Raised intracranial pressure and cerebral blood flow

I. Cisterna magna infusion in primates

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SUMMARY Changes in cerebral blood flow during incremental increases of intracranial pressure produced by infusion of fluid into the cisterna magna were studied in anaesthetized baboons. Cerebral blood flow remained constant at intracranial pressure levels up to approximately 50 mm Hg. At intracranial pressure levels between 50-96 mm Hg a marked increase in cerebral blood flow occurred, associated with the development of systemic hypertension and changes in cerebrovascular resistance. Further increases of intracranial pressure led to a progressive fall in cerebral blood flow. Prior section of the cervical cord prevented both the increase in cerebral blood flow and the systemic hypertension. Alteration of cerebral perfusion pressure by bleeding during the hyperaemia in a further group of animals suggested that autoregulation was at least partially preserved during this phase. After maximum hyperaemia had occurred, however, autoregulation appeared to be lost. The clinical implications of these findings are discussed.

Raised intracranial pressure may adversely affect brain function in a variety of ways, one of the more important being reduction of cerebral blood flow. The dependence of brain tissue on a continuing supply of oxygen and metabolic substrates lends reduced blood flow particular significance, and the resultant effects range from transient reversible neuronal dysfunction to irreversible ischaemic brain damage (Brierley, Brown, Excell, and Meldrum, 1969; Zwetnow, 1970; Graham and Adams, 1971).

Increasing use of continuous measurement of intracranial pressure in neurosurgical patients (Lundberg, 1960; Johnston, Johnston, and Jennett, 1970) has highlighted the need for more precise quantitative information on the relationship between intracranial pressure and cerebral blood flow. In defining this relationship it is important to consider the major factors controlling cerebral blood flow; the pressure differential or cerebral perfusion pressure (defined as the difference between mean arterial and mean intracranial pressures), and the resistance across the cerebral vasculature. It is clear from this that intracranial pressure itself is unlikely to be directly related to cerebral blood flow. Similarly cerebral perfusion pressure, which has been suggested as a more substantial basis for a

quantitative relationship (Zwetnow, 1968, 1970), would have a direct relationship to cerebral blood flow only if the cerebral vascular resistance were to remain constant. This assumption is not justified except in certain situations such as the state of vasomotor paralysis (Langfitt, Weinstein, and Kassell, 1965b).

Previous clinical and experimental work has shown that intracranial hypertension does reduce cerebral blood flow, but no clear relationship between cerebral blood flow and either intracranial pressure or cerebral perfusion pressure has emerged from the various studies (Kety, Shenkin, and Schmidt, 1948; Greenfield and Tindall, 1965; Langfitt, Kassell, and Weinstein, 1965a; Zwetnow, 1970). In particular the level intracranial pressure must reach before flow is reduced has varied considerably and would seem to depend on the rate of development and method of production of the intracranial hypertension. The importance of both factors may lie in the variability of the compensatory mechanisms which act to preserve cerebral blood flow in the face of rising intracranial pressure. These mechanisms include systemic hypertension, which may maintain cerebral perfusion pressure (Spencer and Horsley, 1891; Cushing, 1901), and also alterations in

vascular resistance (Wolff and Forbes, 1928; Fog, 1933). The causal factors behind both these responses remain inadequately understood.

The present experimental study was designed to clarify the relationship between intracranial hypertension and cerebral blood flow. It was also the aim to determine whether a definable quantitative relationship between the two parameters does exist and to study the significance of the compensatory mechanisms described above.

METHODS

Adult baboons, anaesthetized with phencyclidine hydrochloride and thiopentone sodium and maintained on phencyclidine hydrochloride, suxamethonium chloride and nitrous oxide/oxygen, were used in this study. Ventilation was by means of a Starling pump delivering a tidal volume adjusted to produce the required arterial pO_2 and pCO_2 levels.

The following pressures were measured using polythene cannulae connected to a series of pressure transducers (Bell and Howell), calibrated against a mercury column and recording on two-channel paper chart recorders (Devices):

1. *Ventricular fluid pressure (intracranial pressure)*: from the frontal horn of the right lateral ventricle by direct puncture through a twist drill hole placed 1 cm lateral to the bregma.

2. *Cisterna magna pressure*: by direct puncture through the atlanto-occipital membrane.

3. *Arterial pressure*: from the left femoral artery.

Cerebral blood flow was measured using both the ^{133}Xe Xenon clearance method and an electromagnetic flowmeter on the carotid artery in the neck. The right external carotid artery was ligated immediately beyond the carotid bifurcation and a polythene catheter (for injection of Xenon) inserted into the right internal carotid artery via the right lingual artery, which was ligated distal to the point of entry of the catheter. The electromagnetic flowmeter was placed on the exposed right common carotid artery. The Xenon clearance method used is identical with that previously described from this laboratory (Rowan, Harper, Miller, Tedeschi, and Jennett, 1970).

Arterial pO_2 , pCO_2 , pH, jugular venous pO_2 , pH, venous haemoglobin, and PCV values were estimated at the beginning of each cerebral blood flow measurement. End tidal CO_2 was continuously monitored using an infrared analyser and an electrocardiographic tracing run at intervals during each experiment.

Three series of experiments were carried out:

GROUP I (EIGHT ANIMALS) Intracranial pressure was raised by infusion of artificial cerebrospinal fluid

(CSF), at constant temperature, into the cisterna magna. The infusion pressure was kept constant by means of an anaeroid barometer and the resultant pressure in the cisterna magna continuously monitored as described above. After control values had been established the pressure was raised in increments of 5 to 20 mm Hg. After each increase conditions were allowed to stabilize as far as possible and a Xenon clearance curve obtained. The interval between increases of pressure averaged approximately 30 minutes. Elevation of pressure was continued in this manner until a substantial reduction of cerebral blood flow occurred.

GROUP II (FOUR ANIMALS) Before carrying out the procedures outlined above a cervical laminectomy was done and the cervical cord sectioned at C3/4 segment to abolish the systemic hypertension which developed as the intracranial pressure was raised in group I. Ligatures above and below the line of section prevented loss of CSF.

GROUP III (FOUR ANIMALS) In this group, when the intracranial pressure had reached approximately 60 mm Hg (the level at which systemic hypertension and increased cerebral blood flow developed in group I, *vide infra*) progressive reduction of blood pressure was achieved by intermittent withdrawal of blood from an additional catheter in the right femoral artery. After initial reduction the blood pressure in this group was subsequently raised again by intravenous infusion of pressor drugs.

At the end of each experiment the animal was killed using intravenous pentobarbitone sodium. Those in group I were perfused with fixative and the brain removed for histological examination.

RESULTS

The results in the three groups outlined above will be described separately. The findings in the first two groups will be considered under three headings; changes in cerebral blood flow, compensatory mechanisms, and the relationship between cerebral perfusion pressure and cerebral blood flow.

GROUP I

CHANGES IN CEREBRAL BLOOD FLOW All eight animals maintained cerebral blood flow within the control range during the initial increases of intracranial pressure (up to 50 mm Hg). The majority showed a slight increase in flow during this phase but one animal, with a high resting flow, showed a slight fall. At intracranial pressure levels between 50 and 96 mm Hg all

TABLE 1
SUMMARY OF DATA FROM EXPERIMENTS IN GROUP I

		MAP (mm Hg)	ICP (mm Hg)	CPP (mm Hg)	CVR	CBF (ml./100g/min)
Experiment 1	a	115	10	105	2.28	56
	b	203	80	70	1.30	98
	c	155	116	47	0.72	44
Experiment 2	a	117	25	92	1.93	47
	b	177	75	68	1.32	77
	c	148	107	46	0.88	46
Experiment 3	a	88	1	87	1.17	74
	b	137	71	51	0.69	95
	c	122	75	62	0.74	63
Experiment 4	a	107	11	96	1.65	58
	b	182	96	61	1.18	73
	c	114	112	2	—	0
Experiment 5	a	125	7	118	2.62	45
	b	143	68	85	1.19	68
	c	151	93	67	1.36	46
Experiment 6	a	93	20	73	0.84	87
	b	178	67	63	0.87	126
	c	122	86	67	0.76	47
Experiment 7	a	116	6	110	2.45	42
	b	120	50	70	1.29	54
	c	127	60	67	1.52	44
Experiment 8	a	105	24	81	2.89	28
	b	170	85	30	1.73	49
	c	117	112	51	—	0

MAP: mean arterial pressure. ICP: intracranial pressure. CPP: cerebral perfusion pressure. CVR: cerebrovascular resistance. CBF: cerebral blood flow.
(a) control values, (b) values at maximum cerebral blood flow, (c) values when cerebral blood flow had returned to control levels or below.

FIG. 1. Changes in cerebral blood flow (CBF), mean arterial pressure (MAP), cerebral perfusion pressure (CPP), and cerebrovascular resistance (CVR) with progressive increase in intracranial pressure (ICP). Data from one experiment.

TABLE 2
RANGE OF INCREASE IN MEAN ARTERIAL PRESSURE IN GROUP I EXPERIMENTS

Expt.	Control MAP (mm Hg)	Maximum MAP (mm Hg)	Control levels			Values before max. MAP		
			ICP (mm Hg)	CPP (mm Hg)	CBF (ml./100g/min)	ICP (mm Hg)	CPP (mm Hg)	CBF (ml./100g/min)
1	115	203	10	105	56	80	70	62
2	115	177	22	93	48	75	68	57
3	88	137	1	87	74	71	51	86
4	107	182	11	96	58	96	61	67
5	125	205	7	118	45	146	14	22
6	93	178	20	73	87	67	63	100
7	116	148	13	103	42	112	33	28
8	99	170	23	76	30	85	30	49

Abbreviations as in Table 1.

animals developed a substantial increase in cerebral blood flow ranging from 26% to 85% above control levels for each animal. Increased blood flow was associated with a substantial increase in mean arterial pressure in six of the eight animals, a moderate increase in one, and an unchanged mean arterial pressure in the remaining animal. In only one animal had the cerebral perfusion pressure fallen below 50 mm Hg at the time of maximum hyperaemia, while in seven out of eight animals there had been a marked reduction in cerebrovascular resistance. These changes are detailed in Table 1.

After the development of hyperaemia the cerebral blood flow remained high despite further increase of intracranial pressure over a relatively narrow range. Beyond intracranial pressure levels ranging from 75 to 116 mm Hg, cerebral blood flow fell below control values in each animal, and continued to fall as the intracranial pressure was further increased. By the time intracranial pressure had reached a level ranging from 95 to 153 mm Hg, cerebral blood flow virtually ceased. The full sequence of events from one experiment is illustrated in Fig. 1.

In two animals in which cerebral blood flow was measured after reducing intracranial pressure to normal from levels which had been sufficient to reduce flow substantially, there was a marked increase in flow, from 36 to 107 and 0 to 92 ml./100 g/min respectively. In the latter animal this post-compression hyperaemia was considerably reduced by a 10-minute period of hyperventilation.

COMPENSATORY MECHANISMS 1. *Systemic hypertension* In all animals the mean arterial

pressure rose with increasing intracranial pressure, systolic pressure rising more than diastolic thus increasing the pulse pressure. The range of increase of mean arterial pressure is shown in Table 2. In seven out of the eight animals systemic hypertension developed gradually as intracranial pressure was raised, while in one it occurred abruptly.

In considering possible causative factors for the systemic hypertension a number of points may be noted. The range of intracranial pressure at which maximum systemic hypertension occurred was from 67–146 mm Hg. In all but one case this was less than the control mean arterial pressure. Immediately before the development of maximum systemic hypertension cerebral perfusion pressure ranged from 14 to 70 mm Hg and cerebral blood flow from 22 to 100 ml./100 g/min. Reduction of neither of these parameters was therefore a prerequisite for the occurrence of systemic hypertension. Further, in no case did a substantial gradient between the infusion pressure into the cisterna magna and the intracranial pressure measured supratentorially develop before the systemic hypertension. The values of the various parameters at the time of development of maximum systemic hypertension are given in Table 2.

A comparison of Tables 1 and 2 will show that maximum increase in cerebral blood flow and maximum systemic hypertension occurred at the same level of intracranial pressure in six of the eight animals, suggesting a connection between the two responses. In the two remaining animals the hyperaemia preceded the development of a substantial increase in mean arterial pressure but was associated with a considerable

reduction in cerebrovascular resistance. In these two animals the systemic hypertension did not produce a further increase in cerebral blood flow.

2. Change in vascular resistance Seven animals showed a progressive fall in cerebrovascular resistance until the development of the hyperaemia. In four of the seven cerebrovascular resistance was then maintained during and beyond the hyperaemia; in the remaining three the fall in resistance was continued, although the hyperaemia persisted, until the flow began to fall off progressively, after which no further change in cerebrovascular resistance occurred.

RELATIONSHIP BETWEEN CEREBRAL PERFUSION PRESSURE AND CEREBRAL BLOOD FLOW A composite plot of cerebral perfusion pressure against cerebral blood flow for all experiments, and at all stages of autoregulation indicates a variable relationship (Fig. 2); reduction of one parameter below levels which might be expected to be critical was associated with a very wide range of values of the other parameter. For example, reduction of cerebral blood flow below the level of 40 ml./100 g/min was associated with cerebral perfusion pressure values from 0 to 68 mm Hg, while reduction of cerebral perfusion pressure below 40 mm Hg was associated with cerebral blood flow values from 0 to 59 ml./100 g/min.

Curves of the relationship between cerebral perfusion pressure and cerebral blood flow showed three distinct phases as illustrated in

the curve from one experiment (Fig. 3). During the first stage the points (1–6) represent a period of normal autoregulation. High flows occurred with further increases of intracranial pressure, but at cerebral perfusion pressure levels at or above control (points 7–8); cerebral blood flow remained high despite falling cerebral perfusion pressure over a narrow range. Lastly, after

FIG. 3. Relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) in one experiment. Each point represents a Xenon clearance measurement; numbers indicate temporal sequence.

maximum hyperaemia had occurred, cerebral blood flow fell with falling cerebral perfusion pressure in linear fashion suggesting failure of autoregulation (points 9–12).

SUMMARY The inter-relationship between intracranial hypertension and cerebral blood flow exemplified by these experiments may be summarized as follows: During initial increase of intracranial pressure (levels below 50 mm Hg) cerebral blood flow remains around control levels despite the tendency of mean arterial pressure to rise and cerebral perfusion pressure to fall. At intracranial pressure levels between 50 and 96 mm Hg, an increase in cerebral blood flow develops which is maintained over a narrow range of further increase of intracranial pressure. This increased flow seems to depend on a substantial increase in mean arterial pressure, or on a definite reduction in cerebrovascular resistance, or a combination of these two factors. After the

FIG. 2. Composite plot of relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). Data taken from all group I experiments, and at all stages of autoregulation.

development of maximum hyperaemia cerebral blood flow then falls progressively as intracranial pressure is further increased and the cerebral perfusion pressure/cerebral blood flow curve becomes linear, suggesting failure of the cerebral vessels to autoregulate to changes in perfusion pressure. This sequence of events is illustrated in Fig. 1.

GROUP II

The aim in this group was to prevent the development of systemic hypertension by prior section of the cervical cord (C3/4 segment) and to determine whether this also prevented development of the hyperaemia described in group I.

CHANGES IN CEREBRAL BLOOD FLOW All four animals showed a progressive fall in cerebral blood flow which began with the first increase of intracranial pressure in three, and with the second increase in one animal; in this case the control intracranial pressure was particularly low due to loss of CSF during preparation. No animal showed the sustained hyperaemia seen in group I and, in fact, flow had virtually ceased in this group at intracranial pressure levels of 27 to 52 mm Hg. Two of the four animals did, however, show late, transient increases in flow in association with rhythmic fluctuations of mean arterial pressure which the changes of flow accurately reflected.

In two animals in this group release of intracranial pressure after zero flow was associated in one with return of flow to approximately control levels and in the other with no return of flow whatever; postcompression hyperaemia occurred in neither.

COMPENSATORY MECHANISMS 1. *Systemic hypertension* A sustained increase in mean arterial pressure did not occur after cervical cord section. In two of the four animals mean arterial pressure remained around control levels throughout the period of raised intracranial pressure, while the remaining two showed marked transient rhythmic fluctuations of mean arterial pressure associated with alterations in pulse rate and rhythm at intracranial pressure levels of 42 and 52 mm Hg respectively. No obvious precipitating cause for these changes was detected.

2. *Change in vascular resistance* In two animals the cerebrovascular resistance increased

as intracranial pressure increased, while in one it remained relatively constant and in the fourth animal fell somewhat. In general, substantial changes in cerebrovascular resistance did not occur; in particular there was no evidence of significant vasodilatation with increased intracranial pressure in this group.

RELATIONSHIP BETWEEN CEREBRAL PERFUSION PRESSURE AND CEREBRAL BLOOD FLOW Cerebral perfusion pressure fell progressively as intracranial pressure was increased in this group, apart from transient increases at the time of the fluctuations in mean arterial pressure described above. Cerebral perfusion pressure/cerebral blood flow curves for these four animals showed an approximately linear relationship throughout as exemplified in Fig. 4.

SUMMARY After cervical cord section sustained systemic hypertension did not occur with increased intracranial pressure and no sustained hyperaemia was encountered in any animal. Rhythmic fluctuations of mean arterial pressure were noted in two of the four animals and were associated with substantial transient changes in cerebral blood flow in the same direction. The cerebral perfusion pressure/cerebral blood flow curves were approximately linear throughout, suggesting absence of autoregulation.

FIG. 4. Relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP) after cervical cord section. Data from one experiment. Each point represents a Xenon clearance measurement; numbers indicate temporal sequence.

FIG. 5. Changes in cerebrovascular resistance (CVR), mean arterial pressure (MAP), and cerebral blood flow (CBF) with initial increase of intracranial pressure (ICP) and subsequent alteration of mean arterial pressure by bleeding or intravenous infusion. Data from one experiment.

FIG. 6. Relationship between cerebral blood flow (CBF) and cerebral perfusion pressure (CPP). Data from one experiment.

GROUP III

The objective in this group was to study auto-regulation of cerebral blood flow to changes in mean arterial pressure (and therefore in cerebral

perfusion pressure) during and after the period of hyperaemia described in group I. The mean arterial pressure was altered either by withdrawal of blood or by intravenous infusion of fluid.

DURING HYPERAEMIA In three of the four animals hyperaemia either persisted or increased slightly despite reduction of cerebral perfusion pressure by reduction of the mean arterial pressure, as exemplified in Fig. 5 taken from one experiment. There was, therefore, a fall in the calculated cerebrovascular resistance suggesting increasing vascular dilatation as the means whereby the high flow rates were maintained or increased. The range of cerebral perfusion pressure over which the hyperaemia was maintained was quite narrow, being between 10 and 32 mm Hg.

AFTER HYPERAEMIA Further reduction of cerebral perfusion pressure by bleeding at this stage produced a steady fall in cerebral blood flow in all four animals. In three of the four an attempt was made to restore the mean arterial pressure by intravenous infusion after a series of reductions of mean arterial pressure (and therefore of cerebral perfusion pressure). In two animals whose mean arterial pressure rose with infusion of 0.9% saline alone, the cerebral blood flow rose as the cerebral perfusion pressure increased and fell again with further reduction of cerebral perfusion pressure by subsequent withdrawal of blood. In the third animal it was possible to raise the mean arterial pressure (cerebral perfusion pressure) only with the addition of dextran and noradrenaline to the saline and in this animal, although the cerebral perfusion pressure rose from 9 to 50 mm Hg, cerebral blood flow did not alter.

SUMMARY These findings suggest that autoregulation is preserved during the period of hyperaemia and systemic hypertension (although it may be somewhat impaired) judging by the cerebral perfusion pressure/cerebral blood flow curves (Fig. 6a). After maximum hyperaemia has occurred autoregulation to cerebral perfusion pressure changes seems to be lost and the cerebral perfusion pressure/cerebral blood flow curves become linear (Fig. 6b).

DISCUSSION

While the results of the present study agree with earlier work in showing that cerebral blood flow may be reduced by intracranial hypertension, important points of divergence do, however, emerge. These concern the sequence of changes in blood flow with progressive increase of

intracranial pressure and the nature of the compensatory mechanisms by which flow is preserved. Such observations focus attention on two further points: the autoregulatory function of the cerebral vessels to changes in cerebral perfusion pressure brought about by rising intracranial pressure, and the clinical relevance of these and other experimental findings.

Previous experimental studies on the relationship between intracranial hypertension and cerebral blood flow have shown two distinct patterns. In some cases cerebral blood flow was maintained until the intracranial pressure reached a certain level, beyond which there was a progressive reduction in blood flow. This applies both to increased pressure due to infusion of fluid into the subarachnoid space (Häggendal, Löfgren, Nilsson, and Zwetnow, 1970; Zwetnow, 1970), and due to progressive expansion of an extracerebral balloon (Langfitt, Kassell, and Weinstein, 1965a). The critical level of intracranial pressure varied from 50 to 100 mm Hg. In others, however, rapid expansion of a supratentorial balloon caused a progressive fall in cerebral blood flow starting with the initial increments of pressure (Langfitt *et al.* 1965a).

Early clinical studies, using arteriovenous oxygen differences to measure cerebral blood flow, did not show any reduction with intracranial hypertension due to supratentorial lesions, although some reduction was noted in patients with posterior fossa neoplasms (Williams and Lennox, 1939; Courtice, 1940). Subsequently Kety *et al.* (1948), using nitrous oxide inhalation, found a progressive reduction of cerebral blood flow with intracranial pressure levels exceeding 30 mm Hg. Greenfield and Tindall (1965), by infusing fluid into the lumbar subarachnoid space in patients, also found a progressive reduction of cerebral blood flow at intracranial pressure levels beyond 35 mm Hg, with flows falling by approximately 25% of control values at intracranial pressure levels of 70 mm Hg. Studies during spontaneously occurring plateau waves in patients with intracranial hypertension have shown a definite reduction of cerebral blood flow associated with an increase in cerebral blood volume and angiographic appearances suggesting cerebral vasodilatation (Lundberg, Cronqvist, and Kjällquist, 1968; Risberg, Lundberg, and Ingvar, 1969).

Previous clinical and experimental studies have therefore indicated that, in most circum-

stances, cerebral blood flow is initially maintained despite rising intracranial pressure, but that beyond a certain level of intracranial pressure the situation changes and further increases in pressure are associated with a progressive fall in cerebral blood flow. The present experimental findings demonstrate a somewhat more complex sequence of events. During initial increase of intracranial pressure cerebral blood flow is, indeed, maintained. At intracranial pressure levels from 50 to 96 mm Hg, however, a marked increase in cerebral blood flow occurs, associated with either a marked increase in mean arterial pressure alone or a combination of increased mean arterial pressure and reduced cerebrovascular resistance. This hyperaemia is maintained over a narrow range of further increase of intracranial pressure before a progressive fall in cerebral blood flow occurs, culminating in cessation of flow at intracranial pressure levels from 96 to 153 mm Hg.

A number of explanations may be offered to account for the discrepancies in the clinical and experimental results discussed above. Firstly, the means by which intracranial pressure is raised may be important. With local expanding lesions substantial regional flow changes may occur and much will depend on whether cerebral blood flow is measured locally or total flow is calculated. The development of intracranial pressure gradients, such as across the tentorium, may also alter the compensatory mechanisms to rising intracranial pressure (Thompson and Malina, 1959; Weinstein, Langfitt, Bruno, Zaren, and Jackson, 1968). On the other hand, when intracranial pressure is raised by infusion, the fluid may alter the chemical status of the CSF and therefore affect vascular reactivity.

A second factor which may be of considerable significance is the time course of the increase in intracranial pressure. It is apparent from clinical practice that a substantially larger mass lesion may be accommodated within the cranium without overt evidence of neurological dysfunction if its development has been gradual rather than rapid. Experimental studies have involved relatively rapid rises in pressure by clinical standards, although the time course has varied considerably between different series of experiments. The intermittent marked increases in intracranial pressure seen clinically (Lundberg, 1960; Johnston *et al.* 1970) have no counterpart in experimental observations.

Differences in the methods of estimating cerebral blood flow may also contribute to the discrepancies between different studies. Discussion of the relative merits and the sources of possible inaccuracy in the various methods may be found in recent reviews by Reivich (1969) and Harper (1969). Finally, the experimental conditions, such as the type and ease of anaesthetic, the nature of the surgical procedures, together with the age and health of the animal may influence the results, in particular by affecting autoregulation.

The manner in which these various factors act to alter the responses of cerebral blood flow to intracranial hypertension in different circumstances is, in general terms, by influencing the compensatory mechanisms which may be brought into play in such situations. It is, therefore, apposite to consider these mechanisms, the most important of which are changes in systemic blood pressure and alterations in the diameter of the cerebral resistance vessels.

Systemic hypertension in raised intracranial pressure may act to preserve cerebral perfusion pressure. That such systemic hypertension may be associated with raised intracranial pressure was well known before the turn of the century (Naunyn and Schreiber, 1881; Spencer and Horsley, 1891; Hill, 1896), but it is Cushing's description which is usually quoted (Cushing, 1901, 1903). Indeed, systemic hypertension is one of the main features of the Cushing response, the other components of which are bradycardia and alteration of respiratory rhythm. According to most studies, it would seem that the intracranial pressure must approach the systolic blood pressure before marked systemic hypertension occurs (Cushing, 1901, 1903; Wright, 1938; Rodbard and Saiki, 1952; White and Borison, 1955; Weinstein, Langfitt, and Kassell, 1964; Kramer and Tuynman, 1967; Zwetnow, 1970). It must be noted, however, that some authors have found such increase of intracranial pressure to occur without any significant systemic hypertension whatever and have questioned the reliability of such a sign as a clinical index of intracranial hypertension (Browder and Meyers, 1936, 1938; Meyers, 1942; Evans, Espey, Kristoff, Kimbell, and Ryder, 1951; Greenfield and Tindall, 1965). More recently, continuous monitoring of both intracranial and mean arterial pressures in patients with raised intracranial pressure has confirmed the unpredictable nature of the relationship between

these two parameters (Lundberg, 1960; Johnston, Rowan, Harper, and Jennett, in preparation).

The present experimental study differs from much of the earlier work in showing a substantial rise in mean arterial pressure with relatively moderate increases in intracranial pressure, levels well within the range of intracranial pressure seen clinically. The level of intracranial pressure which may precipitate the vasopressor response leading to systemic hypertension clearly has considerable bearing on the efficacy of this response as a means of preserving adequate cerebral blood flow. Indeed, if systemic hypertension were called into play only at extreme levels of intracranial pressure, as has been suggested, it would seem, teleologically, a rather inefficient means of maintaining cerebral blood flow. In fact no great significance has hitherto been placed on systemic hypertension in the preservation of cerebral blood flow in raised intracranial pressure (Zwetnow, 1970).

To place this vasopressor response in proper perspective it is necessary to understand how it is produced. Various stimuli have been postulated as evoking the response. These include ischaemia or hypoxia (either generalized or localized to the brain-stem) (Cushing, 1901, 1903; Zwetnow, 1970), local distortion of the brain-stem (Thompson and Malina, 1959; Weinstein *et al.*, 1964), direct stimulation of the brain-stem or spinal cord (Suh, Wang, and Lim, 1936; Alexander and Kerr, 1964; Evans and Geddes, 1967; Hoff and Reis, 1970), and alteration in cerebral perfusion pressure acting through unidentified intracranial baroreceptors (Rodbard and Saiki, 1952; Dickenson and McCubbin, 1963). The present findings argue against ischaemia or hypoxia in not finding any significant prior reduction in total cerebral blood flow; against brain-stem distortion in not finding any intracranial pressure gradients; and also against changes in cerebral perfusion pressure. By exclusion, therefore, a direct pressure effect on either the brain-stem or spinal cord is favoured as the stimulus which evokes the systemic hypertension seen in raised intracranial pressure.

Change in the resistance across the cerebral vasculature is the other major means whereby cerebral blood flow may be maintained in intracranial hypertension. Both pial and cortical surface vessels have been seen to dilate with raised intracranial pressure (Cushing, 1901; Wolff and Forbes, 1928; Fog, 1933), although in a recent study such dilatation was not found

(Hekmatpanah, 1970). Calculation of the cerebrovascular resistance from the present data certainly suggests that vasodilatation does occur with increased intracranial pressure and may play a significant role in the development of the hyperaemia described above.

The mechanism by which such changes in vascular diameter are mediated, and indeed the site at which these changes occur remain obscure. The function of the nerve fibres which abound on the pial vessels is a controversial subject. Recent studies using fluorescence microscopy to demonstrate noradrenaline have suggested that such innervation may be of greater significance than was previously thought (Nielsen and Owman, 1967; Falck, Nielsen, and Owman, 1968). Neurogenic factors rather than changes in transmural pressure or in local metabolic states, may, therefore, control changes in vascular diameter in raised intracranial pressure.

If this is so, a unifying hypothesis may be postulated to account for the present experimental findings. It is suggested that raised pressure on the neuraxis directly excites sympathetic efferent neurones and the intense sympathetic activity produces marked systemic hypertension. Dilatation of the cerebral resistance vessels also occurs. This may reflect a change in the autoregulatory capacity of these vessels, due to the systemic hypertension, or possibly a primary effect of the sympathetic activity, mediated through a β -receptor mechanism.

Beyond a certain level of intracranial pressure, ranging from 75 to 116 mm Hg in the animals in group I of the present series, the cerebral vessels lose the power to autoregulate to changes in cerebral perfusion pressure. Such loss of autoregulation appears to be progressive and to take place during the hyperaemic phase described above. In addition, the systemic hypertension is not maintained as intracranial pressure is further increased, and the mean arterial pressure starts to fall. The resultant fall in cerebral perfusion pressure in a non-autoregulating system leads to a progressive reduction in cerebral blood flow. A linear relationship between cerebral perfusion pressure and cerebral blood flow is then seen.

In considering the clinical relevance of these and other experimental findings considerable caution is required, and due weight must be given to differences in the mechanism and the time course of the increase in intracranial pressure in determining the changes in cerebral

blood flow. It is clear, however, that a knowledge of intracranial pressure alone, or even of the cerebral perfusion pressure at a given moment, is unreliable as a guide to the cerebral blood flow at that moment. This is because the response of the cerebral circulation to changes in these parameters depends on the autoregulatory capacity of the vessels at the time and, therefore, on the previous history of the system. If it could be established that autoregulation had been lost, however, a knowledge of either intracranial pressure or cerebral perfusion pressure might be of considerable value in predicting changes in cerebral blood flow.

The authors wish to thank the technical and biochemical staff of the Wellcome Surgical Research Institute for their invaluable assistance throughout these experiments.

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