Systemic vascular responses to increased intracranial pressure

2 The 'Cushing' response in the presence of intracranial space-occupying lesions: systemic and cerebral haemodynamic studies in the dog and the baboon

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SUMMARY Continued expansion of an artificial space-occupying lesion produced further increases in mean supratentorial and infratentorial pressures associated with increases in mean arterial pressure, heart rate, and systemic vascular resistance—the 'Cushing' or systemic hypertensive response. These primary changes resulted in an increase in transtentorial pressure gradient and a decrease in arrhythmia index. Immediately before the onset of the systemic hypertensive response, supratentorial perfusion pressure was low, and the period of systemic hypertension did not appear to produce any worthwhile improvement in the perfusion pressure or in the blood flow in the supratentorial compartment. The studies demonstrated also that the systemic hypertensive response was a pre-terminal event and was followed rapidly by circulatory failure.

Since the beginning of the nineteenth century, increased intracranial pressure and the mechanisms by which it acted have been the subjects of many investigations both in the experimental animal and in the clinical situation. As early as 1811, Ravina studied the effects of increased intracranial pressure after inserting glass windows in the skull. A few years later, Astley Cooper (1824) found that, in animals, mechanical pressure against the surface of the brain would produce a decrease in heart rate. In 1880, von Bergmann was able to induce a decrease in pulse rate and depression of respiration by increasing the intracranial pressure. In addition, he showed that when the intracranial pressure equalled the systolic arterial pressure in the carotid artery, death would follow. Since the observations of Kocher (1901) and Cushing (1901), it has been accepted widely that alterations in

intracranial pressure may produce profound changes in cardiovascular haemodynamics, the most frequently cited manifestation of this relationship being the association between increased intracranial pressure and the increase of the systemic arterial pressure, the systemic hypertensive or 'Cushing' response (SHR). Systemic vascular responses to increased intracranial pressure in animals with artificial space-occupying lesions occurring before the onset of the SHR have been studied previously (Fitch and McDowall, 1977). The present investigation deals with the relationships existing between the SHR and the levels of intracranial pressure in different intracranial compartments during and after the period of increased arterial pressure. In addition, in one group of investigations, cerebral blood flow has been studied to assess the perfusion of the brain at the time of the initiation of the SHR and to determine whether or not increases in cerebral perfusion resulted from the systemic hypertension.

Methods

Three groups of investigations have been carried

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out, two in dogs and one in baboons. In each animal an artificial space-occupying lesion was created by the placement of a small balloon in the extradural space over one hemisphere. Volume changes of this artificial mass lesion were produced by the addition of fluid to the balloon. In dogs, the fluid was either added rapidly (1 ml fluid administered over 2 min: group A) or infused slowly (1 ml fluid administered over 20 min: group B). The detailed methodology of these investigations has been described by Fitch and McDowall, 1977.

GROUP C (SLOW INFLATION: BABOONS)

In five baboons, premedicated with phencyclidine (8 mg), anaesthesia was induced with nitrous oxide, oxygen, and halothane, and was continued with these agents during the surgical preparation. Muscular relaxation was obtained by the intramuscular injection of pancuronium and controlled ventilation was employed. The minute volume of ventilation was adjusted as required to maintain normocapnic conditions throughout the experiment. As detailed previously for the dogs, an extradural balloon was positioned over the anterolateral surface of the parietal cortex, and this balloon was inflated continuously (except for one experiment where the regime was 20 min of inflation followed by 10 min halothane) with 1 ml/hr approximately.

Supratentorial pressure was measured using a thin-walled balloon placed in the subarachnoid space of the opposite cerebral hemisphere. A catheter, inserted into the cisterna magna, permitted measurement of infratentorial pressure. Both carotid arteries were exposed in the neck and electromagnetic flow probes (Statham) were placed on both common carotid arteries after ligation of all the branches of both external carotid circulations. In addition, on the side opposite to the space-occupying lesion, a catheter was inserted into the common carotid artery via one of the ligated branches. Through this catheter 0.5 ml ^{133}Xe dissolved in saline was injected and

cerebral blood flow was determined from the rate of change of the xenon concentration detected by an external scintillation counter mounted over the cerebral hemisphere opposite to the artificial mass lesion.

Results

As the results relating to the changes taking place in circulatory haemodynamics and intracranial pressure up to the initiation of the systemic hypertensive response (phase 1) have already been described (Fitch and McDowall, 1977), only those results obtained during and after the period of systemic hypertension (phase 2) will be discussed here. With this in mind, it should be noted that the values ascribed to intracranial pressure, cardiac output, systemic vascular resistance, stroke volume, heart rate, cerebral perfusion pressure, and transtentorial pressure gradient as the 'maximum' values are not necessarily the maximum changes observed in each of these individual indices, but are those values of intracranial pressure, cardiac output, and so on, which correspond to the point of *maximum arterial pressure increase*.

The values are presented as mean $\pm$ SEM and the results have been calculated as described by Fitch and McDowall (1977).

One animal in group B and one animal from group C did not show a typical 'Cushing' response, circulatory failure ensuing without the appearance of systemic hypertension. The results from these two animals are not included in those described below since in this communication we are studying the hypertensive response.

GROUP A (RAPID INFLATION: DOGS)

The changes observed, both in the intracranial and cardiovascular indices, in the six animals subjected to rapid inflation (1 ml fluid added over 2 min) of the artificial supratentorial mass lesion are presented in Table 1a (intracranial indices) and in Table 1b (cardiovascular indices and displayed in the Figure.

Table 1a *Effects of SHR (systemic hypertensive response) on the intracranial indices in six animals subjected to rapid inflation of the extradural balloon (group A)*

	Immediately before onset of SHR	At peak of SHR	Five minutes after peak of SHR	15 minutes after peak of SHR
Mean supratentorial pressure kPa (mmHg)	10.1 $\pm$ 0.53 (76 $\pm$ 4)	22.2 $\pm$ 2.7 (167 $\pm$ 20)*	17.6 $\pm$ 1.9 (132 $\pm$ 14)	13.4 $\pm$ 1.9 (101 $\pm$ 14)
Mean supratentorial perfusion pressure kPa (mmHg)	3.1 $\pm$ 0.53 (23 $\pm$ 4)	6.7 $\pm$ 1.7 (50 $\pm$ 13)	5.1 $\pm$ 0.93 (38 $\pm$ 7)**	3.2 $\pm$ 2.8 (24 $\pm$ 21)

Results are expressed as mean $\pm$ SEM. Significant differences between values obtained immediately before onset of SHR: * $p < 0.05$; ** $p < 0.01$

Table 1b Effects of SHR on the cardiovascular indices in six animals subjected to rapid inflation of the extradural balloon (group A)

	Immediately before onset of SHR	At peak of SHR	Five minutes after peak of SHR	15 minutes after peak of SHR
Heart rate beats/min	67 ± 12	148 ± 23	189 ± 25*	200 ± 17***
Mean arterial pressure kPa (mmHg)	13.2 ± 0.4 (99 ± 3)	27.8 ± 3.6 (209 ± 27)**	22.6 ± 2.4 (170 ± 18)**	15.8 ± 2.8 (119 ± 21)
Systolic arterial pressure kPa (mmHg)	17.2 ± 0.4 (129 ± 3)	35.1 ± 4.3 (264 ± 32)**	26.2 ± 2.8 (197 ± 21)*	18.4 ± 3.4 (138 ± 30)
Diastolic arterial pressure kPa (mmHg)	11.2 ± 0.67 (84 ± 5)	24.0 ± 3.3 (181 ± 25)*	19.7 ± 2.3 (148 ± 17)*	14.6 ± 2.8 (110 ± 21)
Pulse pressure kPa (mmHg)	6.0 ± 0.8 (45 ± 6)	11.0 ± 1.2 (83 ± 9)	6.5 ± 1.5 (49 ± 11)	3.7 ± 0.93 (28 ± 7)
Cardiac output (litre/min)	2.31 ± 0.34	2.62 ± 0.23	2.97 ± 0.18	3.47 ± 0.25**
Stroke volume (ml/beat)	33 ± 8	20 ± 4	17 ± 3	18 ± 1
Systemic vascular resistance (dyn sec cm ⁻⁵)	3840 ± 451	6613 ± 951**	4648 ± 450	2935 ± 486
Arrhythmia index (%)	94 ± 27	21 ± 13*	10 ± 10**	0
Arrhythmia absolute (beats)	60 ± 4	23 ± 12*	10 ± 10**	0

Results are expressed as mean ± SEM. Significant differences between values obtained immediately before onset of SHR: *P < 0.05; **P < 0.01; ***P < 0.001.

Intracranial indices

Immediately before the initiation of the systemic hypertensive response 8.0 ml ± 0.5 had been added to the balloon. This induced abrupt changes in the supratentorial pressure and by the time the total balloon volume had reached 10.0 ml ± 0.2 a marked SHR was evident in each animal. Immediately before the appearance of the SHR, mean supratentorial pressure ranged from 7.7 kPa (58 mmHg) to 11.6 kPa (87 mmHg) (average 10.1 kPa ± 0.53 (76 mmHg ± 4)). At this point, mean supratentorial perfusion pressure was 3.1 kPa ± 0.53 (23 mmHg ± 4) (range 1.1 kPa (8 mmHg) to 4.9 kPa (37 mmHg)). However, although mean arterial pressure increased significantly with the onset of the SHR (*vide infra*), supratentorial pressure increased also +12.1 kPa ± 3.2 (+91 mmHg ± 24) with the result that the increase in supratentorial perfusion pressure was only 3.5 kPa ± 1.7 (26 mmHg ± 13) (range -0.67 kPa (-5 mmHg) to 11.2 kPa (84 mmHg)). It was noted that supratentorial perfusion pressure increased in five of the animals and decreased in one. As a result, the overall change in perfusion pressure in the supratentorial compartment was not significant. In this particular group of animals, there were only two in which infratentorial pressure was measured and thus in which values of infratentorial perfusion pressure and transtentorial pressure gradient could be calculated. In these two animals there was little change in the posterior fossa pressure, presumably because of already existing tentorial impaction. As a result of the increase in mean arterial pressure, infratentorial perfusion pressure in these two animals increased from 9.8 kPa (74 mmHg) and 9.4 kPa (71 mmHg) to 17.7 kPa (133 mmHg) and 12.6

kPa (95 mmHg) respectively. In addition, the transtentorial pressure gradient increased by 4.3 kPa (32 mmHg) and 2.9 kPa (22 mmHg) subsequent to the increase in supratentorial pressure.

Cardiovascular indices

Immediately before the appearance of the SHR response, mean arterial pressure ranged from 11.7 kPa (88 mmHg) to 14.4 kPa (108 mmHg) and, as a result of the increase in balloon volume, mean arterial pressure increased, in each of the animals, to a mean value of 27.8 kPa ± 3.6 (209 mmHg ± 27) (range 18.9 kPa (142 mmHg) to 40.2 kPa (302 mmHg)). Both the systolic and the diastolic pressures were observed to increase significantly, but the increase in systolic pressure 18.0 kPa ± 4.0 (135 mmHg ± 30) was greater than that in the diastolic pressure (12.9 kPa ± 3.6 (97 mmHg ± 27)), so that the pulse pressure increased significantly also.

The peak of the SHR was associated with increases in heart rate in five of the animals (range +15 beats/min to +190 beats/min), and with a decrease in heart rate in the remaining animal (-25 beats/min). There was thus no significant change in heart rate at the peak of the SHR. However, heart rate continued to increase once the peak arterial response had passed and by 10 min to 20 min after the peak arterial pressure the heart rate, which had continued to increase in all of the animals, showed significant changes overall. A study of the other cardiovascular indices would support the contention that the SHR was the result of a marked and significant increase (+42%) in the systemic vascular resistance. At the peak of the SHR there was no significant

Figure Mean values, with standard errors, for heart rate (HR), mean arterial pressure (MAP), supratentorial intracranial pressure (STP), supratentorial perfusion pressure (STPP), cardiac output (CO), and systemic vascular resistance (SVR) during phase 2. Results from six animals from group A (●—●), nine animals from group B (○ --- ○), and four animals from group C (■—■).

change in cardiac output, although it was true that in four of the animals cardiac output had increased (range 0.25 l/min to 1.20 l/min), and in these particular animals these changes may well have played a part in the production of the hypertension.

Measurements made during the 20 min immediately after the peak of the arterial pressure response (Figure) would tend to support the findings that the SHR is a pre-terminal event. The values obtained all pointed to a collapse of the circulation associated with vasodilatation, decreasing mean arterial pressure, and increasing heart rate.

Supratentorial and infratentorial pressures decreased in line with the decreasing mean arterial pressure showing that vasoparalysis was present, and as a result the perfusion in both compartments decreased steadily. Cardiac output, however, was noted to increase significantly during this period, presumably in an attempt to maintain systemic tissue perfusion.

GROUP B (SLOW INFLATION: DOGS)

Five animals with parietally-placed artificial space-occupying lesions were subjected to slow inflation (1 ml fluid administered over 20 min), and of these

four animals developed a marked SHR. The five animals with frontally-placed mass lesions all developed systemic hypertension. Although the balloon volume required to initiate the SHR was significantly less ($p < 0.05$) in the animals with frontally-placed ($5.8 \text{ ml} \pm 0.4$) than in those with parietally-placed lesions ($8.0 \text{ ml} \pm 0.6$), for the purposes of the present discussion both groups have been considered together. The changes in the nine animals, taking place between the initiation of the SHR and the circulatory collapse after the period of systemic hypertension, are shown in Table 2a (intracranial indices), Table 2b (cardiovascular indices), and the Figure.

Mean arterial pressure was found to increase in each of the animals studied, the overall increase being significant ($11.3 \text{ kPa} \pm 1.6$ ($85 \text{ mmHg} \pm 12$)) and ranging from an increase of 4.4 kPa (33 mmHg) to one of 17.3 kPa (130 mmHg). Mean supratentorial pressure increased significantly also from $9.3 \text{ kPa} \pm 0.4$ ($70 \text{ mmHg} \pm 3$) immediately before the onset of the pressor response to $20.8 \text{ kPa} \pm 1.9$ ($156 \text{ mmHg} \pm 14$) at the peak of the arterial hypertension. Mean infratentorial pressure increased also, but the changes in this para-

meter were small (mean change of $+1.3 \text{ kPa}$ (10 mmHg)) so that there was a marked and significant increase in the transtentorial pressure gradient to $14.6 \text{ kPa} \pm 1.6$ ($110 \text{ mmHg} \pm 12$) at the peak of the systemic hypertension. Out of the nine animals, only four showed an increase in supratentorial perfusion pressure (range $+1.9 \text{ kPa}$ (14 mmHg) to $+4.0 \text{ kPa}$ (30 mmHg)), supratentorial perfusion pressure decreasing in the remainder (range -0.93 kPa (7 mmHg) to -3.5 kPa (26 mmHg)). Thus, taken overall, there was no significant change in perfusion pressure in the supratentorial compartment in this group of animals. In contrast, however, infratentorial perfusion pressure did increase significantly by $9.8 \text{ kPa} \pm 1.2$ ($74 \text{ mmHg} \pm 9$) (range 3.7 kPa (28 mmHg) to 15.4 kPa (116 mmHg)).

Significant increases were noted also in both the systolic and diastolic arterial pressures and, as was found in the animals of group A, the systolic pressure increase ($14.1 \text{ kPa} \pm 1.7$ ($106 \text{ mmHg} \pm 13$)) was greater than the increase in diastolic pressure ($9.8 \text{ kPa} \pm 1.6$ ($74 \text{ mmHg} \pm 12$)) so that the pulse pressure increased significantly also.

In each of the nine animals, heart rate increased

Table 2a Effects of SHR on the intracranial indices in nine animals subjected to slow inflation of the extradural balloon (group B)

	Immediately before onset of SHR	At peak of SHR	Five minutes after peak of SHR	15 minutes after peak of SHR
Mean supratentorial intracranial pressure kPa (mmHg)	9.3 ± 0.4 (70 ± 3)	20.8 ± 1.9 (156 ± 14)***	18.6 ± 1.3 (140 ± 10)***	13.0 ± 0.53 (98 ± 4)***
Mean infratentorial intracranial pressure kPa (mmHg)	4.8 ± 0.4 (36 ± 3)	6.1 ± 0.67 (46 ± 5)*	6.0 ± 0.67 (45 ± 5)	4.7 ± 0.53 (35 ± 4)
Transtentorial pressure gradient kPa (mmHg)	4.7 ± 0.27 (35 ± 2)	14.6 ± 1.6 (110 ± 12)***	12.6 ± 1.3 (95 ± 10)***	8.4 ± 0.8 (63 ± 6)***
Mean supratentorial perfusion pressure kPa (mmHg)	3.7 ± 0.67 (28 ± 5)	3.6 ± 1.1 (27 ± 8)	1.9 ± 1.1 (14 ± 8)	0.13 ± 0.53 (1 ± 4)***
Mean infratentorial perfusion pressure kPa (mmHg)	8.4 ± 0.8 (63 ± 6)	18.2 ± 1.5 (137 ± 11)***	14.6 ± 1.2 (110 ± 9)***	8.2 ± 1.1 (62 ± 8)

Results are expressed as mean $\pm$ SEM. Significant differences between values obtained immediately before onset of SHR: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 2b Effects of SHR on the cardiovascular indices in nine animals subjected to slow inflation of the extradural balloon (group B)

	Immediately before onset of SHR	At peak of SHR	Five minutes after peak of SHR	15 minutes after peak of SHR
Heart rate beats/min	81 ± 10	156 ± 21 **	198 ± 18 ***	191 ± 14 ***
Mean arterial pressure kPa (mmHg)	13.2 ± 0.67 (99 ± 5)	24.3 ± 1.7 (183 ± 13)***	20.4 ± 1.3 (153 ± 10)***	13.2 ± 0.93 (99 ± 7)
Systolic arterial pressure kPa (mmHg)	18.0 ± 0.93 (135 ± 7)	32.1 ± 2.1 (241 ± 16)***	24.6 ± 1.6 (185 ± 12)***	15.8 ± 0.93 (119 ± 7)
Diastolic arterial pressure kPa (mmHg)	10.8 ± 0.53 (81 ± 4)	20.5 ± 1.6 (154 ± 12)***	18.1 ± 1.2 (136 ± 9)***	12.1 ± 0.8 (91 ± 6)
Pulse pressure kPa (mmHg)	7.2 ± 0.8 (54 ± 6)	11.5 ± 1.2 (86 ± 9)**	6.5 ± 0.67 (49 ± 5)	3.9 ± 0.4 (29 ± 3)**
Arrhythmia index (%)	75 ± 12	13 ± 10 ***	6 ± 6 ***	2 ± 2 ***
Arrhythmia absolute (beats)	63 ± 12	15 ± 12 ***	10 ± 10 *	3 ± 3 ***

Results are expressed as mean $\pm$ SEM. Significant differences between values obtained immediately before onset of SHR: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

(range 12 beats/min to 146 beats/min) the overall increase being significant. This was accompanied by significant decreases in both the absolute arrhythmia and the arrhythmia index since there was no detectable arrhythmia in most of the animals at the peak of the hypertensive response.

As in the animals of group A, the changes taking place immediately after the peak of the systemic pressor response were those of a failing circulation (Figure). Heart rate continued to increase as the mean arterial pressure decreased steadily. Mean supratentorial pressure decreased along with the mean arterial pressure; there was little difference between the measured values of the two indices since supratentorial perfusion pressure was virtually non-existent.

GROUP C (SLOW INFLATION: BABOONS)

A systemic hypertensive response appeared in four of the five animals, and as in the two previous groups it appeared very late in the expansion of the space-occupying lesion. The balloon volume, the supratentorial pressure, and the supratentorial perfusion pressure at which the arterial hypertension occurred are given in Table 3. From this it can be seen that, as in the two previous groups, the supratentorial perfusion pressure had decreased to low values immediately before the onset of the SHR (3.3 kPa $\pm$ 0.13 (25 mmHg $\pm$ 1)).

Unlike the situation with the dogs of group B, however, posterior fossa pressure monitoring was found to be unreliable in the baboons; the pressure records ceased to show pulsations, indicating blockage of the catheter tip, presumably because of brain herniation. Such blockage occurred in three of the four baboons before, but close to, the appearance of the SHR. In the fourth animal, there was no pressure gradient until the arterial pressure and the intracranial pressure began to increase when the pulsation of the posterior fossa

pressure recording disappeared. Before the loss of reliable recordings, however, there was no evidence of the development of transtentorial pressure gradients in this group of animals.

In the experiments in which bilateral carotid flow measurements were obtained, the flow on both sides was similar; there was no evidence that flow was systematically lower on the side of the lesion. Immediately before the onset of the SHR, carotid blood flow had decreased markedly to 60%, 46%, and 31% of control value in the three experiments for which carotid flow values were available (Table 3). Xenon clearance was markedly reduced also (to 46% and 20%). The SHR did not lead to any marked augmentation of carotid blood flow and indeed in one experiment a previously low xenon clearance was converted to virtually no clearance at the peak of the SHR. This failure of cerebral perfusion to improve was due partly to the vasomotor paralysis that existed by this stage in the development of the SHR so that intracranial pressure increased in parallel with arterial pressure, or nearly so. Nonetheless, there were, in two animals, improvements in cerebral perfusion pressure as conventionally defined, and yet one of these showed absent xenon clearance. This was probably due to the presence of tissue oedema which would have reduced perfusion pressure at the microcirculation level to very low values.

Pupillary changes

Immediately before the appearance of the systemic hypertensive response, pupillary changes were evident (Fitch and McDowall, 1977). These changes progressed in association with the increasing balloon volume and increased intracranial pressure so that at the peak of the arterial pressure the pupils were fully dilated and unresponsive to light in all but one animal. In this animal, the

Table 3 Effects of SHR on supratentorial perfusion pressure, carotid blood flow, and mean cerebral blood flow (CBF) in four baboons subjected to inflation of an extradural balloon (group C)

Experiment	Balloon volume	Supratentorial perfusion pressure kPa (mmHg)		Carotid blood flow (ml/min)		Mean CBF (ml/100 g/min)	
		Before onset of SHR	At peak of SHR	Before onset of SHR	At peak of SHR	Before onset of SHR	At peak of SHR
1	2.8 ml (at 2.0 ml/hr)	3.2 (24)	3.2 (24)	37 (60% of control)	39	—	—
2	3.7 ml (at 1.2 ml/hr)	3.7 (28)	—	27 (46% of control)	—	16 (46% of control)	—
3	4.7 ml (at 1.2 ml/hr)	3.6 (27)	5.1 (38)	16 (right) (31% of control)	16 (right)	8 (18% of control)	No Xenon clearance
4	4.1 ml	3.2 (24)	6.3 (47)	—	—	—	—

pupil ipsilateral to the mass lesion was fully dilated, the control pupil being approximately half-dilated.

Discussion

The present series of investigations have shown that the majority, although not all, of the animals exhibited a systemic pressor response when subjected to the progressive expansion of an artificial intracranial mass lesion. It was observed that, immediately before the onset of the SHR, supratentorial perfusion pressure was low and systemic hypertension did not appear to produce any worthwhile improvement in supratentorial perfusion. These changes occurred whether the balloon was inflated rapidly or more slowly, although differences did exist in the speed of onset of the changes depending on the site of the artificial mass lesion. Finally, these studies have demonstrated that the SHR was an agonal event, and was followed in a matter of minutes by circulatory failure.

A considerable literature has accumulated on the SHR since Cushing (1901, 1902) reported the results of the first extensive experimental investigation into the effects of acutely increased intracranial pressure on the systemic circulation. Unfortunately, no unanimity of views has resulted, even among those who have used the Cushing technique of fluid infusion into the subarachnoid space to increase the intracranial pressure.

The present studies show that the SHR appeared to start as the mean supratentorial pressure approached the diastolic arterial pressure (Tables 1a, 1b, 2a, 2b), the mean supratentorial pressure in groups A and B being within approximately 10 mmHg of the diastolic arterial pressure immediately before the onset of the SHR. If this were indeed the case, one could envisage conditions under which blood flow in the supratentorial compartment would no longer be continuous but intermittent.

At the beginning of the hypertensive response, supratentorial perfusion pressure ranged from 1.1 kPa (8 mmHg) to 6.7 kPa (50 mmHg) in the dogs and from 3.2 kPa (24 mmHg) to 3.7 kPa (28 mmHg) in the baboons. It is known that decreases in cerebral perfusion pressure to values between 4.0 kPa (30 mmHg) and 6.7 kPa (50 mmHg) can lead eventually to decreases in cerebral blood flow and to the appearance of biochemical evidence of cerebral tissue hypoxia (Zwetnow, 1968; Kjällquist *et al.*, 1969; Kaasik *et al.*, 1970; Zwetnow, 1970).

In the 19 animals studied in this investigation, it was found that, immediately before the onset of the SHR, two had supratentorial perfusion pres-

ures between 5.3 and 6.7 kPa (40 and 50 mmHg); two between 4.0 and 5.3 kPa (30 and 40 mmHg); 12 between 2.7 and 4.0 kPa (20 and 30 mmHg); one between 1.3 and 2.7 kPa (10 and 20 mmHg); and two at less than 1.3 kPa (10 mmHg).

It is possible to speculate, therefore, that ischaemia of the cerebral hemisphere may trigger the hypertensive response, presumably via brain stem centres (Hoff and Reis, 1969). The triggering would probably be in the nature of the removal of normal supratentorial inhibition of brain stem vasopressor centres with the resultant release of sympathomimetic influences (Hoff and Reis, 1970), leading to the increase in heart rate and the marked peripheral vasoconstriction. Cushing himself believed that the SHR was a result of brain ischaemia, but he implicated direct ischaemia of the brain stem. In the present study, this might be true of the baboons of group C which showed no transtentorial pressure gradient and which, therefore, had low infratentorial perfusion pressures concurrently with low supratentorial perfusion pressures. However, in groups A and B the infratentorial perfusion pressures were adequate. Thus, one must conclude that although low infratentorial perfusion pressure may account for a hypertensive response in some circumstances, the SHR can occur also in the presence of adequate perfusion in the posterior fossa.

If the supratentorial ischaemic hypothesis is correct, then it should be possible to trigger a vasopressive response in the presence of a space-occupying lesion by a sudden decrease in arterial pressure. In this way, supratentorial perfusion pressure would be decreased suddenly until it reached the ischaemic range. This possibility was not explored deliberately in these experiments, but in experiment 1 of group C when intermittent halothane was being studied also, a hypertensive response was triggered by the hypotension which accompanied a brief period of halothane administration. Similarly in experiment A of group C, the hypertensive phase was initiated by an accidental haemorrhage from the arterial line which, by decreasing the mean arterial pressure, brought the supratentorial perfusion pressure below 4.0 kPa (30 mmHg).

It is worth noting, however, that, after the infusion of fluid into the cisterna magna, Johnston and colleagues (1973) observed sustained hypertensive responses before decreases in supratentorial cerebral perfusion pressure and cerebral blood flow had been recorded.

Cushing also reported that systemic hypertension would result in an increase of intracranial perfusion pressure which would be of advantage

to the animals. The present studies have shown that infratentorial perfusion was augmented in each animal by the arterial hypertension. The effects of the systemic hypertension on the perfusion in the supratentorial compartment were varied. Supratentorial perfusion increased in nine animals and decreased in the remaining 10 animals. The overall effects were a slight but not significant increase in the animals in group A, no change in those of group B, and a decrease in the baboons studied in group C.

An alternative hypothesis proposed by Thompson and Malina (1959) would ascribe the hypertensive response to axial rotation of the brain stem which in their experiments was associated with large transtentorial pressure gradients. In the dogs studied in group B (and in the two animals of group A in which it was calculated) there were indeed large transtentorial pressure gradients both before the onset of SHR and at its peak. However, in group C (baboon studies) there was no progressively increasing transtentorial pressure gradient, but the infratentorial pressure record suddenly ceased to show arterial pulsations indicating, probably, impaction at the tentorium. We postulate that one reason for the absence of the transtentorial pressure gradients in these baboons may be the use of young animals with very compliant dural membrane, and it is possible that major shifts or brain stem rotation such as described by Thompson and Malina (1959) could have occurred in the absence of tentorial impaction or transtentorial pressure gradients.

The typical findings recorded by Cushing (1901) were of systemic hypertension plus bradycardia. Although increases in heart rate were observed in the animals in these studies during the initiation of, and immediately after, the pressor response, it should be noted that progressive bradycardia had been shown previously to be present from the beginning of the balloon inflation until immediately before the appearance of the arterial pressure response (Fitch and McDowall, 1977). Indeed, in many of the animals bradycardia persisted during the initial development of the hypertensive response, but by the time the peak arterial pressure had been reached, the bradycardia had changed to a progressive increase in heart rate in all but one animal. Similar findings of an increase in heart rate have been reported by Brown (1956), Tarlov *et al.* (1959), Richardson *et al.* (1965), Brashear and Ross (1970) and Gonzalez *et al.* (1972). It was interesting to note that both the absolute arrhythmia and the arrhythmia index decreased markedly in association with the increasing mean heart rate such that in the majority

of animals no value could be ascribed to these two indices.

The association between vasoconstriction and the systemic hypertensive response has been accepted by many workers (Brown, 1956; Richardson *et al.*, 1965; Ducker *et al.*, 1968) although Brashear and Ross (1970) and Gonzalez *et al.* (1972) found no change in the peripheral resistance at the time of the hypertensive response. An increase in cardiac output has been associated also with the hypertensive response (Richardson *et al.*, 1965; Ducker *et al.*, 1968; Brashear and Ross, 1970; Gonzalez *et al.*, 1972). However, in each of these studies the intracranial pressure was increased acutely over the space of a few seconds or minutes to values around 100 to 200 mmHg. As a result, it was difficult to define the exact moment in time when the cardiac output increased, although Richardson *et al.* (1965) noted that the increase in cardiac output was not present at the peak of the arterial pressure response but followed some two to three minutes later. In the present investigation, at the peak of the arterial pressure response, cardiac output had increased in four of the six animals in which it was determined, although the overall effect was one of no significant change. However, 10 min after the peak arterial pressure, a significant increase in cardiac output was noted, and at 20 minutes after the peak pressor effect even greater values for cardiac output were obtained. It is possible that these changes were terminal events in an attempt to bolster the failing circulation. It is evident that the circulatory failure was peripheral, and not cardiac, in origin.

Conclusions

AETIOLOGY

In the light of these investigations, it would seem probable that the SHR can result from two mechanisms. It can follow inadequate perfusion pressure in the supratentorial compartment or may result from the production of tentorial impaction, evidenced in the dog studies by the progressively increasing transtentorial pressure gradients, and in the baboon experiments by blockage of the pulse pressure transmission to the posterior fossa before or at the time of, the SHR.

CLINICAL IMPLICATIONS

These experiments support the clinical observations that the systemic hypertension of the 'Cushing' response is a very late phenomenon and is, indeed, a pre-terminal event. It should be noted also that typical 'Cushing' response was not an

invariable accompaniment of increased intracranial pressure. In two of the animals circulatory failure appeared without well-defined hypertensive responses being seen.

In an attempt to find a sequence of signs which might give evidence of clinical value of the expansion of an intracranial mass lesion a simple scoring system was evolved. This took into account the findings of the dog experiments in the present paper and those of the previous paper (Fitch and McDowall, 1977) which looked into the events occurring from the start of the balloon inflation to the start of the systemic hypertension. Five points were given to the first sign to appear, four to the second, and so on. The results (Table 4) show that bradycardia was an early and fairly consistent sign, especially in the animals with parietally-placed lesions (group A and part of group B), and so was the arrhythmia index. Indeed, taken overall, arrhythmia index achieved a better score than bradycardia itself. Next came constriction of both pupils, with unilateral pupillary dilatation and widening of the pulse pressure sharing next place. Finally, elevation of mean arterial pressure was found to be the last of these six indices to appear in each animal.

Table 4 Diagnostic signs observed in the animals of groups A and B: the first sign to appear was given five points, the second four points, and the last no points

	Group A	Group B	
		Parietal	Frontal
Bradycardia	28	25	14
Arrhythmia	28	23	24
Pupillary constriction	19	15	15
Unilateral pupillary dilatation	10	6	10
Increase in pulse pressure	10	9	5
Increase in mean arterial pressure	0	0	0

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