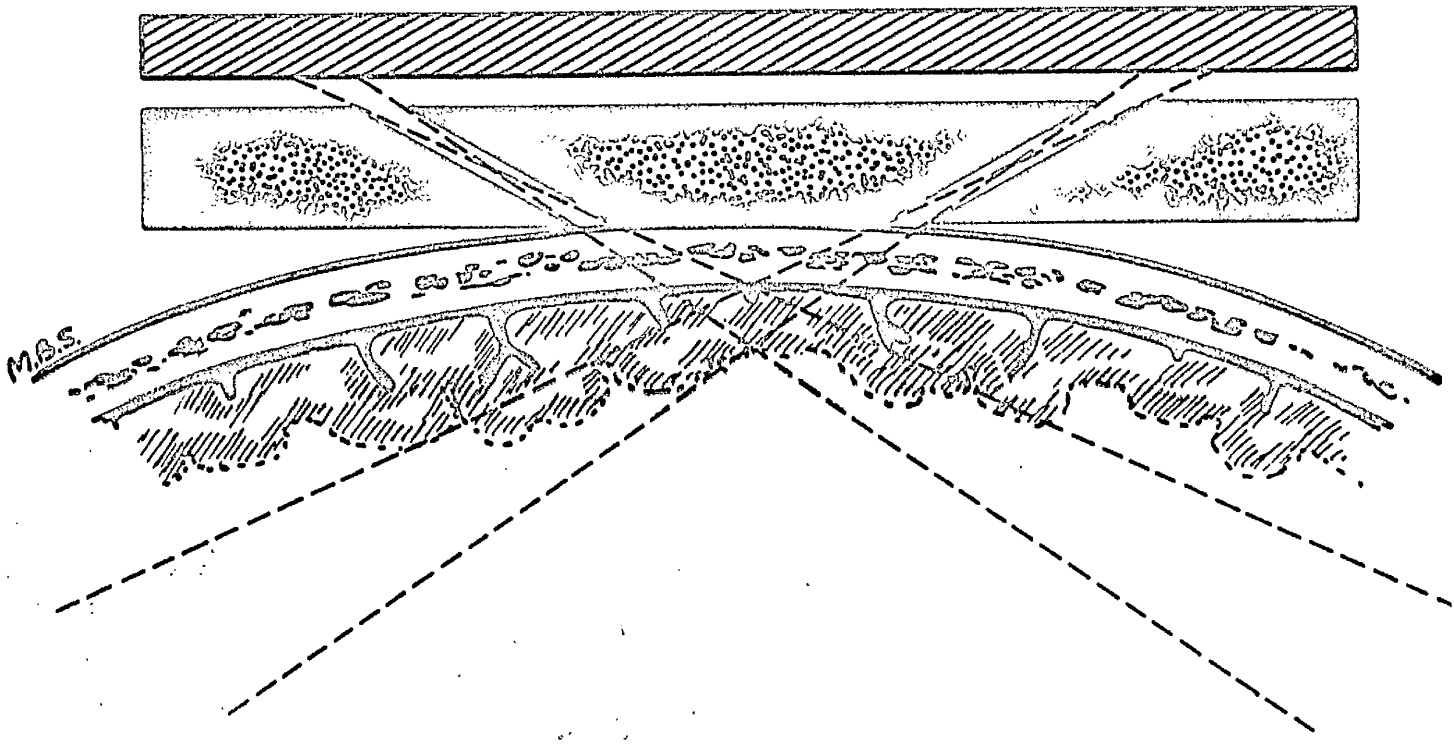

Fig.27 - Diagrammatic representation of simple collimator - see text (page 111).

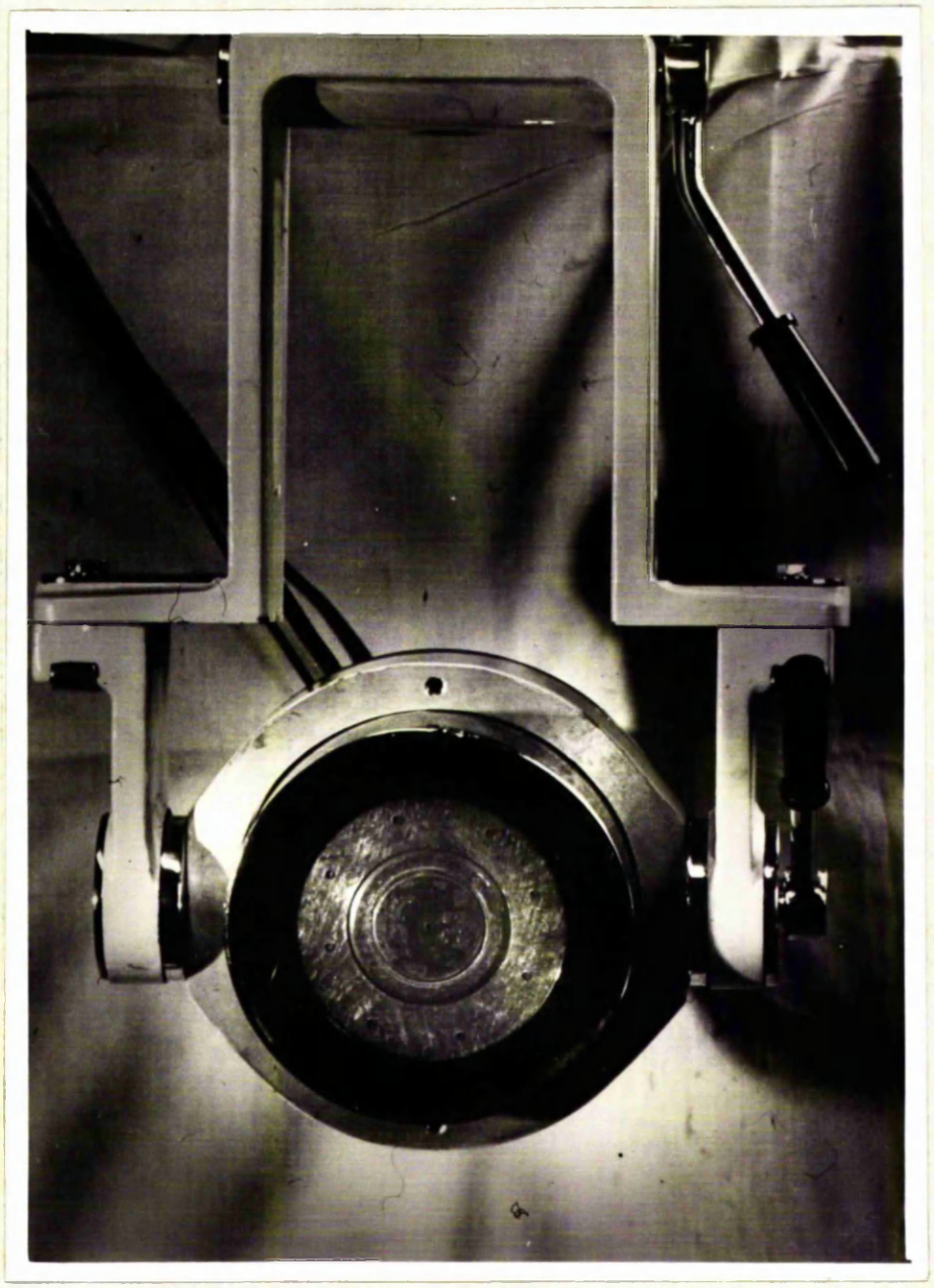

Fig.28 - End view of collimator. The scintillation crystal and photo-multiplier are mounted behind.

Collimator Characteristics.

The following is taken from a report by Glass (1964):

> "The maximum response of the detector to a point source of Xenon in air occurred 1.75 cm. from the collimator face on the central axis. The width of the central axis response curve at 10% and 1% of the maximum response was 1.4 cms and 2 cms respectively. If the point was moved 2 cms from the central axis the maximum response was 10%.
>
> If these measurements were repeated with a point source of Xenon in a water-filled skull, the width of the central axis response at 10% and 1% of the maximum was 1.4 cms and 3.5 cms respectively. However, due to absorption of the Xenon in the fluid, the off-axis response was reduced to 6.5%."

Discussion on efficiency of collimator.

The measurements cited above were made with a point source of radioactivity, whereas a collimator placed over the brain will view a diffuse source of radioactivity. This will therefore make the collimator less efficient

in practice at localizing radioactivity in depth than might have been expected from the calibration figures using a point course.

Glass calculated that if one assumed a uniform distribution of activity in the tissue "seen" by the collimator, 50% of the total response would be due to a tissue cylinder of radius 2 cms and depth 1.5 cms from the top of the brain surface with the outermost layers (i.e. cortex) playing a dominant rôle during the initial part of the clearance curve.

However, as the grey matter has a much faster blood flow than the white matter, the concentration of radioactivity in grey matter after a rapid injection of Xenon would be very much greater than that in white matter. Glass calculated, therefore, that with the collimator of his design, the effect on the initial slope of the clearance of Xenon 133 from the brain which could be attributed to clearance from white matter was only 5 to 10%. With a longer injection of, say, 100 secs., the effect would be correspondingly greater and might be as high as 20%. In calculating this figure, he assumed (a) that the blood flow through the grey matter was 5 times as great as flow through white matter (Kety and co-workers 1955), and (b) that the brain consisted

of 60% grey matter (Rose 1935).

Therefore, although the collimator is efficient at focusing in depth when calibrated against a point source of radioactivity, it is not nearly so effective when viewing a diffuse source of radioactivity; and therefore the initial slope of a clearance curve of Xenon 133 will reflect mainly cortical blood flow, not so much because of the collimator but more because of preferential "loading" of the cortex with radioactivity (due to its blood flow being much more rapid and more generous than that of the underlying white matter).

Radiation hazard.

Xenon 133 is cleared very rapidly from the lungs and its biological half-life is a matter only of minutes. The radiation dose to the lungs for a two-minute re-breathing of a concentration of Xenon of 1 mc./litre of inspired air is 70 millirads and the dose following an intravascular injection of 0.5 mc. is much smaller (Matthews, Fowler, and Turner, 1962). Patients undergoing cerebral angiography would have about 20 skull radiographs taken, with a radiation dose to the skull many times more than the radiation received for each injection of Xenon 133.

As the expired gas from the patient is led to the outside atmosphere, the radiation hazard to persons in the theatre is negligible.

Method of measurement of cortical blood flow in man.

Xenon 133 was received in 100 mc. doses in a sealed glass ampoule. This was connected to a glass reservoir which had been previously evacuated with a vacuum pump. On breaking the seal, the gas entered the reservoir and the remaining space was filled with normal saline. Aliquots of the solution, each of 20 ml., were withdrawn into syringes. Each syringe contained approximately 0.5 - 1 mc. of radioactivity.

Measurements of cortical blood flow were made on anaesthetised patients undergoing cerebral angiography for suspected intracranial lesions. Anaesthesia was induced with thiopentone and maintained with 75% N_2O and oxygen. D-tubocurarine (15-25 mg.) was administered for initial endotracheal intubation and additional doses of 10 mg. were given as required to allow intermittent positive pressure ventilation with a Barnett ventilator. This ensured control of the $PaCO_2$. An open circuit was used and the expired gases led to the outside atmosphere through a thick-walled plastic

tube.

The detector consisted of the focusing collimator, a 5-in. diameter sodium iodide crystal, and a photo-multiplier. The last was connected to a ratemeter and direct writing recorder. The focusing collimator was mounted in front of the crystal and localized the area of cortex under view. The collimator was lowered by a special stand on to the patient's scalp, when the centre of the collimator lay above the posterior part of the frontal cortex.

After percutaneous puncture a catheter was inserted into the internal carotid artery via the common carotid artery. The position of the catheter was confirmed by radiography.

About 10-15 ml. of the saline solution of Xenon 133 was injected, rapidly at first, then more slowly into the cannula over approximately 100 seconds. On completion of the injection, a clearance curve was obtaine on the recorder. This was transposed on to semi-logarithmic paper and the flow calculated from the half-life of the initial slope of the clearance curve, using the formula, flow (ml./g./min.) = $\frac{\lambda \log_e 2 \times 60}{T\frac{1}{2}}$ (see page 20), where $T\frac{1}{2}$ = half-life in seconds of the initial slope of the clearance curve and λ = brain-blood

partition coefficient for Xenon 133. The value used for the latter was 0.80 (Mallet and Veall, 1963). A sample of blood was taken from the carotid artery after each flow estimation, for the measurement of the arterial carbon dioxide tension on the micro-Astrup apparatus (Siggard Andersen, Engel, Jørgensen, and Astrup, 1960).

Results.

Measurements of blood flow through the postero-frontal cortex were made in seven patients undergoing cerebral angiograms. Four of the patients had normal angiograms, one had an aneurysm of the basilar artery, one a small subdural haematoma, and one a right parietal tumour. In five of the patients duplicate determinations were made, before and after passive hyperventilation, with the Barnett ventilator. Fig.29 (page 120) shows the clearance curves obtained from one patient during "normal" ventilation and hyperventilation. The results of measurements in the seven patients are listed in Table 15 (page 121). There appears to be a wide scatter of values but these relate extremely well to changes in arterial PCO_2. In Table 16 (page 122) the flow measurements have been divided into two groups,

those measured at arterial PCO_2 values greater than 35 mm.Hg and those less than 30 mm.Hg. (The second result from one patient has been excluded, as no $PaCO_2$ value was obtained). The mean value for flow measurements at a mean $PaCO_2$ of 43 was 0.77 ml./g./min. At a mean $PaCO_2$ of 25 mm.Hg, the mean flow value is 0.45 ml./g./min.

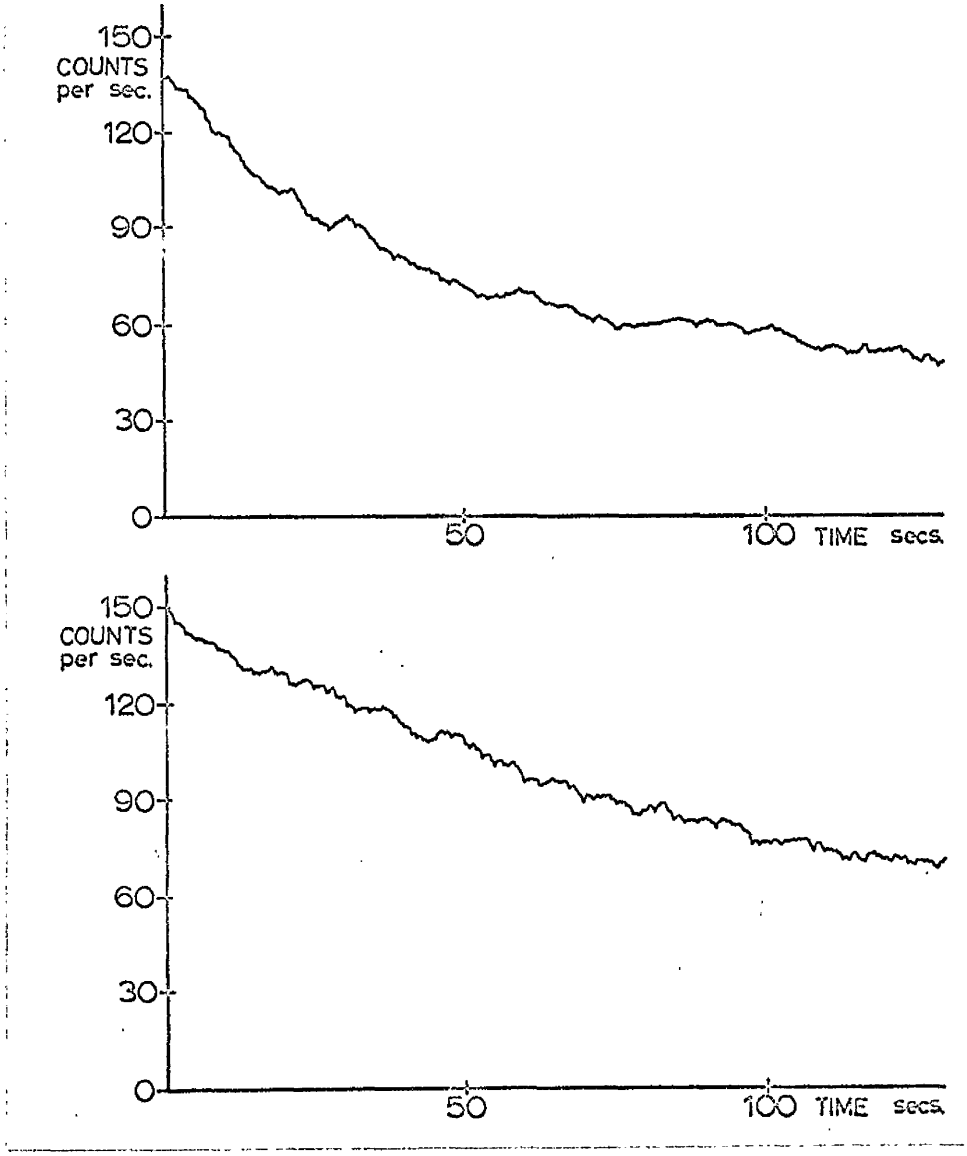

Fig.29 - Clearance curves obtained during normal ventilation and following hyperventilation. Blood flow is calculated from a semi-logarithmic plot of these curves following subtraction of background radioactivity.

Patient	Arterial PCO_2 (mm.Hg)	Blood Flow (ml./g./min.)	Angiogram
G.G.	35	0.65	Aneurysm basilar artery.
F.B.	42	0.76	Normal
	20	0.44	
W.I.	27.5	0.44	Normal
A.S.	29.5	0.52	Subdural haemotoma.
	19.5	0.38	
A.B.	27.5	0.53	Right parietal tumour.
	-	0.28	(glioblastoma)
B.G.	56	0.92	Normal
	30	0.38	
F.R.	40	0.75	Normal
	20	0.44	

Table 15 - Results of blood flow through brain cortex and arterial carbon dioxide tension in subjects studied.

	Group 1 (PCO_2 > 35)		Group 2 (PCO_2 < 30)	
	Flow	PCO_2	Flow	PCO_2
	0.65	35	0.44	20
	0.76	42	0.44	27.5
	0.92	56	0.52	29.5
	0.75	40	0.38	19.5
			0.53	27.5
			0.38	30
			0.44	20
Mean	0.77	43	0.45	25
S.D.	0.11	9	0.006	5
Coefficient of variation (1%)	14.5	21	13.3	20

Table 16 - Blood flow results at carbon dioxide tensions greater than 35 mm.Hg and less than 30 mm. Hg.

Discussion.

Arterial recirculation.

The discussion on the validity of the Krypton 85 clearance method in Part 1 of this thesis is relevant to the results obtained with Xenon in man. However, one

point of difference between Krypton and Xenon must be emphasized. The air-blood partition coefficient for Krypton is 20:1, while for Xenon only 10:1 (Veall and Mallett 1965). Therefore, Xenon will not be excreted so efficiently in a single cycle through the lungs as Krypton and there is thus more likelihood of arterial recirculation with subsequent distortion of the clearance curve. It was found that intravenous injections of Xenon 133 over 100 seconds gave a maximal count rate over the brain of 5% of that obtained when the same quantity of the isotope was injected into the carotid artery. The net effect of this recirculation is that flow values calculated from the initial slope of the clearance curve will err slightly on the low side. In patients with lung damage, however, the problem of recirculation will be very much greater and may significantly affect the flow values. Care was taken, therefore, to use the method only on patients with clinically normal lung function.

Radiation from extracerebral sources.

In the measurements reported in Table 15 (page 121), the injections of Xenon 133 were made into the internal carotid artery, thus preventing any distortion of the

clearance curve by radiation from extracerebral tissues, as would occur with injections made into the common carotid artery as employed by some subsequent workers (Lassen et al. 1963).

Estimates of cortical blood flow.

There was no significant difference in the blood flow results between patients with normal and those with abnormal angiograms. However, these patients were carefully selected beforehand on the grounds that they were fully conscious, rational and had minimal clinical symptoms. In addition, measurements were made at some distance from the lesion. The blood flow estimations at a mean arterial PCO_2 of 43 mm.Hg gave a value of 0.77 ml/gm./min. However, this is likely to be an under-estimate of cortical blood flow due to some radioactivity being recorded from cerebral white matter (see page 115) and due to slight arterial recirculation. The exact error is difficult to determine but the flow values given in Table 15 (page 121) are probably under-estimated by 10 to 20%.

External counting of the gamma emissions of Krypton 85 has been used by Lassen and co-workers (1963) to

determine cerebral blood flow. The method used was to give a very rapid injection of the isotope and to separate the clearance curve into two exponential components, one with a fast rate of clearance and the other with a much slower rate of clearance. Ingvar, Cronquist, Ekberg, Risberg and Høedt-Rasmussen (1965) have suggested tentatively that these may represent grey and white matter and the blood flow calculated separately for each. Although there is, as yet, little experimental evidence for such an assumption, the value they attribute to the blood flow for cerebral grey matter (0.79 ml/gm./min) in conscious human volunteers agrees closely with that found in the anaesthetised patients reported in the present studies.

Results in Hyperventilated Patients.

The results shown in Table 16 (page 122) show that the method is sufficiently sensitive to detect changes in blood flow. The cortical blood flow fell by 42% on lowering the $PaCO_2$ from 43 to 25 mm.Hg (mean values). This corresponds to a change of 2.3% in the blood flow per millimetre change in PCO_2 compared with the 2.5% change per mm. PCO_2 found for cortical blood flow in

the animal experiments (page 70). It appears, therefore that although the absolute values for cortical blood flow using Xenon 133 may err on the low side, the method can detect relative changes in blood flow which approximate closely to those found in the animal experiments.

Possible Clinical Applications.

Besides experimental applications in the investigation of the effect of vasodilator drugs and anaesthetics on the cerebral blood flow, the Xenon 133 clearance method has potential value as a diagnostic and investigative tool in the clinical field.

It could have particular value in circumstances in which a change in blood flow affecting only one area of the brain is suspected. The method is at present being used in the Neurosurgical Unit, Killearn Hospital, Glasgow to study two conditions which illustrate this point. Firstly, it is being used to find out if there is any diminution in blood flow in patients with carotid artery stenonis, and whether there is any change in blood flow following disobliteration of the stenosed vessel. And secondly, the method is being used as a test of the adequacy of the collateral circulation

before ligation of the carotid artery for certain intracranial aneurysm. During test periods of carotid artery occlusion in the operating theatre, patients who suffer a serious reduction in cerebral blood flow can be recognized and carotid ligation, with the risk of subsequent hemiplegia, avoided.

As the method requires an injection into the carotid artery, measurements of blood flow using Xenon 133 are best combined with angiography and can be used to give information on the blood flow through the cortical tissue, which could be a valuable supplement to the information on the cerebral circulation provided by angiography.

SUMMARY OF PART 3.

The radioactive inert gas clearance method for the measurement of cortical blood flow described in Part 1 of this thesis was adapted for use in man by substituting the gamma emitting isotope Xenon 133 for Krypton 85, thus making it possible to record the level of radio-activity in the brain by means of external counting. An attempt was made to localize the area of brain recorded from by means of a depth-focusing collimator.

Quantitative measurements of local blood flow in the cerebral cortex through the intact skull were made in anaesthetised patients undergoing carotid angiography. Blood flow was calculated from the rate of clearance from the cortex of Xenon 133 following its injection into the carotid artery. The values obtained in patients during normal ventilation and hyperventilation were reported. A mean value for cortical blood flow of 0.77 ml/gm./min at a $PaCO_2$ of 43 mm.Hg was found. Reasons are given why this value was thought to be a slight under-estimate. However, it was observed that the method could detect the changes that took place in blood flow when the carbon dioxide tension of the arterial blood was altered.

The method could very easily be employed in cases undergoing angiography as a routine diagnostic procedure in the assessment of cerebro-vascular disorders, and might well furnish valuable supplementary information.

CONCLUSION

Part one of this study described a technique for the calculation of blood flow through the cerebral cortex based on the measurement of the rate of clearance from the cortex of an inert radioactive gas Krypton 85. The validity of the method was established in animal experiments. The mean value for blood flow obtained in dogs under standard experimental conditions was found to be 0.93 ml. per gram of cortical tissue per minute.

Part two reports experiments designed to elucidate some aspects of the "intrinsic control" of the cerebral circulation. It was observed that cortical blood flow could be altered by changing the carbon dioxide tension of the arterial blood. However, in conditions of arterial hypotension this phenomenon was reduced or absent. It was established that there was "autoregulation" of cortical blood flow in response to changes in the systemic blood pressure. The absence of autoregulation in conditions of hypercapnia was noted. These experiments suggested a sensitive mechanism for the maintenance of a constant "milieu

intérieur" for the brain tissue.

Part three describes an adaptation of the inert gas clearance method to the measurement of blood flow through the cerebral cortex in man. The mean for blood flow was 0.77 ml/gm./min. The method proved sufficiently sensitive to detect induced changes in blood flow and is thought to have a potential clinical application.

T A B L E S

&

F I G U R E S

TABLE 4.

Repeated estimations under constant experimental conditions.

Experiment No.	Time (mins)	B.P. (mm.Hg)	PCO_2 (mm.Hg)	Flow (ml/gm/min)
1.	0	160	41.0	1.05
	95	160	38.0	0.97
	120	155	40.0	0.86.
	140	155	38.0	1.11
	170	165	37.0	0.95
	190	155	38.0	0.97
	215	145	37.0	0.86
3.	0	160	40.0	0.99
	45	160	40.0	1.18
	90	160	40.0	0.95
	125	160	39.0	0.97
	185	170	41.0	0.95
	220	165	42.0	0.90
4.	0	155	38.0	1.18
	25	160	41.0	1.64
	50	145	38.0	0.92
	65	150	38.0	1.11
	90	155	40.0	1.05
	120	140	35.0	0.95
	155	145	39.0	1.22
5.	0	175	46.0	1.02
	35	170	42.0	1.00
	75	175	41.0	0.82
	110	170	41.0	0.90
	160	170	39.0	0.82
	180	160	43.0	0.73
	205	165	42.0	0.82
	230	160	41.0	0.76
	250	160	42.0	0.76
	275	175	44.0	0.82

TABLE 4 (Contd.)

Experiment No.	Time (mins)	B.P. (mm.Hg)	PCO_2 (mm.Hg)	Flow (ml/gm/min)
8.	0	145	35.0	0.93
	20	150	36.0	0.90
	50	145	39.0	0.97
	70	145	39.0	0.99
	95	150	38.0	1.06
	115	155	38.0	0.92
	125	155	36.0	0.97
	140	160	36.5	0.93
	160	155	36.0	0.95
16.	0	175	40.0	0.74
	20	155	39.0	0.79
	30	155	-	0.71
	35	145	40.0	0.74
	45	130	-	0.74
	65	140	41.0	0.71
	70	160	-	0.80

TABLE 5.

ACIDOSIS

Exp. No.	pH	pCO_2 (mm.Hg.)	M.A.B.P. (mm.Hg.)	Respiration Pump Output (l./min.)	Flow (ml./g./min.)
P.1	7.36	34	145	4.55	0.84
	7.30	35	155	4.55	0.88
	7.19	38	155	4.55	0.89
	7.14	39	155	4.81	0.83
	7.13	36	145	4.81	0.90
	6.97	35	135	5.46	0.84
P.2	7.34	37	140	5.85	0.86
	7.31	38	145	5.85	0.97
	7.30	37	140	5.85	0.94
	7.28	36	145	6.11	0.81
	7.27	39	145	5.85	0.79
	7.20	36	150	6.37	0.78
	7.16	39	155	6.11	0.82
	7.11	37	165	6.37	0.64
	7.05	38	165	6.37	0.84
	6.81	41	165	6.37	0.86
P.3	7.39	34	170	6.50	0.82
	7.35	34	175	6.50	0.68
	7.30	32	190	6.89	0.67
	7.26	32	195	6.76	0.80
	7.14	32	175	6.76	0.74
	7.13	32	185	6.76	0.71
	6.89	33	180	6.76	0.90
	6.89	33	180	7.41	0.68
	6.85	33	180	6.76	0.62
	6.81	33	180	6.76	0.69
P.4	7.32	35	185	4.55	0.99
	7.28	35	200	4.81	0.64
	7.26	39	200	4.55	0.86
	7.19	36	210	4.81	0.72
	7.19	35	220	4.81	0.72
	7.12	35	230	5.09	0.65
	6.96	37	210	5.07	0.65
	6.74	37	210	5.07	0.73
P.5	7.26	37	145	4.16	0.88
	7.25	38	145	4.03	0.81
	7.22	37	160	4.16	0.86
	7.16	36	160	4.16	0.81
	6.98	42	160	3.90	0.80
	6.85	35	170	4.29	0.84
	6.82	42	160	3.90	0.95

TABLE 5.

ALKALOSIS

Exp. No.	pH	pCO_2 (mm.Hg.)	M.A.B.P. (mm.Hg.)	Respiration Pump Output (l./min.)	Flow (ml./g./min.)
P.6	7.29	36	195	7.15	0.95
	7.33	36	200	6.76	0.98
	7.34	39	190	6.76	0.83
	7.39	40	190	7.28	0.88
	7.44	39	185	7.80	0.75
	7.47	38	185	7.80	0.81
	7.49	39	160	6.76	0.82
	7.51	36	190	7.80	0.74
	7.58	39	175	7.80	0.83
	7.59	41	170	8.06	0.86
P.7	7.28	38	145	3.25	0.86
	7.39	40	145	3.25	0.87
	7.45	39	140	3.51	0.68
	7.47	42	140	3.51	0.58
	7.69	42	130	4.29	1.04
P.8	7.23	37	130	3.90	0.60
	7.25	37	130	4.16	0.61
	7.33	38	135	4.29	0.54
	7.38	38	140	4.55	0.47
	7.45	39	135	4.68	0.56
	7.51	37	130	5.20	0.58
	7.53	39	130	5.46	0.52
	7.58	38	130	5.98	0.50
	7.65	36	120	6.63	0.51
	7.71	36	115	7.02	0.52
P.9	7.28	37	140	6.89	1.00
	7.31	36	145	7.41	0.79
	7.40	34	165	8.06	0.96
	7.45	33	170	8.45	0.98
	7.54	34	155	8.84	0.76
	7.55	35	175	8.32	0.80
	7.59	36	155	9.23	0.72
P.10	7.32	33	150	8.32	1.14
	7.40	36	160	8.56	0.86
	7.46	32	160	8.97	0.82
	7.58	36	160	9.62	0.85
	7.76	35	155	11.70	0.89
	7.80	37	155	13.00	1.09

TABLE 7.

HYPERCAPNIA AT NORMOTENSION

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
C.1	155	7.26	36	1.02	0.94
	165	7.18	47	1.28	1.16
	165	7.11	63	1.72	1.56
	170	7.07	69	2.12	1.93
	170	7.04	75	2.22	2.02
	165	6.99	87	2.18	1.98
Mean & S.D.	165± 5.5				
C.2	190	7.31	36	1.18	0.93
	185	7.27	46	1.42	1.12
	180	7.24	47	1.48	1.17
	190	7.22	51	1.61	1.27
	180	7.19	56	1.62	1.28
	180	7.16	62	1.89	1.49
	180	7.12	68	1.84	1.45
	180	7.12	75	2.22	1.75
	183± 4.6				
C.3	145	7.28	31	0.75	0.83
	155	7.20	43	0.92	1.02
	160	7.17	49	1.15	1.28
	165	7.12	58	1.08	1.20
	165	7.09	67	1.11	1.23
	170	7.04	80	1.51	1.68
	165	7.00	86	1.75	1.94
	161± 8.4				
C.4	155	7.17	35.5	0.56	0.90
	150	7.11	48	0.76	1.23
	150	7.07	54	0.89	1.44
	170	7.06	60	1.09	1.76
	170	7.05	60	1.13	1.82
	175	7.01	70	1.24	2.00
	162±11.3				
C.5	180	7.33	30	0.70	0.83
	185	7.24	44	0.95	1.13
	180	7.22	48	1.08	1.29
	175	7.17	58	1.48	1.76
	180	7.15	59	1.64	1.95
	170	7.13	64	1.80	2.14
	175	7.08	73	1.76	2.10
	170	7.04	86	1.89	2.25
	177± 5.3				

Hypercapnia at Normotension (Contd.)

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
C.6	165	7.34	32	0.91	0.91
	165	7.25	44	1.05	1.05
	160	7.22	55	1.30	1.30
	160	7.16	64	1.68	1.68
	150	7.10	78	1.99	1.99
	170	7.08	85	2.16	2.16
	165	7.06	94	1.89	1.89
	165	7.02	98	1.94	1.94
Mean & S.D.	163± 6.0				
C.7	160	7.28	33	0.88	0.88
	165	7.25	39	1.14	1.14
	170	7.22	43	0.90	0.90
	165	7.18	51	1.26	1.26
	165	7.18	53	1.26	1.26
	160	7.14	62	1.57	1.57
	164± 3.8				
C.8	180	7.28	36	0.61	0.97
	175	7.23	46	0.67	1.06
	175	7.17	58	0.93	1.48
	180	7.13	67	1.30	2.06
	170	7.10	72	1.51	2.40
	175	7.03	87	1.68	2.67
	176± 3.8				
C.9	145	7.36	37	0.76	0.92
	145	7.30	46	0.98	1.18
	140	7.21	57	1.37	1.65
	135	7.14	71	1.45	1.75
	140	7.13	72	1.51	1.82
	135	7.08	86	1.43	1.72
	140± 4.5				
C.10	130	7.30	41	0.90	1.05
	130	7.23	54	1.37	1.60
	130	7.16	67	1.57	1.83
	130	7.12	75	1.43	1.66
	135	7.12	75	1.51	1.76
	130	7.09	82	1.57	1.83
	135	7.08	88	1.45	1.69
	130	7.05	93	1.54	1.79
	130	7.04	96	1.72	2.00
	131± 2.2				

TABLE 8.

HYPOCAPNIA AT NORMOTENSION

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
H.1	160	7.25	38	0.88	0.96
	160	7.26	37	0.80	0.87
	165	7.33	26	0.51	0.55
	160	7.39	20	0.48	0.52
	170	7.41	16	0.46	0.50
	175	7.40	17	0.49	0.53
Mean & S.D.	165± 6.3				
H.2	125	7.14	38	1.08	1.08
	105	7.16	36	0.86	0.86
	115	7.20	31	0.76	0.76
	110	7.22	28	0.59	0.59
	105	7.25	23.5	0.63	0.63
	125	7.27	21	0.63	0.63
	125	7.29	19.5	0.55	0.55
	135	7.32	17.5	0.60	0.60
	130	7.34	15.5	0.60	0.60
	130	7.33	15.5	0.57	0.57
	121±10.9				
H.3	130	7.17	42	1.06	1.20
	125	7.22	38.5	0.82	0.93
	125	7.24	34	0.66	0.75
	130	7.34	23	0.55	0.63
	125	7.36	19	0.56	0.64
	125	7.42	14	0.60	0.68
	120	7.44	11.5	0.49	0.56
	126± 3.4				
H.4	130	7.31	35	0.61	0.76
	140	7.36	29	0.65	0.81
	130	7.40	26	0.58	0.72
	140	7.48	18	0.45	0.56
	135	7.49	16	0.56	0.70
	135	7.52	13.5	0.56	0.70
	145	7.54	12	0.53	0.66
	140	7.58	10.25	0.56	0.70
	137± 5.3				
H.5	140	7.28	35	1.04	0.93
	130	7.38	27	0.64	0.57
	140	7.40	19.5	0.62	0.55
	130	7.45	17	0.69	0.62
	130	7.52	13.5	0.76	0.68
	130	7.58	11	0.60	0.54
	130	7.59	10	0.54	0.48
	133± 4.9				

Hypocapnia at Normotension (Contd.)

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
H.6	115	7.30	35	0.90	0.90
	120	7.36	29	0.79	0.79
	120	7.40	26	0.69	0.69
	120	7.44	24	0.73	0.73
	120	7.46	21	0.63	0.63
	120	7.49	18	0.76	0.76
	115	7.49	16	0.70	0.70
	115	7.52	14.5	0.76	0.76
Mean & S.D.	118± 2.6				
H.7	160	7.25	40	0.74	1.06
	165	7.27	36	0.64	0.91
	160	7.31	33	0.53	0.76
	165	7.36	28	0.46	0.66
	170	7.39	25	0.47	0.67
	165	7.42	22	0.41	0.59
	165	7.45	19	0.41	0.59
	165	7.48	17.5	0.43	0.61
	160	7.54	16	0.43	0.61
	160	7.59	13.5	0.42	0.60
	155	7.62	11	0.42	0.60
	155	7.64	10.25	0.46	0.66
	162± 4.5				
H.8	140	7.27	40	1.02	1.00
	155	7.34	30	0.71	0.70
	160	7.32	27	0.58	0.57
	155	7.36	23	0.59	0.58
	150	7.42	22	0.54	0.53
	152± 7.6				
H.9	155	7.27	36	1.24	0.99
	150	7.31	31	0.90	0.72
	150	7.38	26	0.95	0.76
	145	7.42	22.5	0.66	0.53
	145	7.47	19.5	0.73	0.58
	150	7.50	17	0.59	0.47
	150	7.53	15	0.59	0.47
	145	7.57	12	0.59	0.47
	130	7.61	10.5	0.61	0.49
	135	7.62	10	0.57	0.46
	150± 7.6				

TABLE 9.

HYPERCAPNIA AT B.P. 100 mm.Hg.

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
C.11	100	7.23	32	0.32	0.94
	100	7.15	43	0.35	1.03
	100	7.10	54	0.39	1.15
	100	7.07	58	0.41	1.21
	100	7.02	72	0.50	1.47
	100	6.98	86	0.57	1.68
	100	6.97	94	0.54	1.59
C.12	105	7.28	31	0.66	0.80
	105	7.28	31	0.67	0.81
	105	7.19	42	0.85	1.02
	105	7.10	54	0.95	1.14
	105	7.08	57	1.20	1.45
	105	7.09	68	1.43	1.72
	100	7.09	68	1.35	1.62
	105	7.07	78	1.45	1.74
	105	7.05	78	1.43	1.72
C.13	100	7.26	32	0.57	1.00
	100	7.23	36	0.55	0.96
	100	7.13	44	0.56	0.98
	100	6.98	50	0.63	1.11
	100	6.87	62	0.68	1.19
	100	6.86	68	0.71	1.25
	100	6.83	78	0.72	1.26
C.14	100	7.28	30	0.68	0.92
	100	7.21	38	0.84	1.14
	100	7.16	46	0.80	1.09
	100	7.12	51	1.05	1.41
	100	7.09	64	0.76	1.03
	100	7.05	80	0.85	1.15
	100	7.02	88	0.97	1.31
C.15	100	7.25	37	1.02	1.02
	100	7.22	38	0.95	0.95
	100	7.22	38	1.02	1.02
	100	7.14	38	0.90	0.90
	100	7.11	44	1.08	1.08
	100	7.08	60	1.35	1.35
	100	7.00	68	1.61	1.01
	100	6.95	80	1.76	1.76

Hypercapnia at B.P. 100 mm.Hg. (Contd.)

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
C.16	100	7.21	33	0.55	0.82
	100	7.19	35	0.61	0.91
	100	7.18	42	0.76	1.14
	100	7.13	50	0.71	1.06
	100	7.13	49	0.79	1.18
	100	7.10	54	0.95	1.42
	100	7.10	58	0.95	1.42
	100	7.09	60	0.90	1.34
	100	7.04	73	0.97	1.45
	100	7.03	79	1.02	1.52
	100	7.03	82	1.06	1.58
C.17	100	7.26	40	0.76	1.00
	105	7.19	52	0.81	1.07
	105	7.17	55	0.84	1.11
	110	7.12	68	0.88	1.16
	105	7.04	84	0.88	1.16
	110	7.02	100	0.98	1.29

TABLE 10.

HYPOCAPNIA AT B.P. 100 mm.Hg.

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO2 (mm.Hg)	Blood Flow (ml/gm/min)	F/F_{40}
H.10	100	7.24	36.5	0.79	0.90
	100	7.27	31.5	0.74	0.84
	105	7.31	30.0	0.82	0.93
	100	7.34	26.0	0.64	0.73
	100	7.39	23.0	0.64	0.73
	100	7.44	19.0	0.56	0.64
	100	7.45	16.5	0.66	0.75
	100	7.50	13.5	0.69	0.78
H.11	95	7.21	32.0	0.89	0.89
	100	7.28	26.0	1.14	1.14
	100	7.28	24.0	0.85	0.85
	100	7.38	20.0	0.77	0.77
	100	7.44	15.0	0.84	0.84
	100	7.45	11.5	0.82	0.82
H.12	100	7.14	48.0	1.05	1.25
	100	7.18	41.0	0.74	0.88
	100	7.28	30.0	0.63	0.75
	100	7.31	26.0	0.77	0.92
	100	7.35	23.5	0.73	0.87
	100	7.39	21.0	0.69	0.82
	100	7.46	17.0	0.66	0.78
	100	7.50	12.0	0.66	0.78
H.13	100	7.24	38.0	1.26	1.05
	100	7.17	35.0	1.02	0.85
	100	7.09	34.0	0.97	0.81
	100	7.16	27.5	0.68	0.57
	100	7.23	19.0	0.71	0.59
	100	7.29	15.5	0.70	0.58
	100	7.36	12.5	0.71	0.59
H.14	100	7.14	50.0	1.07	1.19
	100	7.20	41.0	0.84	0.93
	100	7.34	28.0	0.78	0.87
	100	7.43	20.0	0.71	0.79
	100	7.41	17.0	0.71	0.79
	100	7.47	12.5	0.80	0.89

TABLE 11.

HYPERCAPNIA AT B.P. 50 mm.Hg.

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
C.18	40	7.21	36	0.33	0.97
	40	7.18	36	0.34	1.00
	40	7.10	41	0.37	1.09
	43	7.04	49	0.39	1.15
	40	6.95	57	0.31	0.91
	42	6.88	63	0.29	0.85
	42	6.84	72	0.31	0.91
	40	6.75	80	0.29	0.85
	42	6.65	103	0.28	0.82
C.19	50	7.23	26	0.68	1.15
	50	7.09	25	0.56	0.95
	50	6.95	32	0.63	1.07
	50	6.85	44	0.61	1.03
	50	6.75	49	0.64	1.09
	50	6.69	59	0.54	0.92
	50	6.66	67	0.49	0.83
	50	6.61	89	0.58	0.98
C.20	50	7.32	29	0.51	1.00
	50	7.28	36	0.52	1.02
	50	7.18	43	0.47	0.92
	50	7.07	46	0.54	1.06
	50	6.85	55	0.52	1.02
	50	6.76	65	0.62	1.22
	50	6.73	71	0.58	1.14
	50	6.63	90	0.55	1.08
C.21	50	7.17	40	0.79	1.32
	50	7.17	38	0.56	0.93
	50	7.08	48	0.50	0.83
	50	6.97	55	0.53	0.88
	50	6.79	74	0.63	1.05
C.22	50	7.19	26	0.63	1.05
	50	6.98	32	0.69	1.15
	50	6.92	38	0.68	1.13
	50	6.84	54	0.52	0.87
	50	6.81	60	0.69	1.15
	50	6.73	68	0.61	1.02
	50	6.71	69	0.53	0.88
	50	6.69	84	0.60	1.00

TABLE 12.

HYPOCAPNIA AT B.P. 50 mm.Hg.

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO2 (mm.Hg.)	Blood Flow (ml/gm/min)	F/F_{40}
H.15	50	7.02	40.0	0.73	1.04
	50	6.86	41.0	0.64	0.91
	50	6.89	30.0	0.74	1.06
	50	6.95	25.5	0.66	0.94
	50	7.01	19.5	0.74	1.06
	50	7.03	17.5	0.69	0.99
	50	7.08	14.0	0.51	0.73
	50	7.10	12.5	0.53	0.76
H.16	60	7.28	36.0	0.67	1.00
	60	7.18	33.0	0.65	0.97
	60	7.21	30.0	0.66	0.99
	60	7.33	23.5	0.73	1.09
	60	7.42	19.0	0.65	0.97
	60	7.47	16.0	0.58	0.87
H.17	50	7.12	43.5	0.64	1.02
	50	7.08	30.0	0.55	0.87
	50	7.06	27.0	0.68	1.08
	50	7.31	17.5	0.69	1.10
H.18	50	7.13	34.0	0.62	0.94
	50	6.99	32.0	0.62	0.94
	50	6.97	28.0	0.71	1.08
	50	6.91	20.5	0.67	1.02
	50	7.04	15.0	0.56	0.85
	50	7.06	13.5	0.58	0.88
H.19	50	6.84	38.5	0.71	1.06
	50	6.83	36.5	0.67	1.00
	50	6.89	27.0	0.67	1.00
	50	6.88	25.5	0.67	1.00
	50	6.93	19.0	0.64	0.96
	50	6.97	13.0	0.65	0.97
	50	7.05	12.0	0.66	0.99

TABLE 13.

HYPOTENSION AT NORMOCAPNIA

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)
B.1	165.0	7.32	32	0.90
	160.0	7.33	33	0.97
	150.0	7.33	32	0.99
	140.0	7.34	31	0.83
	130.0	7.32	32	0.88
	120.0	7.31	32	0.90
	105.0	7.29	33	0.92
	90.0	7.24	37	0.77
	52.5	7.18	30	0.71
	32.5	7.11	26	0.44
Mean & S.D.			31.8 ± 2.8	
B.2	150.0	7.33	35	0.91
	135.0	7.25	34	0.73
	120.0	7.28	32	0.71
	125.0	----	--	0.76
	110.0	7.22	32	0.67
	90.0	7.20	29	0.77
	77.0	7.15	31	0.64
	57.0	7.00	31	0.43
	37.0	6.92	31	0.34
			31.9 ± 1.9	
B.3	155.0	7.26	42	0.70
	150.0	----	--	0.74
	135.0	7.20	44	0.84
	110.0	7.15	41	0.86
	97.0	7.12	43	0.80
	95.0	7.14	41	0.70
	90.0	7.18	41	0.71
	83.0	7.15	43	0.66
	83.0	----	--	0.63
	75.0	7.16	41	0.57
	70.0	----	--	0.50
	65.0	7.13	42	0.52
	57.5	7.11	42	0.50
	50.0	7.09	41	0.49
	42.5	7.05	39	0.43
	35.0	6.98	36	0.28
	22.5	6.93	36	0.21
			40.9 ± 2.4	
B.4	127.0	7.26	38	0.74
	130.0	7.27	38	0.73
	110.0	7.23	35	0.66
	80.0	7.22	34	0.57
	70.0	7.16	39	0.58
	60.0	7.11	39	0.51
	45.0	6.88	39	0.51
	40.0	6.83	41	0.48
	25.0	6.92	--	0.30
			37.9 ± 2.3	

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min)
B.5	150.0	7.31	34	0.72
	155.0	7.33	32	0.72
	120.0	7.32	29	0.71
	105.0	7.32	28	0.59
	105.0	7.28	31	0.66
	92.0	7.27	30	0.46
	82.0	7.23	35	0.57
	72.0	7.22	33	0.49
	57.0	7.21	31	0.47
	42.0	7.19	32	0.46
	28.0	7.14	25	0.32
Mean & S.D.			30.9 ± 2.9	
B.6	135.0	7.28	35	0.71
	155.0	7.30	36	0.83
	145.0	7.33	34	1.05
	135.0	7.33	33	0.87
	125.0	7.31	33	0.81
	112.0	7.29	32	0.85
	100.0	7.24	34	0.96
	90.0	7.22	35	0.96
	80.0	7.19	38	0.86
	60.0	7.17	37	0.85
	40.0	7.02	30	0.56
			34.3 ± 2.3	
B.7	180.0	7.39	34	0.82
	170.0	----	--	0.83
	155.0	7.38	35	0.89
	130.0	----	--	0.82
	120.0	7.35	37	0.95
	100.0	----	--	0.91
	85.0	7.29	38	0.71
	60.0	----	--	0.52
	40.0	7.12	38	0.26
			36.4 ± 1.8	
B.8	170.0	7.30	39	0.84
	155.0	7.32	37	1.18
	140.0	7.32	37	0.80
	125.0	7.30	37	0.98
	110.0	7.27	40	0.95
	100.0	7.26	44	0.95
	90.0	7.28	38	0.90
	80.0	7.27	39	0.98
	70.0	7.25	39	0.86
	62.5	7.21	37	0.84
	50.0	7.08	37	0.71
	35.0	7.02	37	0.63
	12.5	7.18	35	0.24
			38.2 ± 2.2	

TABLE 14.

HYPOTENSION AT HYPERCAPNIA

Exp. No.	M.A.B.P. (mm.Hg.)	pH	pCO_2 (mm.Hg.)	Blood Flow (ml/gm/min.)
B.9	145	7.10	68	1.20
	140	7.00	70	1.02
	110	7.07	72	0.93
	100	7.05	71	0.76
	80	7.00	66	0.58
Mean & S.D.			69.4 ± 2.4	
B.10	135	7.02	83	1.89
	120	7.02	83	1.28
	105	7.02	78	1.22
	100	6.97	83	1.16
	90	6.97	88	1.11
	85	6.99	84	0.93
	70	7.01	79	0.84
	55	6.98	85	0.65
	40	6.93	86	0.39
			74.9 ± 3.2	
B.11	143	7.04	68	1.45
	135	7.03	68	1.45
	125	7.01	71	1.37
	115	6.94	71	1.268
	95	6.83	68	0.99
	75	6.81	63	0.73
			68.2 ± 2.9	
B.12	170	7.13	80	1.80
	160	7.15	73	1.51
	145	7.10	82	1.35
	130	7.04	91	1.26
	110	7.03	91	1.02
	90	7.02	91	0.69
	70	6.97	91	0.65
	45	6.90	90	0.47
			86.1 ± 6.9	

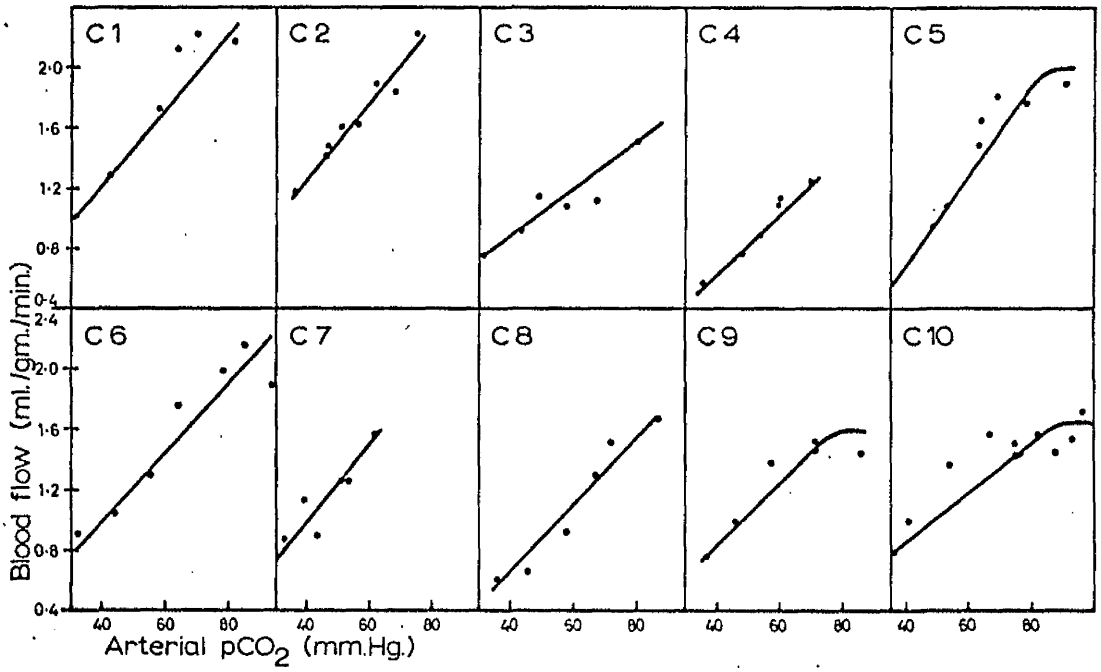

Fig.9 - Blood flow response in individual dogs during hypercapnia.

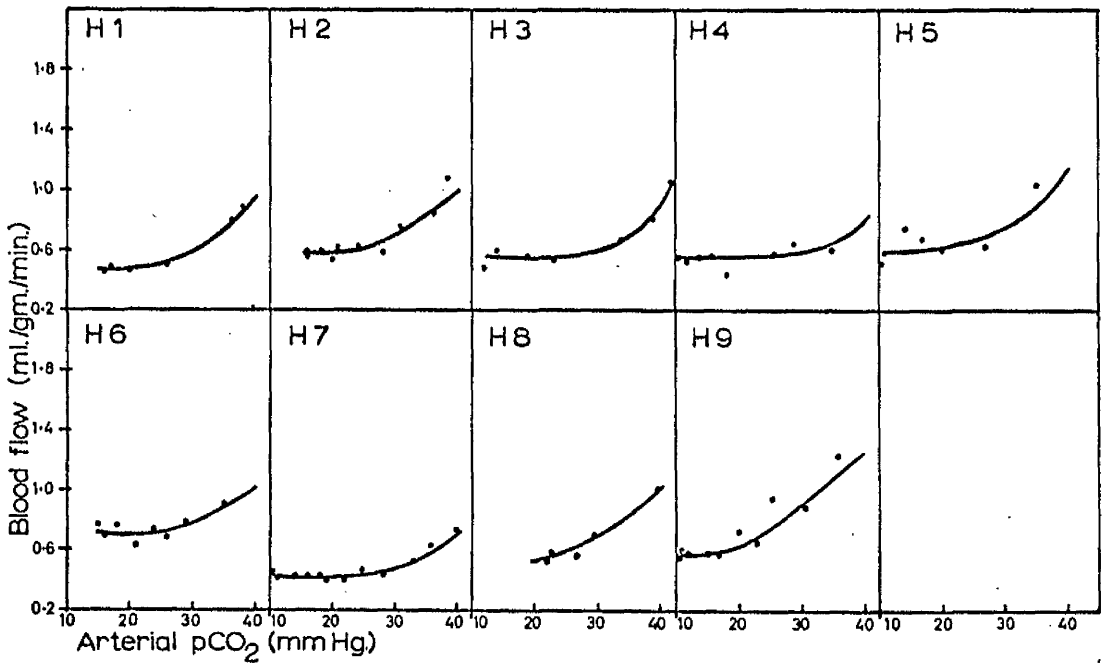

Fig.10 - Blood flow response in individual dogs during hypocapnia.

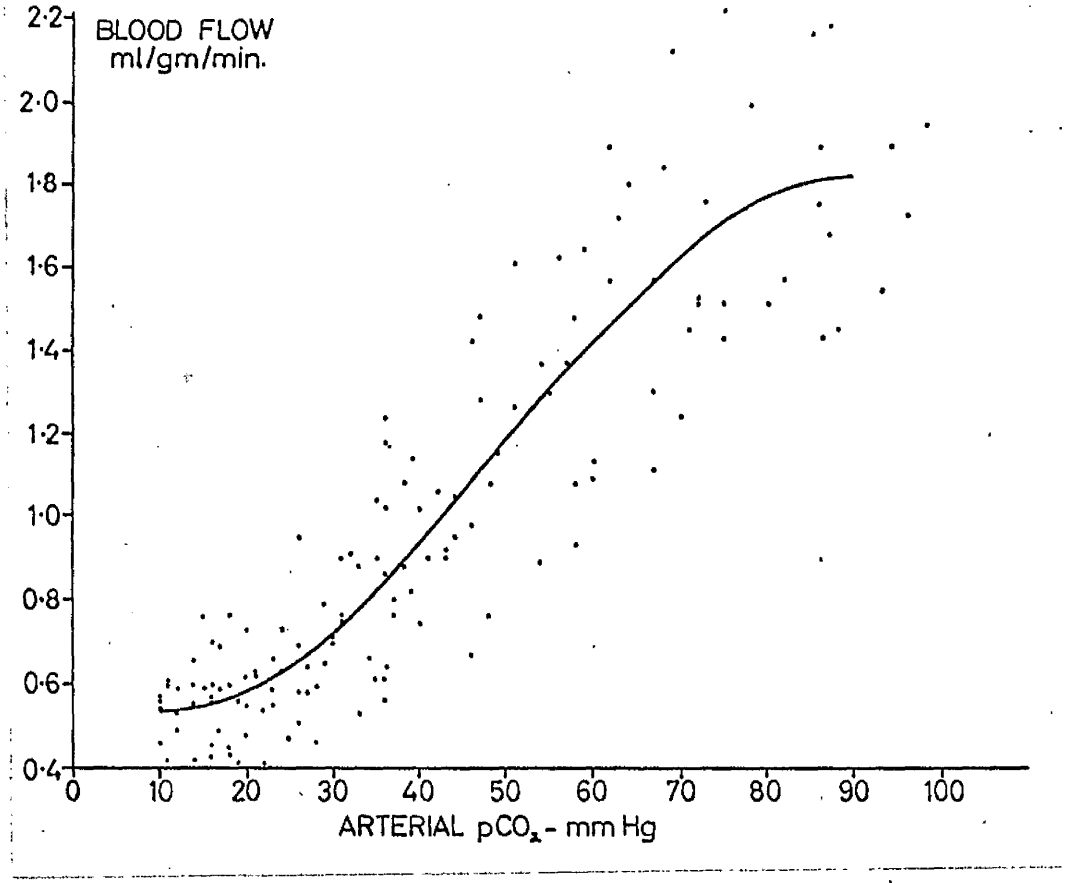

Fig.11 - Blood flow/PCO_2 response in normotensive dogs.

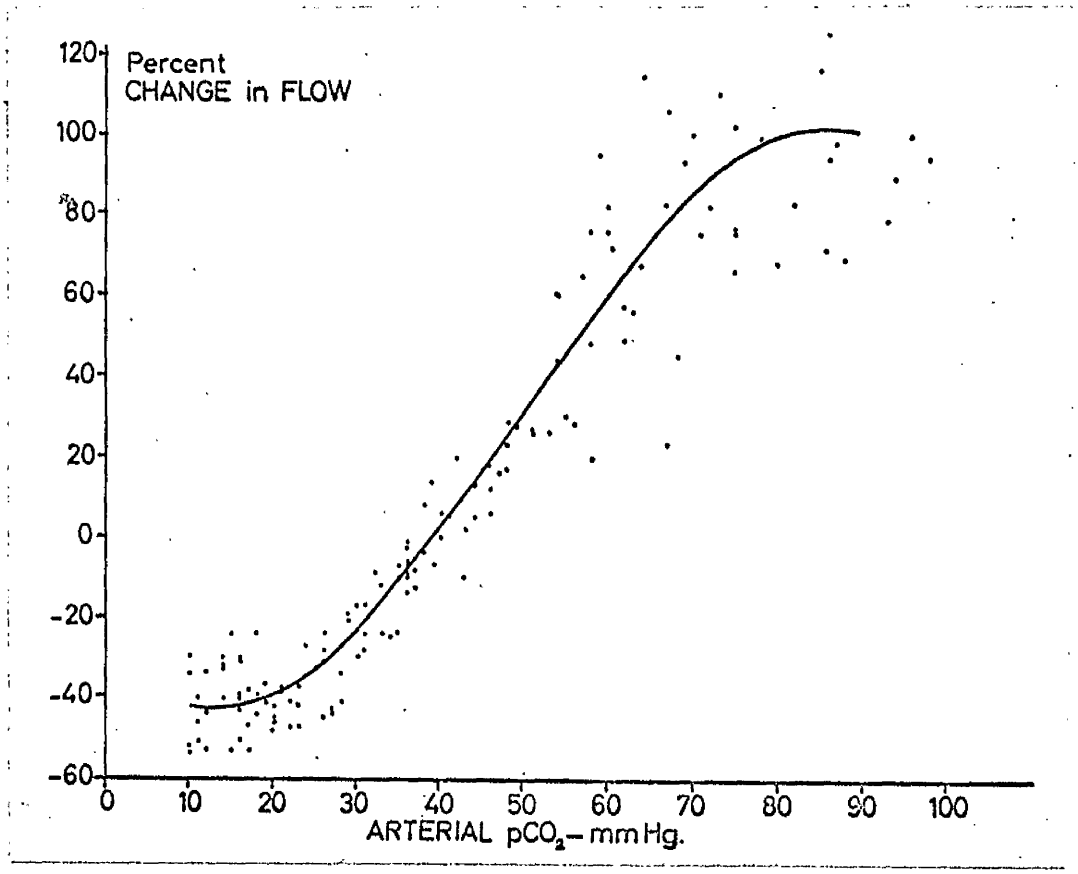

Fig.12 - Blood flow/PCO_2 response in normotensive dogs. Zero reference is at $PaCO_2$ of 40 mm.Hg.

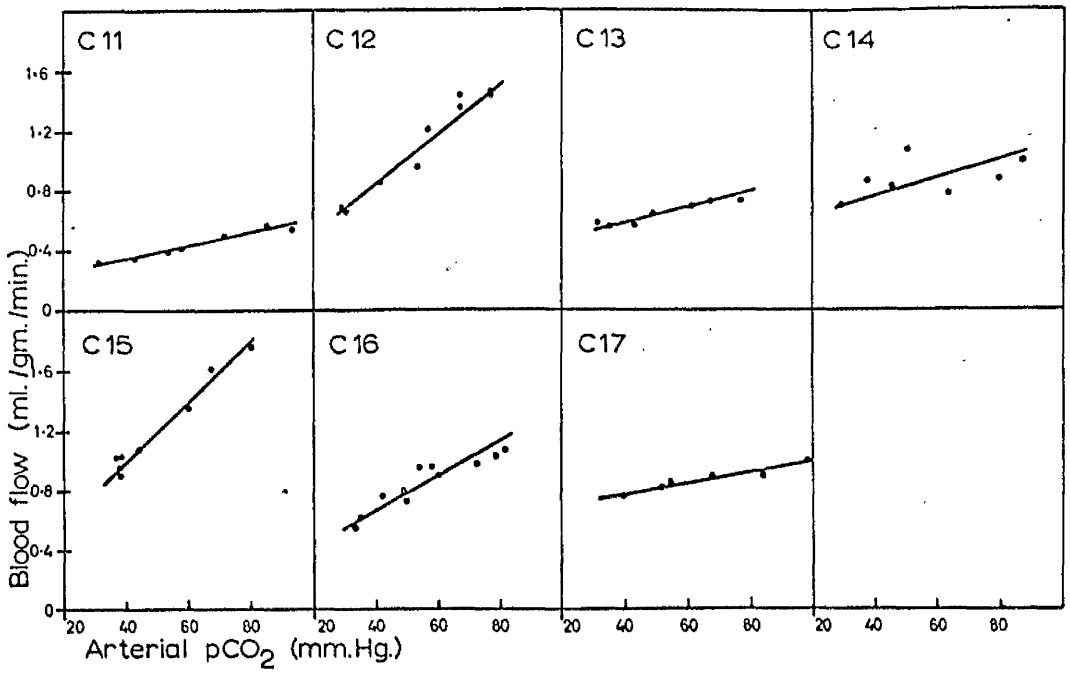

Fig.13 - Blood flow response in individual dogs during hypercapnia (M.A.B.P. 100 mm.Hg.)

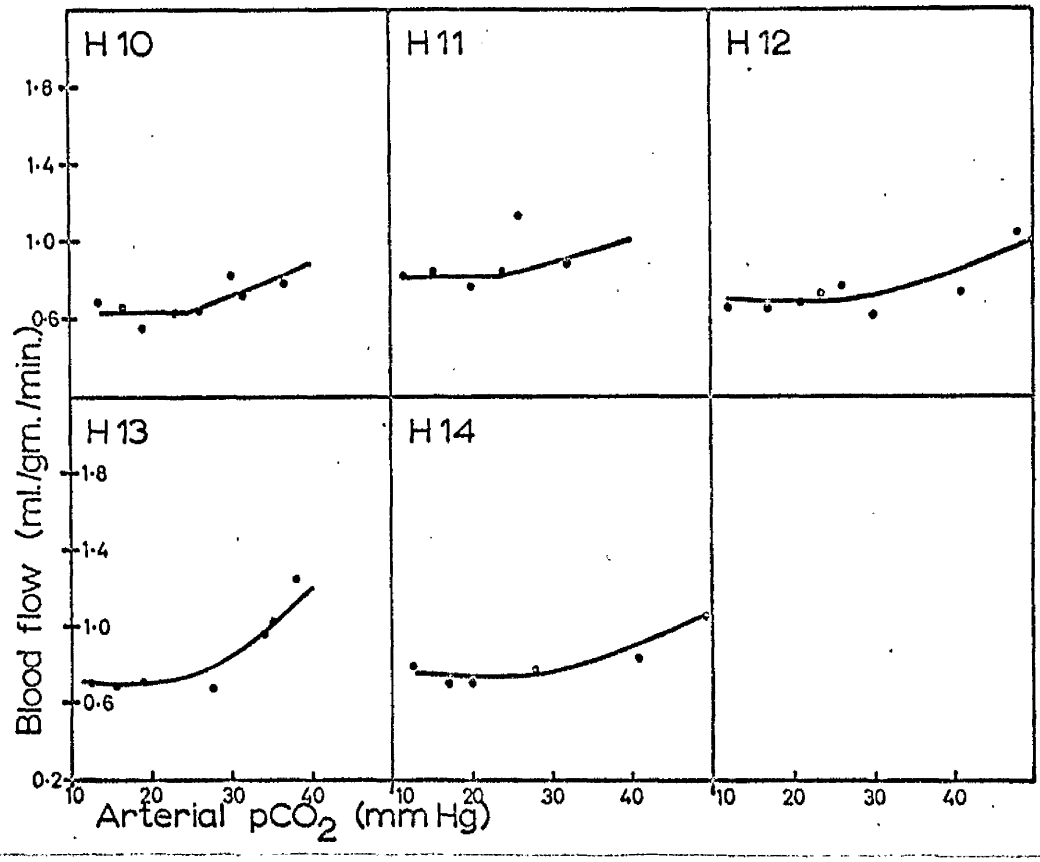

Fig.14 - Blood flow response in individual dogs during hypocapnia (M.A.B.P. 100 mm.Hg.)

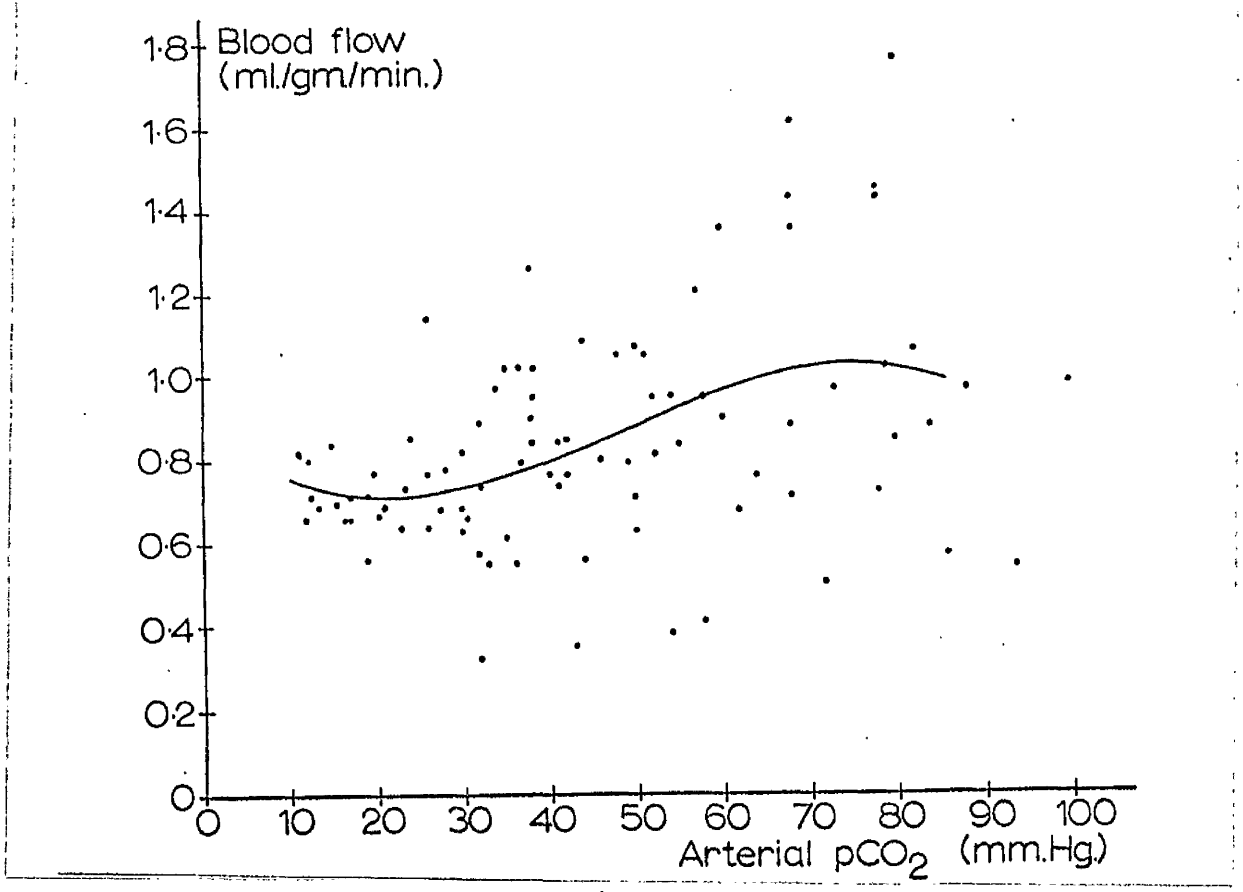

Fig.15 - Blood flow/PCO_2 response in hypotensive dogs (M.A.B.P. 100 mm.Hg.)

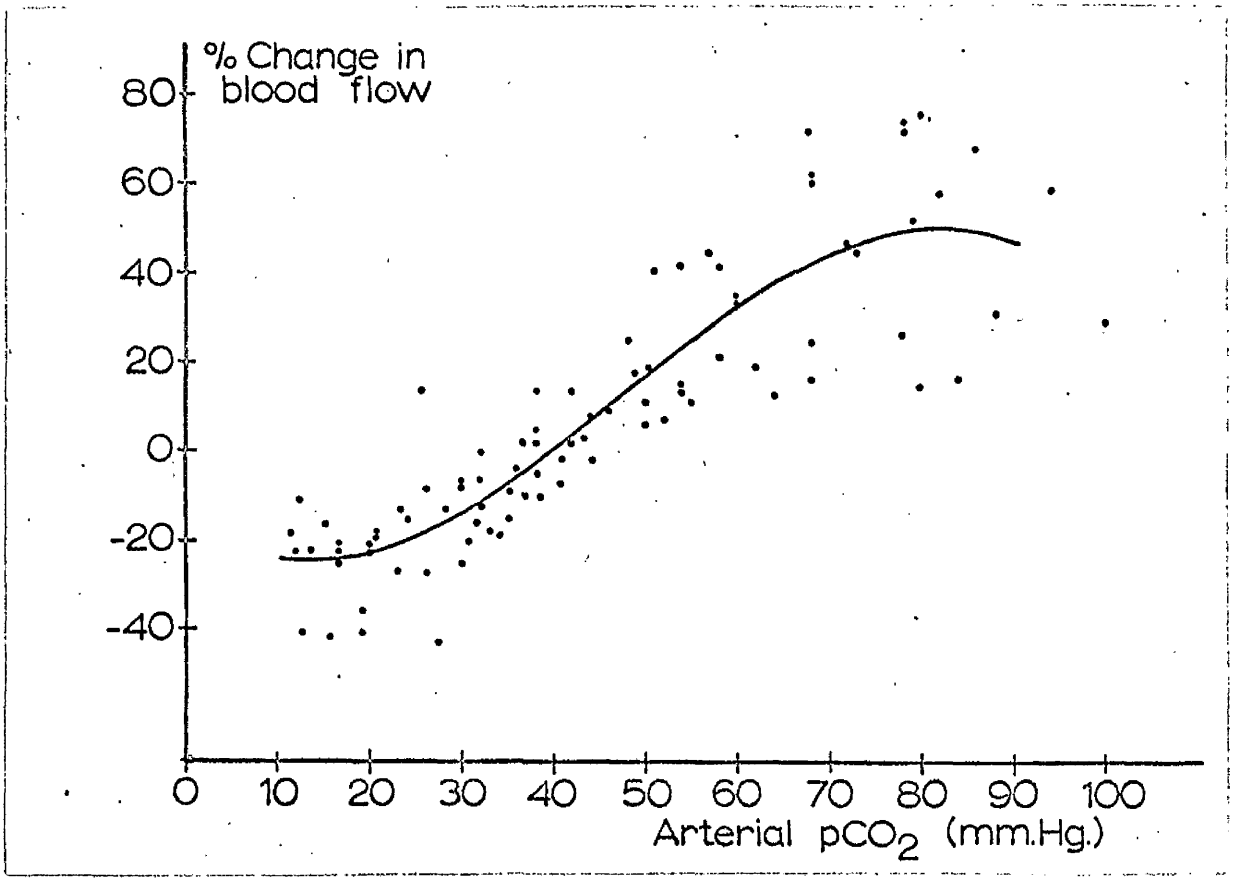

Fig.16 - Blood flow/PCO2 response in hypotensive dogs. Zero reference is at $PaCO_2$ of 40 mm.Hg.

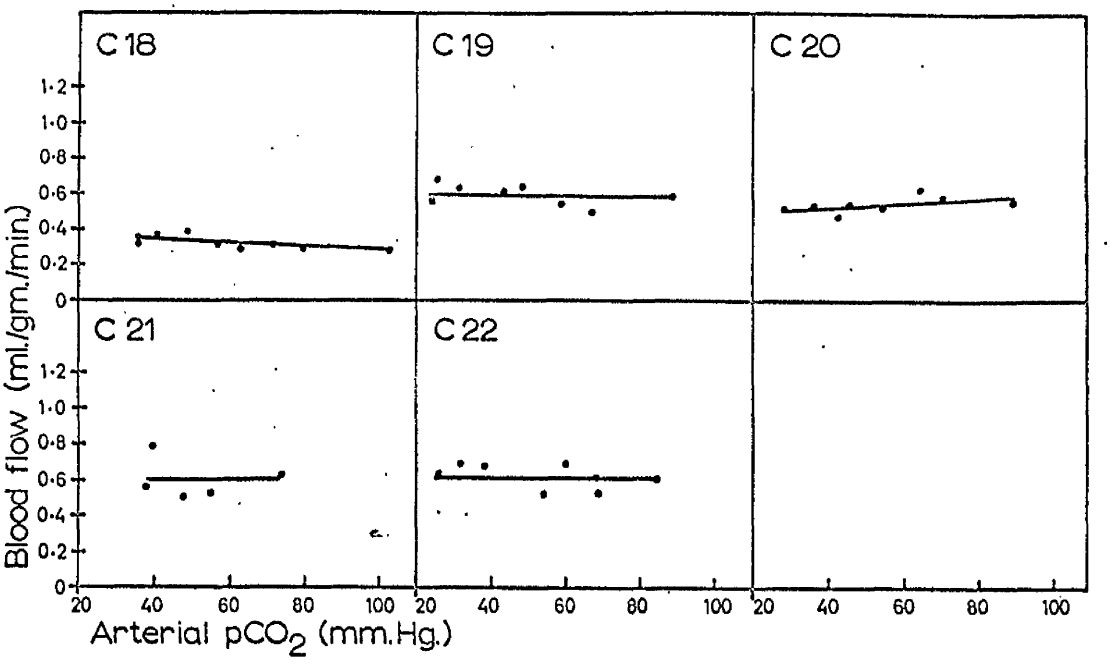

Fig.17 - Blood flow response in individual dogs during hypercapnia (M.A.B.P. 40-50 mm.Hg.)

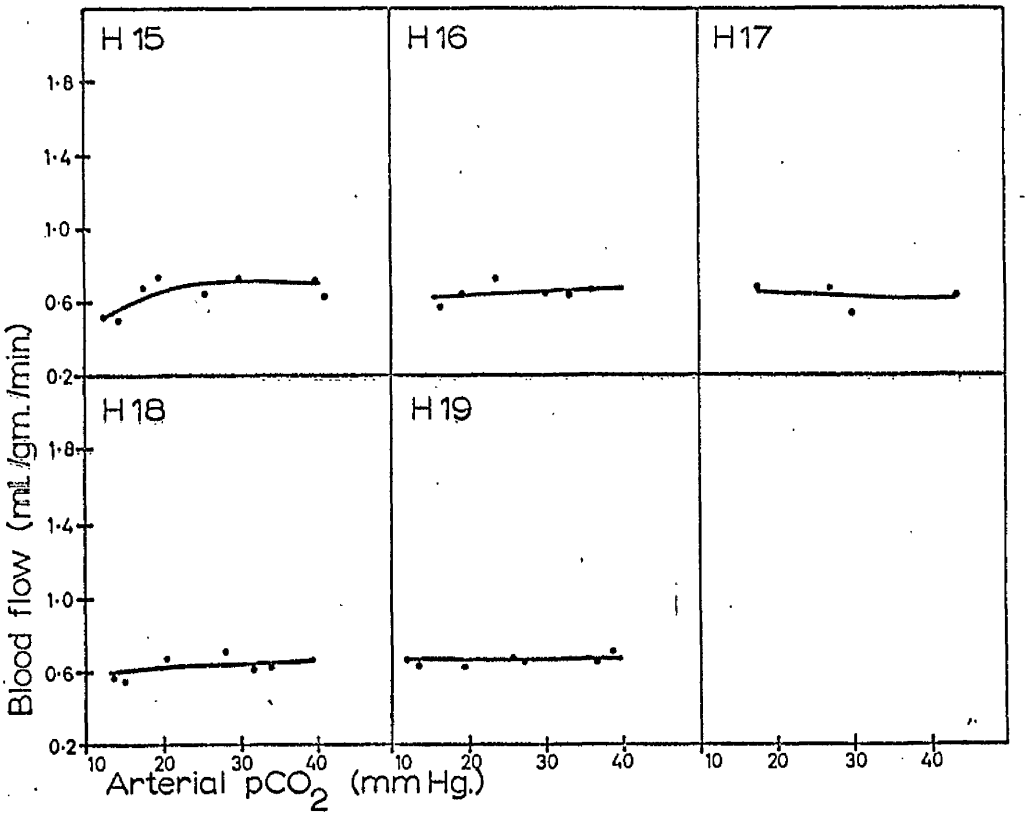

Fig.18 - Blood flow response in individual dogs during hypocapnia (M.A.B.P. 40-50 mm.Hg.)

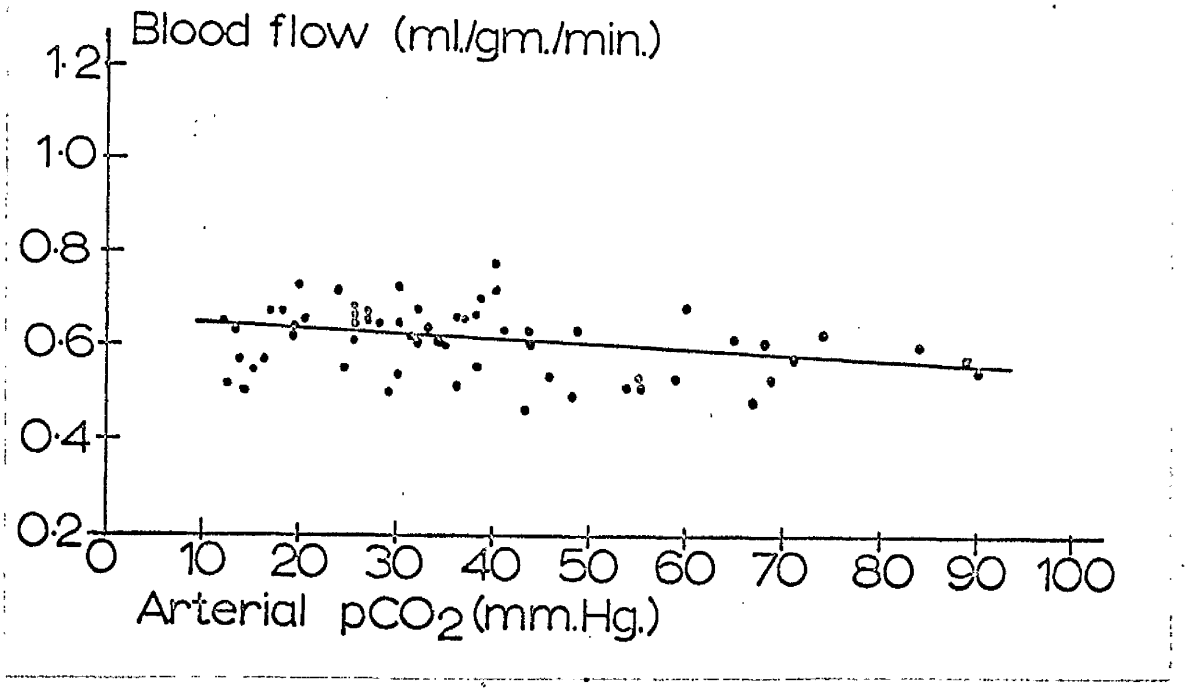

Fig.19 - Blood flow/PCO_2 response in hypotensive dogs (M.A.B.P. 40-50 mm.Hg.)

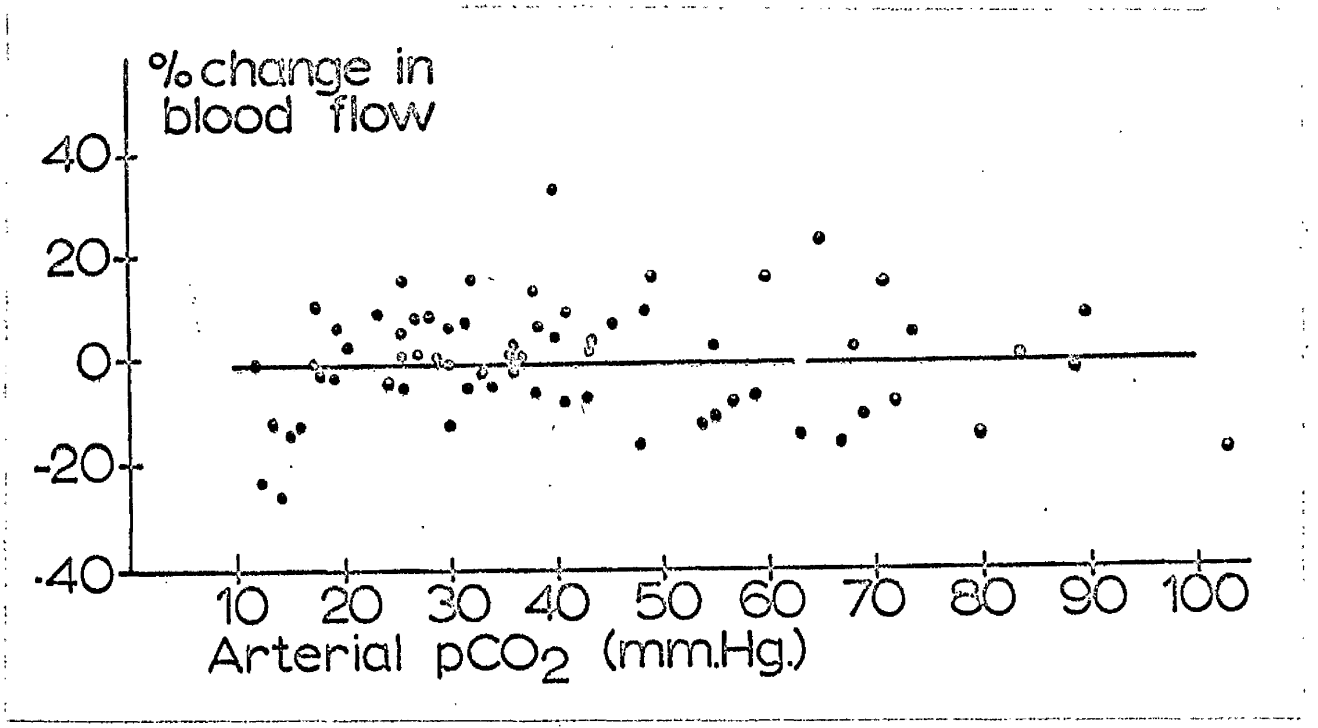

Fig.20 - Blood flow/PCO_2 response in hypotensive dogs. Zero reference is at $PaCO_2$ of 40 mm.Hg.

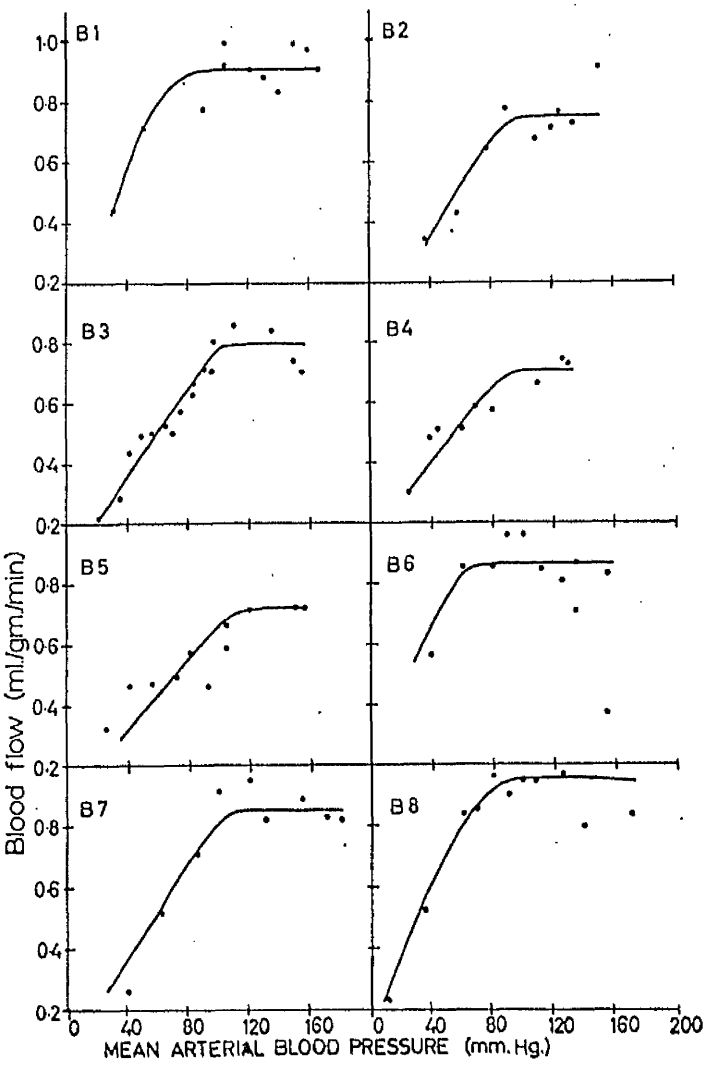

Fig.22

Blood flow/ blood pressure response in individual normocapnic dogs.

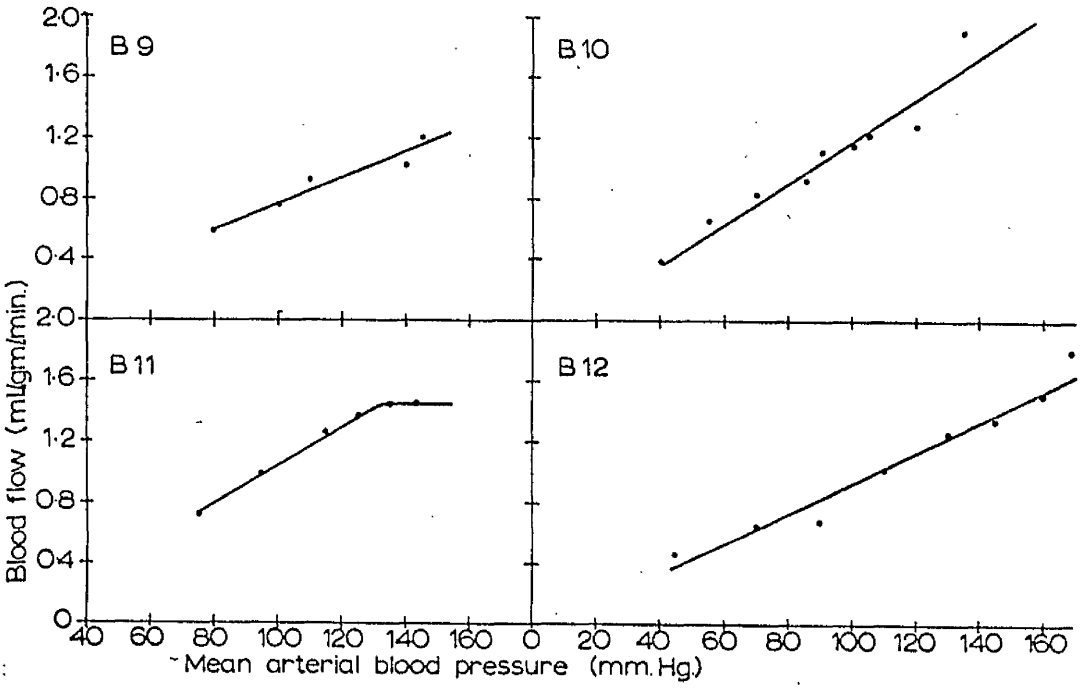

Fig.23 - Blood flow/blood pressure response in individual hypercapnic dogs.

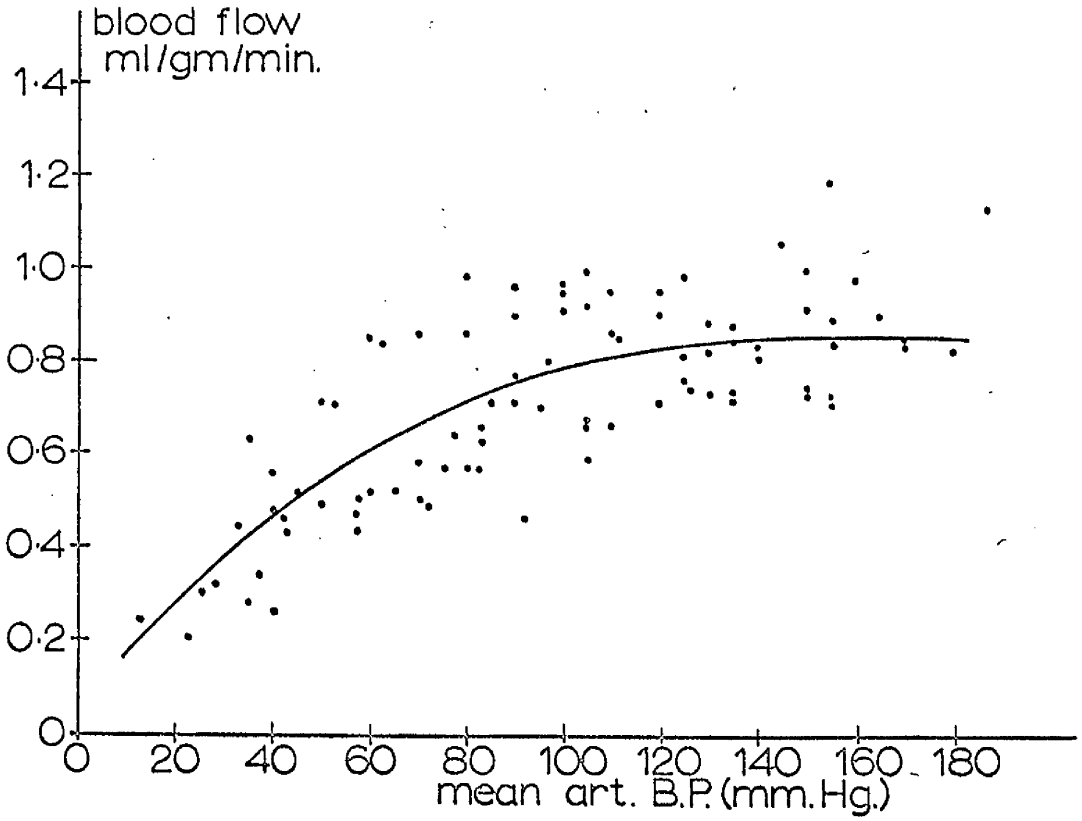

Fig.24 - Blood flow/blood pressure response in normocapnic dogs.

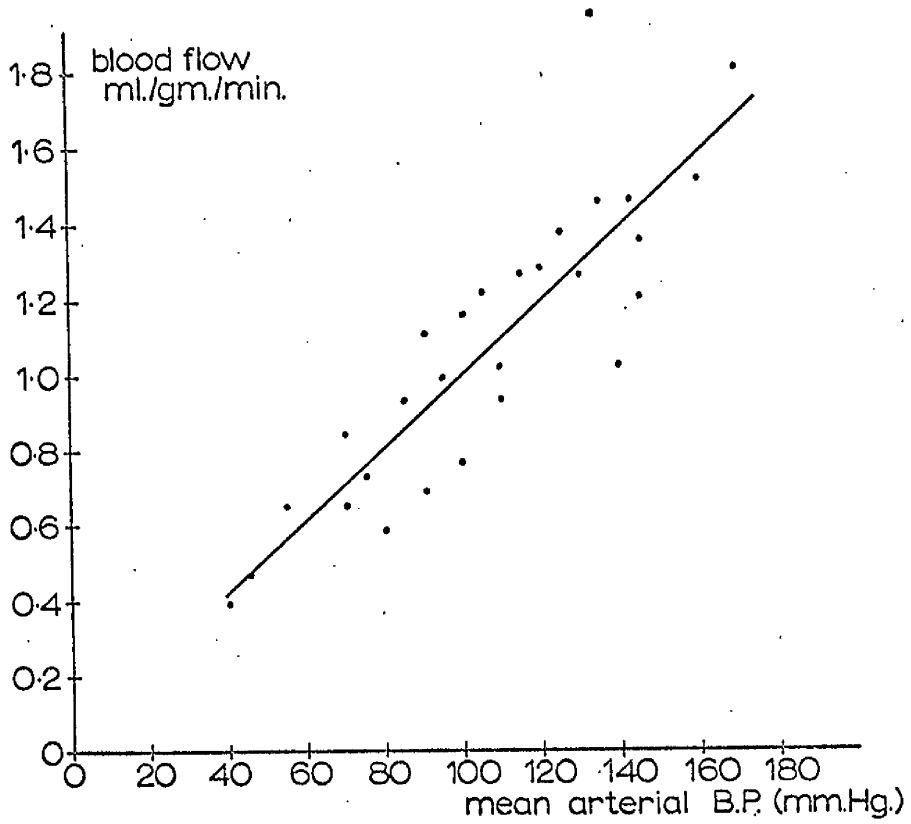

Fig.25 - Blood flow/blood pressure response in hypercapnic dogs.

APPENDIX

MEASUREMENT OF BLOOD pH AND PCO_2.

In the experiments reported in this thesis, the pH and PCO_2 of the arterial blood were measured on a micro-Astrup apparatus. This consists of a pH meter, a tonometer and an electrode system.

pH measurement.

The pH sensitive element of the equipment is a glass electrode. Heparinised blood is sucked anaerobically into the electrode through a polythene capillary. The tip of the capillary is immersed in the KCl well of a calomel electrode which provides a constant potential. Between the calomel electrode and the glass electrode, an electromotive force (EMF) is produced which is measured on the pH meter. This EMF expresses the potential of the glass electrode since the potential of the calomel electrode is constant. Therefore, blood pH can be measured directly on the pH meter after it has been calibrated with buffer solutions of known pH.

$PaCO_2$ measurement.

The pH of the blood sample is measured. Two aliquots of blood (0.2 ml) are placed in two vibrating glass chambers of the tonometer and separately equilibrated with two humidified O_2/CO_2 gas mixtures of known tensions (usually 4% CO_2 in O_2 and 8% CO_2 in O_2). The pH's of the equilibrated blood samples is then measured. These are plotted on a nomogram devised by Dr. Siggaard Andersen, which has the pH as the abscissa and $\log CO_2$ as the ordinate, and a straight line drawn between the two points. The point at which the pH of the unequilibrated blood sample touches this line is noted and the $PaCO_2$ read off the nomogram. As the nomogram used for determining $PaCO_2$ was calculated for man, in some experiments $PaCO_2$ measurements were also made using a Severinghaus electrode system in order to determine the justification of using Siggaard Andersen's nomogram for the calculation of $PaCO_2$ in the dog. The Severinghaus method is more direct and depends on the change in pH of a bicarbonate solution when it has equilibrated (as far as CO_2 is concerned) with the blood sample.

The following table shows a comparison of $PaCO_2$ values obtained in one dog with the micro-Astrup

apparatus and with the Severinghaus electrode. The $PaCO_2$ was altered by adding CO_2 to the respiratory mixture.

Analysis Pairs	1	2	3	4	5	6	7	8	9	10	11	12
Severinghaus $PaCO_2$ mm.Hg.	24.0	22.3	31.9	35.5	52.5	50.5	60.5	60.0	78.0	73.0	100.0	104.0
Astrup $PaCO_2$ mm.Hg.	23.0	21.5	30.4	34.5	48.5	51.0	61.0	61.5	79.0	70.0	99.0	105.0
(S - A) Difference	+1.0	+0.8	+1.5	+1.0	+4.0	-0.5	-0.5	-1.5	-1.0	+3.0	+1.0	-1.0

Mean difference = 0.65. mm.Hg.
No significant difference between methods.

It was concluded that there was no significant difference obtained in the $PaCO_2$ values with the more "direct" Severinghaus method and with the "indirect" micro-Astrup method, and that nomogram devised by Dr. Siggaard Andersen for the calculation of $PaCO_2$ in man was also valid for the dog.

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