An experimental study of traumatic cerebral vascular spasm

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Apparent narrowing of cerebral vessels in arteriograms after subarachnoid haemorrhage of aneurysmal origin had been described by many authors.

It has been accepted by most neurosurgeons as indicating spasm of the vessels secondary to subarachnoid haemorrhage, and there has been much discussion about the nature and mechanism of origin of this vascular spasm. In experimental conditions, narrowing of cerebral vessels in response to trauma or other forms of stimulation has been produced in cat pial vessels (Echlin, 1942; Lende, 1960) and in primate vessels in the circle of Willis (Harvey and Rasmussen, 1951; Symon, 1961; Corday, Rothenberg, and Irving, 1963; Echlin, 1965). In human neurosurgery, direct observation has repeatedly confirmed the capacity of major cerebral vessels to constrict in response to trauma (Gillingham, 1958; Johnson, Potter, and Reid, 1958).

The present investigation was undertaken to study the characteristics of the response of major cerebral vessels to traumatic stimuli under experimental conditions. It seems important to establish a range of comparison between the behaviour of such experimental phenomena, and those observed clinically at angiography, since it is by means of the latter indirect evidence that any therapeutic attempt to influence vasospasm must be assessed, although the preliminary screening of drugs potentially useful in the treatment of vasospasm is almost always performed in the laboratory.

METHOD

Nineteen baboons (*Papio nubius* or *Papio cynocephalus*) weighing between 6 and 14 kilograms were used. After basal sedation with phencyclidine, 1 mg. per kilogram intramuscularly, anaesthesia was induced with Thiopentone (10 mg. per kilogram) intravenously, and maintained with α Chloralose 50 to 60 mg. per kilogram intravenously, supplemented as necessary. Systemic blood pressure was continuously recorded by a femoro-aortic catheter connected to a Satham strain gauge (model P23G). Tracheostomy was performed and the end tidal CO_2 concentration was continuously recorded from the

trachea by an infrared gas analyser (Beckman Spinco model LB-1). A right parietal craniotomy was performed to expose the greater part of the lateral surface of the cerebral hemisphere, and blood pressure recorded from one or more superficial branches of the middle cerebral artery through small catheters introduced under a dissecting microscope, and connected to one or more Satham gauges (Symon, 1963). Relative blood flow changes were recorded in ten experiments by means of small bead thermistors (Veco type 32 A.1) resting lightly on branches of the middle cerebral artery (Meyer and Denny-Brown, 1957). Femoral and cerebral catheters were filled with a solution of heparin (2 I.U. per ml.) and the animal heparinized by the administration of one dose of 1,000 international units per kilogram intravenously when the preparation had been completed. The output of the recording devices, strain gauges, gas analyser, and thermistors passed through appropriate D.C. connexions to a Beckman type R. dynograph. In experiments where the effect of alteration in arterial pCO_2 was to be assessed, spontaneous respiration was abolished with gallamine triethiodide (Flaxedil), 1 mg. per kilogram intravenously, repeated as necessary, and respiration maintained by a Starling pump (C. F. Palmer Limited, model no. 16/24). Arterial samples were obtained from a left femoral catheter and pCO_2 estimations made using a Severinghaus electrode (Radiometer, Copenhagen) under resting conditions, and when alteration in arterial pCO_2 was intentionally produced. Artificial respiration was adjusted to produce a resting 'normal' arterial pCO_2 between 35 and 45 mm. of mercury. The proximal portion of the middle cerebral artery was exposed by retraction of the temporal lobe, and the arachnoid of the basal cistern breached. Traumatic stimuli were applied to the first 5 mm. of the middle cerebral artery by light repetitive compression with non-toothed dissecting forceps, fitted with a stop between the blades to prevent pressure on the artery beyond complete apposition of the tips of the forceps. Various forms of mechanical stimulators were tried, but the difficulty of application of such devices without damage to the small perforating vessels has so far proved insuperable. Electrical methods A.C. or D.C., stimulation, used successfully in the leptomeningeal circulation (Lende, 1960), were found unsuitable for use at the base of the brain when stimulation without change of blood pressure was desired; such stimuli usually provoked some rise in blood pressure even in the animal immobilized with gallamine.

RESULTS

In all except two animals, traumatic stimulation of the middle cerebral artery resulted in a diminution of intravascular pressure and in pulse pressure measured from a surface cortical branch of the artery. In six animals where the main vessel was repeatedly inspected under these circumstances, the area traumatized, some 2 mm., and the area immediately distal to it for some 4 to 5 mm., were much narrower than before. With stimulation of approximately the same area on successive occasions over the course of the day, the traumatized segment gradually failed to constrict as succeeding stimuli were applied, sometimes even becoming dilated. The constriction just distal to the area of trauma could regularly be evoked, and paralleled closely the change in pulse and intravascular pressure which appeared in the recording from the cortical catheter.

Measurement of the spasm evoked, therefore, could be made from the blood pressure trace obtained remote from the area of stimulus. It was thus unnecessary to expose the main vessel repeatedly to assess the presence or absence of spasm. There was therefore no need to mop fluid from the vessel under study and retraction of surrounding brain was unnecessary save during the actual administration of a traumatic stimulus. The evolution and resolution of spasm could be observed as a modification of the distal intravascular and pulse pressure, free from adventitious disturbance incidental to direct observation.

The form of response in pulse and intravascular pressure is seen in Figure 1. The response has a very brief latent period, which, often scarcely measurable, was certainly not more than 15 seconds, a period of increment to a maximum and a gradual decrement thereafter. The characteristics were expressed by three measurements. The development was measured to the maximal reduction of pulse pressure and referred to as 'time to maximum'. The duration of the response was expressed by measurements from the traumatic stimulus itself to the return of pulse and intravascular pressure to the level which obtained before the disturbance incidental to stimulation. Retraction of the brain before the application of the stimulus frequently caused a slight rise in systemic and cerebral arterial pressure, and care was necessary to obtain an adequate base line by which to assess subsequent recovery. The intensity of the response was expressed as the percentage reduction of the pulse pressure, at its minimal level, compared with the pulse pressure level before the disturbance incidental to application of the traumatic stimulus.

It was found possible in three animals where

FIG. 1. Recording of endtidal CO_2 (E.T. CO_2), arterial pressure in a superficial branch of the middle cerebral artery some 300 μ in size (M.C.P.), flow in a superficial branch of the middle cerebral artery (M.C.F.), and systemic blood pressure recorded from the right femoral artery (S.B.P.) in a baboon. At the arrow 'S' a traumatic stimulus was applied to the proximal middle cerebral artery within 5 mm. of its origin. At the point indicated by the black square, blood was collected from the left femoral artery and analysed for arterial pCO_2 .

'time to maximum' was over five minutes in several stimuli, to assess the effect of a second stimulus administered during development of spasm following a first traumatic stimulus. From this it seemed that the development of the response was in no way enhanced by the second stimulus provided that the first had been sufficient to evoke the typical pattern of gradually declining pulse and intravascular pressure before the second was applied. The administration of a second stimulus during the phase of recovery from spasm produced extremely variable results from which no consistent pattern could be deduced, except that some exacerbation of the spasm was usual under these circumstances. The repeated application of similar stimuli would produce approximately similar responses only provided full recovery was allowed between each one.

In seven animals, repeated stimulation under basal conditions with an arterial pCO_2 level of 35 to 45 mm. of mercury was performed. The variation in response is shown for these seven animals in Table I. It is clear that there was appreciable variation in response to similar stimuli, particularly in the intensity of the spasm produced, although the duration and time to maximum were rather more constant. Such repetitive stimulation required the maintenance of a constant preparation over a period of some three to four hours. Where the effects of

TABLE I

AN ANALYSIS OF THE VARIABILITY OF VASOSPASTIC EPISODES PRODUCED IN REPEATED OBSERVATIONS AT NORMOCAPNIA IN SEVEN BABOONS

Experiment No.	No. of Observations	Duration of Spasm (min.)			Time to Maximum (min.)			Percentage Reduction in Pial Pulse Pressure		
		Maximum	Minimum	Mean and S.D.	Maximum	Minimum	Mean and S.D.	Maximum	Minimum	Mean and S.D.
9	5	21.1	10.0	17.9 ± 4.7	3.5	1.8	2.3 ± 0.9	50	33	36.4 ± 7.6
10	6	35.0	19.6	29.8 ± 5.9	10.8	4.6	7.5 ± 2.1	60	20	38.8 ± 12.9
11	5	34.5	14.0	22.6 ± 10.8	8.4	2.6	3.9 ± 2.6	50	38	41.6 ± 8.5
12	5	19.3	10.6	12.6 ± 3.8	4.0	3.6	3.8 ± 0.6	66	20	44.5 ± 18.6
13	5	16.6	12.2	15.1 ± 3.0	4.9	1.8	3.3 ± 1.2	33	20	29.4 ± 5.4
16	5	18.3	11.9	15.3 ± 2.5	5.0	3.5	4.1 ± 0.6	56	20	33.4 ± 13.7
17	5	26.2	14.8	20.7 ± 5.3	5.0	3.2	3.9 ± 2.7	61	30	53.2 ± 10.9

alteration in arterial pCO₂ or the influence of pharmacological agents was to be assessed, therefore, fewer control values were taken at intervals through the experiment and the mean of these observations then calculated. These means, together with the mean value of the seven animals described in Table I are shown in Table II.

TABLE II

AVERAGE VALUES FOR THE PARAMETERS OF VASOSPASM PRODUCED IN SEVENTEEN BABOONS

Experiment No.	No. of Observations	Mean Duration (min.)	Mean Time to Maximum (min.)	Mean Percentage Reduction in Pulse Pressure
9	5	17.9	2.3	36.4
10	6	29.8	7.5	38.8
11	5	22.6	3.9	41.6
12	5	12.6	3.8	24.5
13	5	15.1	3.3	29.4
16	5	15.3	4.1	33.4
17	5	20.7	3.9	5.3
18	3	13.3	2.7	53
19	3	14.4	3.3	37
20	3	20.3	3.3	41.5
21	3	20.3	3.4	47
22	3	19.0	1.8	46
24	3	16.2	1.9	49
26	3	28.0	6.0	54
27	3	28.6	6.5	30
29	3	22.4	3.4	45
30	3	18.5	4.4	50
Mean		19.7	3.9	42.8
S.D.		± 5.2	± 1.5	± 7.9

The duration of spasm produced in 57 observations in 17 animals was in the region of 20 minutes (mean 19.7 S.D. ± 5.2). The average time for the spasm to reach its maximum was 3.8 minutes (S.D. ± 1.5) and the average reduction in pulse pressure was 42.8% (S.D. ± 7.9). In 10 animals, measurements of relative blood flow were made using bead thermistors. These showed that the decline in pulse and intravascular

pressure with development of spasm in the main middle cerebral artery was accompanied by a decline in blood flow in superficial branches of the middle cerebral artery on the surface of the hemisphere. In six animals, recordings of intravascular pressure from a temporal and a frontal branch of the middle cerebral artery were made, together with thermistor recordings from adjacent temporal and frontal branches. Comparable reductions in pulse and intravascular pressure were recorded on the two recording catheters, and comparable reductions in flow in the two areas were seen in the thermistor records as illustrated in Figure 2.

FIG. 2. Recordings of endtidal CO₂ and superficial middle cerebral arterial pressure and flow from arterial catheters and thermistor beads in the frontal region (F) and in the temporal region (T) together with systemic blood pressure in a baboon. At the arrow 'S' a traumatic stimulus was administered to the middle cerebral artery within 5 mm. of its origin.

THE EFFECT OF TOPICAL APPLICATION OF PHARMACOLOGICAL AGENTS IN THE PRODUCTION OF ARTERIAL SPASM

A number of agents were applied locally to the middle cerebral artery after breaching the arachnoid cistern at the medial end of the Sylvian fissure and freeing the vessel in preparation for traumatic stimulation. During the application of such agents, arterial $p\text{CO}_2$ was kept within the normal range (35 to 45 mm.Hg). In three animals, fresh blood led from the animal's femoral artery, separated serum either fresh or stored for up to 48 hours, haemolysed human or baboon blood, and fresh cerebrospinal fluid obtained from cases of subarachnoid haemorrhage were applied by drops to the exposed vessel without any reduction in peripheral intravascular or pulse pressure in the middle cerebral branches and with no reduction in thermistor recordings to suggest a fall in peripheral blood flow in the middle cerebral field. In four other animals, fresh solutions of 5 HT, in concentrations of 10, 50, and 100 micrograms per ml. buffered in Locke's solution to a pH of 7.2 and at a temperature of 38°C ., were applied in a similar way also without effect on peripheral pulse pressure, intravascular pressure, and thermistor recording. Concentrations of 5 HT stronger than 100 μg . per ml. applied locally in the area of the middle cerebral artery frequently produced some irregularity in respiration and irregular elevation of blood pressure. In three other animals, topically applied adrenaline or noradrenaline (in concentrations up to 100 μg . per ml.) were also applied with no demonstrable effect on pulse pressure, intravascular pressure, or thermistor flow. A characteristic reduction of pulse and intravascular pressure was often seen after stripping off the arachnoid from the area of the origin of the middle cerebral artery, but was not seen in response to any of the pharmacological agents described in the concentrations used.

EFFECT OF ALTERATION IN ARTERIAL $p\text{CO}_2$ ON THE CHARACTERISTICS OF TRAUMATIC ARTERIAL SPASM

In 12 animals, the effect of alteration in arterial

$p\text{CO}_2$ was assessed. The animals, artificially respired, were given an increased concentration of CO_2 to breathe sufficient to raise the arterial $p\text{CO}_2$ to over 50 mm. of mercury, or had the ventilatory volume increased (to about twice the resting value) sufficiently to reduce the arterial $p\text{CO}_2$ to below 20 mm. of mercury. After six minutes of such a change, which appeared to be an adequate time for a new steady state to be reached as assessed by observation of end tidal CO_2 and systemic arterial blood pressure, a traumatic stimulus was applied to the middle cerebral artery. In 11 animals, it was possible to repeat observations under high and low $p\text{CO}_2$ at least twice, which, with the control periods, generally accounted for the entire time over which constant conditions could be maintained. Under conditions of both high and low ApCO_2 no significant difference in the character of spasm produced could be detected; this is illustrated in Figures 3 and 4. The analysis of the results of 26 observations in 12 animals with raised ApCO_2 and 24 observations of 11 animals with lower ApCO_2 are shown in Table III and compared with the figures from a group of 17 animals as a whole. Analysis of the figures using the t test with common variance showed no significant difference between any of the parameters of spasm measured, under conditions of raised or lowered ApCO_2 .

EVIDENCE OF INTRAVASCULAR AGGREGATION FOLLOWING TRAUMA TO CEREBRAL ARTERIES

In seven experiments, after repeated traumatic stimuli to the middle cerebral artery, there was evidence of intravascular aggregation during the course of the experiment. In four animals, this took the form of complete obliteration of the artery manifested at the peripheral catheter by a progressive disappearance of pulse, and a fall in intravascular pressure to levels comparable to those obtained with occlusions of the middle cerebral artery in monkeys (Symon, 1963, 1967b). In two of these experiments, this occurred towards the end of the day and recovery of pulse and intravascular pressure

TABLE III

AN ANALYSIS OF THE CHARACTERISTICS OF EPISODES OF VASOSPASM PRODUCED IN BABOONS UNDER CONDITIONS OF NORMOCAPNIA, HYPOCAPNIA, AND HYPERCAPNIA

	No. of Animals	No. of Observations	Duration of Spasm (min.) (Mean/S.D.)	Time to Maximum (min.) (Mean/S.D.)	Percentage Reduction in Pial Pulse Pressure (Mean/S.D.)
Normocapnia (ApCO_2 35 - 45 mm.Hg.)	17	57	19.7 ± 5.2	3.9 ± 1.5	42.8 ± 7.9
Hypocapnia ($\text{ApCO}_2 < 20$ mm.Hg.)	11	24	19.2 ± 2.3	4.4 ± 1.1	42.4 ± 7.3
Hypercapnia ($\text{ApCO}_2 > 50$ mm.Hg.)	12	26	17.9 ± 4.6	3.9 ± 1.1	42.6 ± 11.8

FIG. 3. Recordings of endtidal CO_2 , superficial middle cerebral flow and pressure and systolic blood pressure in a baboon. The records in group A were taken under artificial respiration and normocapnia, those in group B under hyperventilation to an arterial pCO_2 of 19 mm. of mercury. At the arrows 'S' in A and B a traumatic stimulus was applied to the middle cerebral artery within 5 mm. of its origin.

did not take place before the animal was sacrificed. In the other two, however, after 40 minutes in one, and 30 minutes in the other, sudden recovery in pulse and blood pressure took place with the momentary appearance in the peripheral middle cerebral circulation of a shower of clear bodies which then disappeared into the intracerebral circulation, often breaking up at superficial vascular bifurcations. They seemed in every way similar to the embolic phenomena described by Denny-Brown (1960) after carotid trauma in monkeys. Portions of the records from one of these experiments are shown in Figure 5. In this instance, the initial trauma produced severe spasm, manifested in the peripheral pulse trace by a rapid and progressive reduction of pulse and intravascular pressure, which, at first recovering in the usual way, without further interference then progressed to virtual abolition of the pulse with an intravascular pressure of 20 mm. of mercury. This state of affairs continued until, at 33 minutes after trauma, there was sudden recovery as shown. A repeat traumatic stimulus resulted in recurrent progressive obliteration of the artery, persisting this time for a further 20 minutes before sharp recovery of pulse and blood pressure took place. Thermistor flow recording paralleled the pressure changes closely. In the other three animals,

FIG. 4. Records of endtidal CO_2 arterial pressure from a superficial branch of the middle cerebral artery and systemic blood pressure in a baboon. The effects of traumatic stimuli at the arrows 'S' under conditions of normocapnia (group A) and hypercapnia (group B) are shown. The interruption in the systemic blood pressure recordings are due to the collection of blood for arterial pCO_2 from the systemic blood pressure catheter.

complete obliteration of the vessel did not occur, but occasional visible emboli were observed towards the end of the day, associated with sudden sharp changes in intravascular recording often during recovery of the vessel from a traumatic stimulus. Several such episodes can be seen in records A and B in Fig. 3 where the contrast between the usually observed gradual change in pulse and intravascular pressure, which are considered to be due to spasm and its recovery, and the sharp super-added pressure changes associated with embolization, may be seen. It was of particular interest that the white, narrow naked-eye appearance of the main vessel during complete obliteration of the distal pulse was extremely difficult to distinguish from the appearance of severe vasospasm whereas the intravascular pressure recordings appeared quite different.

EVIDENCE OF ALTERATION *in vaso* REACTIVITY PRODUCED BY VASOSPASM

In the course of these experiments, there was some evidence that the production of traumatic vasospasm changed the character of response in the vascular bed studied to increased concentrations of carbon dioxide. Under normal circumstances

FIG. 6. Recordings of endtidal CO_2 , middle cerebral arterial pressure from a 350μ temporal branch of the middle cerebral artery at the pial surface, and systemic blood pressure in a baboon. This record was taken towards the end of an experiment in which a traumatic stimulus had been applied to the middle cerebral artery repeatedly, and a total of eight episodes of moderate vasospasm produced. Subsequent examination of the middle cerebral artery showed loss of cellular detail in the media and fragmentation of the intima with a formation of intimal spirals. Peripheral embolism had not been observed. After a period of hyperventilation, inhalation of 6% CO_2 to raise the arterial pCO_2 rapidly produced a dissociated response in cerebral arterial and systemic blood pressures as shown.

in the primate, raised arterial pCO_2 produces no change in the relationship between systemic and pial arterial pressures, both increasing slightly as a rule. In three animals in the present group, after repeated trauma had been applied to the middle cerebral artery, when the arterial pCO_2 was raised rapidly, a dissociation between systemic and pial arterial pressure was observed in that the arterial pressure rose while the pial arterial pressure and

FIG. 5. Recordings of cerebral arterial pressure from superficial branches of the middle cerebral artery in the frontal region (F) and temporal region (T) with thermistor recording of flow in a superficial frontal branch of the artery, and systemic blood pressure recording in a baboon. At the arrows A and A1 a traumatic stimulus was applied to the proximal middle cerebral artery within 5 mm. of its origin. For the first part of this recording, the recording apparatus connected to the frontal cerebral arterial pressure catheter was recording mean pressure.

pial pulse pressure fell. This is illustrated in Figure 6. A similar dissociation has already been reported in the pial circulation of dogs during inhalation of high CO_2 concentrations and is usual after occlusion of the middle cerebral artery in the dog when residual cerebral arterial pressure commonly falls under the influence of raised ApCO_2 (Symon, 1963). This effect has not as yet been observed after middle cerebral occlusion in the monkey, where, however, the residual pial arterial pressure is rather low.¹

HISTOLOGICAL EXAMINATION OF THE ARTERIES AFTER TRAUMA

Arteries from 10 of the animals in the present series were examined by Professor T. Crawford and compared with the contralateral undamaged middle cerebral vessel. He commented that the changes were non-specific, and included rupture of internal elastic lamina, and loss of cellular detail in the media. In severe instances the intestinal elastic lamina had curled up in little spirals which, projecting into the lumen of the vessels, provided a clear nidus for the aggregation of vascular elements. In some instances small granular aggregates were visible adherent to these spirals, but not even in the four cases where the animals had apparently sustained complete obliteration of the artery, was occlusion of the lumen apparent after dissection

¹Since this paper was prepared for publication, a study has appeared, (Brawley, B. W., Strandness, D. E., and Kelly, W. A. (1967). The physiological response to therapy in experimental cerebral ischaemia. *Arch. Neurol. (Chic.)*, 17, 180-187) in which decrease of distal middle cerebral pressure and flow has been recorded in response to CO_2 inhalation. This work studied the pressure distal to occlusion of a branch of the middle cerebral artery, with the result that the distal intravascular pressure was rather higher than the very low pressures observed in the middle cerebral field as a whole following total middle cerebral occlusion in the primate.

and fixation. In two of the 10 animals there was no apparent histological abnormality, although all had shown typical appearances of vasospasm during the experiments. This suggests that the phenomena of vasospasm are not necessarily due to gross damage to the vessel wall, but rather that the experimental technique had added trauma beyond the stimulus necessary to evoke spasm.

DISCUSSION

The analysis of any phenomenon produced in the experimental laboratory in terms of clinical significance is fraught with hazard. In no sphere has this been more evident than that of cerebral vasospasm. Despite clear evidence (Gurdjian *et al.*, 1958) that notable species differences exist between lower mammalia and the primate, evidence obtained, for example in cats (Raynor, McMurtry, and Pool, 1961), still appears in discussion relating to clinical vasospasm. It is unlikely that such evidence has relevance to basal vessels in man.

From the work of Echlin (1942) and Lende (1960) it seems clear that considerable variation of response to any stimulus occurs in laboratory experiments on vasospasm. It is therefore apparent that an adequate statistical analysis of some at least of the parameters of spasm produced should be attempted before attribution of exacerbation or relief be made. This has been notably absent in experimental data published up to the present time, most of which have consisted of simple statements of observation.

When assessment of the calibre of cerebral vessels is to be made, it is essential that those factors which are known to influence such calibre be controlled and this control stated in relation to the results. The particular measurements necessary are those of systemic arterial blood pressure and arterial $p\text{CO}_2$. However, in no recent studies (Lende, 1960; Echlin, 1965) have these been mentioned more than briefly, and there is certainly no evidence of their careful control. It is particularly important that the animal's respiration, systemic blood pressure, and arterial $p\text{CO}_2$ be monitored, preferably continuously (although in the latter case repeated arterial sampling is usually preferred), where manipulation in relation to the diencephalon (circle of Willis) or medulla (vertebrobasilar system) is used to illustrate or produce vasospasm.

The cause and mechanism of vasospasm remains obscure. There is little doubt, especially in lower mammalia, that definite pharmacological reactivity exists in the pial vessels (Forbes, Finley, and Nason, 1933; Fog, 1939). This seems to be considerably greater than in the primate (Gurdjian, Webster, Martin, and Thomas, 1958; Lende, 1960, personal

observations), although, as in the response to trauma, there is evidence (Corday *et al.*, 1963) that basal primate vessels show some response to pharmacological agents. There is no evidence, however, that such pharmacological responses are in any way similar to vasospasm, and indeed the extremely slight constriction which has been shown photographically scarcely seems comparable to the narrowing seen in the present study or in that of Echlin (1965) in response to trauma.

The character of the spasm produced in the present experiments, however, recorded as a wave of pressure change, strongly suggests a pharmacological mechanism of mediation. It may be that the arterial wall damaged by trauma releases locally some agent to which neighbouring muscle will still respond. A clear possibility in this regard is a catechol amine. Periarterial nerves in the adventitia of human and macaque cerebral arteries at the level of the circle of Willis have been demonstrated by histochemical techniques (Fang, 1961) although it has not as yet been shown whether a catechol amine is associated with these nerves. There is evidence, further, that even undamaged basal vessels in the primate will constrict albeit slightly in response to locally applied catechol amines (Corday *et al.*, 1963). The major difficulty in any pharmacological hypothesis, however, seems to be that the intensity of such pharmacologically produced constriction is insignificant compared with the effect of trauma. It may be that factors, such as intramural release and persistence of amine locally, could be sufficient to explain this difference.

A further characteristic of vasospasm emerging from the present work, which was commented upon also by Lende (1960), is the lack of influence of change in arterial $p\text{CO}_2$ upon spasm. He found that inspiration of CO_2 in the cat did not effect traumatic vasospasm in the pial circulation, although the levels of arterial $p\text{CO}_2$ were not stated. The present work shows that apparently similar spasm will occur in the primate basal vessels at arterial $p\text{CO}_2$ levels to the extremes of range from hyperventilation to hypercapnia. This suggests that the vasospastic response is an extremely abnormal one in terms of vasoreactivity. As far as it has been adequately explored, for example in relation to reactivity to arterial pressure change (Harper, 1966), cerebral vasoreactivity appears dependent upon arterial $p\text{CO}_2$ levels within the normal range. A lack of response to change in arterial $p\text{CO}_2$ would seem to be a feature of traumatic vasospasm distinguishing it from vasoconstriction in response, for example, to pharmacological agents externally applied where superadded CO_2 influences can still be made out.

A possible complicating factor in this and other

studies is the presence of anaesthesia. Nembutal anaesthesia has been preferred by many investigators (Lende, 1960; Raynor *et al.*, 1961; Echlin, 1942, 1965) while the author has for many years preferred alpha chloralose. There is some evidence (Symon, 1967b) that the reactivity of the cerebral circulation is rather greater with chloralose than with thiopentone anaesthesia, but it is probable that all anaesthetic agents reduce vasoreactivity in a manner not as yet fully analysed. It is possible that differences in anaesthesia may account for apparently different degrees of reactivity in reported studies.

A further major hazard in the interpretation of experimental work on vasospasm is in regard to intravascular aggregation. The present study shows that such aggregation follows appreciable trauma. Gurdjian *et al.* (1958) have shown that in smaller vessels this may occur after much less severe trauma, and certainly the possibility of its occurrence must be borne in mind when severe and apparently long lasting vasospasm is produced. The bulk of the experimental evidence (Harvey and Rasmussen, 1951; Lende, 1960; Symon, 1961; Echlin, 1965), including the present work, indicates that in response to most traumatic stimuli a narrowing lasting around 20 minutes is the rule. The more severe phenomena described recently by Echlin (1965) suggest the operation of some other factors of which intravascular aggregation may well be the chief. This is particularly likely to occur when the animal is in poor condition with a lowered systemic blood pressure at that time. Unhappily, the photographic appearance of a vessel partially occupied by intraluminal aggregation may be difficult to distinguish from that of vasospasm, although no doubt differentiation may be achieved with care. There is evidence (Dr. Ohta, personal communication) that intravascular aggregation may form even in large vessels in response to pharmacological stimulation (5 HT applied to the circle of Willis in the cat). The present study demonstrates that experimental vasospasm produced by trauma is associated with reduction in blood flow in the peripheral distribution of the spastic artery. This is in agreement with the recently reported study of Waltz, Sundt, and Owen (1966) who found a reduction in cortical blood flow (measured by krypton elution technique) in a number of experiments where the middle cerebral artery had been exposed in monkeys before ligation.

It is possible that there may be clinical significance in the occurrence of intravascular aggregation on traumatized segments of cerebral vessels. Transient fluctuations in neurological state, apparently unrelated to fresh haemorrhage, and hitherto attributed to fluctuating vasospasm, are not uncommon in

cases of subarachnoid haemorrhage of aneurysmal origin. Obliteration of the aneurysmal sac, in part or whole due to the formation of intravascular thrombi, is also well known. Since, at least experimentally, these aggregates appear to be of platelets, and disappear into the intracerebral circulation without occluding the vessels, it may be that their occurrence clinically would be associated with transient deficits only, which would thereafter improve as the aggregates dispersed throughout the circulation.

The observed reduction in cerebral arterial pressure under the influence of carbon dioxide is of particular interest, since it suggests that the damage to the main arterial trunk produced in the experiments has altered the pressure relationships in the vascular bed distal to the damaged area under the influence of increased arterial $p\text{CO}_2$. Under normal circumstances the effect of raised arterial $p\text{CO}_2$ is to produce vasodilatation primarily in the arterioles within the brain substance, but also of the main afferent vessels in the pia. There is considerable increase in blood flow locally, but the perfusion pressure in the pial arteries is either unchanged or rises in parallel with the increased systemic blood pressure which is produced by adrenergic mechanisms secondary to the direct effects of CO_2 on the vasomotor centres of the medulla. When the main middle cerebral artery has been damaged, however, it seems that the input to the vascular bed distal to the damaged vessel is seriously impaired, so that the marked reduction in distal peripheral vascular resistance in effect bleeds out the area distal to the damaged vessel. As a result, the intravascular pressure in the area distal to the damaged vessel is reduced.

The present experiments relate only to the vessels of the carotid distribution at the base of the brain in the region of the circle of Willis. The arterial spasm produced here by trauma produces angiographic appearances similar to those of clinical vasospasm (Symon, 1967a). It is at least possible, however, since Echlin has described entirely different characteristics of vasospasm in the vertebro-basilar circulation of the monkey, that the reactivity of the posterior circulation is much greater than that of the carotid. It would seem essential to investigate the characteristics of the two circulations, bearing in mind the factors of physiological control described above.

SUMMARY

Traumatic vasospasm can be produced in the terminal branches of the internal carotid artery intracranially in the baboon (*Papio nubius* or

cynocephalus), significantly altering distal pulse pressure, intravascular pressure, and blood flow.

Such vasospasm cannot be produced by the application of fresh blood, stored blood, fresh or old serum, or near physiological concentrations of 5 HT or catechol amines, in the anaesthetized preparation.

The level of arterial $p\text{CO}_2$ has no influence on the character or duration of traumatic vasospasm.

Factors complicating the analysis of experimental vasospasm are discussed, in particular the variability of response and the occurrence of intravascular aggregates in the area of trauma.

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