Effects of Intracranial Dopamine Perfusion: Behavioural Arousal and Reversal of Cerebral Arterial Spasm following Surgery for Clipping of Ruptured Cerebral Aneurysms

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There is a high mortality and morbidity in patients with subarachnoid hæmorrhage (SAH) following rupture of cerebral arterial aneurysms. The reason for this is not definitely established but it is associated with constriction of the major cerebral arteries. This cerebral arterial spasm (CAS) is a salient feature of the clinical condition, and appears as a pronounced constriction of one or more of the major cerebral arteries (Fig 1). It may be followed by the development of more generalized spasm which often appears to culminate in cerebral ischæmia. In any event, the prognosis in patients showing CAS is bad (Allcock & Drake 1965). A recent analysis of the results of 100 consecutive surgical cases operated on for ruptured aneurysms at the Radcliffe Infirmary, Oxford (Adams *et al.* 1976) showed an overall mortality of 17% in patients with angiographic evidence of postoperative CAS. In the patients with generalized spasm the mortality was 36%.

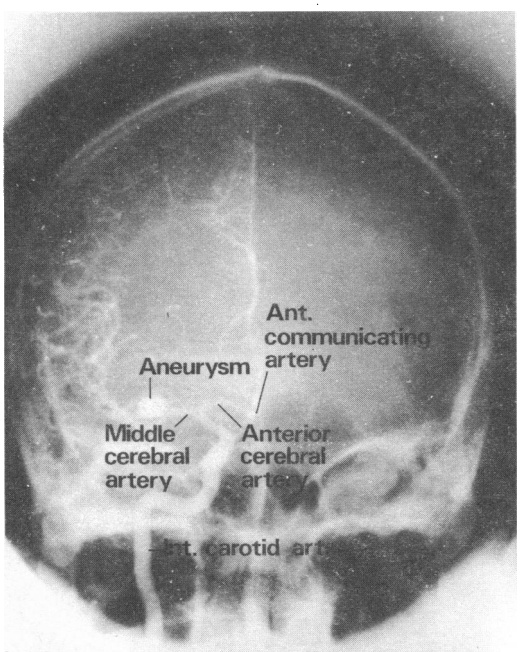


Fig 1 *Angiogram of a 49-year-old male patient with an aneurysm of the middle cerebral artery. The anterior and middle cerebral arteries are constricted, as is the terminal portion of the internal carotid artery. Measurements of arterial calibre are usually made upon the above arteries together with the pericallosal artery*

We do not know the cause of either pre- or postoperative CAS, but they are believed to be due to vasoconstrictor substances originating from blood, most probably circulating in the cerebrospinal fluid (CSF), and acting on the adventitial surfaces of cerebral vessels. Such vasoactive agents have recently been detected in the CSF of patients with preoperative CAS (Boullin *et al.* 1975; Boullin *et al.* 1976; Allen *et al.* 1976).

Possibly because the identity of the vasoactive agents in CSF is still unknown, attempts to prevent or reverse postoperative CAS have so far been unsuccessful. The drugs which have been tested include phenoxybenzamine (Cummins & Griffith 1971), isoprenaline, lignocaine (Sundt *et al.* 1973) and propranolol (Cameron & Haas 1975).

In order to develop substances which effectively prevent or reverse CAS in SAH patients, it is necessary either to identify the causative agent of CAS, or to find pharmacological antagonists, using model systems which simulate CAS in SAH patients. Also it is necessary that the drug be administered by the most appropriate route, bearing in mind our current knowledge regarding the etiology of CAS (Echlin 1971; Odom 1975).

This paper describes the model systems we have used to investigate CAS and to test potentially useful drugs. It then recounts how these data have been extrapolated to the human situation.

Model Systems for Studying CAS

We have used four *in vitro* model systems: the human basilar artery, the baboon basilar and middle cerebral arteries, and the rat aorta, each cut into a spiral strip.

The Isolated Human Basilar Artery

Most of our investigations have been made with this preparation, obtained 1–5 days after death (Starling *et al.* 1975, Boullin *et al.* 1976).

The isolated artery is suspended in an organ bath (Fig 2) in Krebs solution (pH 7.4) at 37°C, gassed with 5% CO_2 in O_2. The artery is contracted by many drugs, including 5-hydroxy-tryptamine (5-HT) and prostaglandins (Fig 3). The contractions are dose-dependent (Fig 4), and characteristically 5-HT is more potent than noradrenaline in contracting this cerebral artery, whereas the

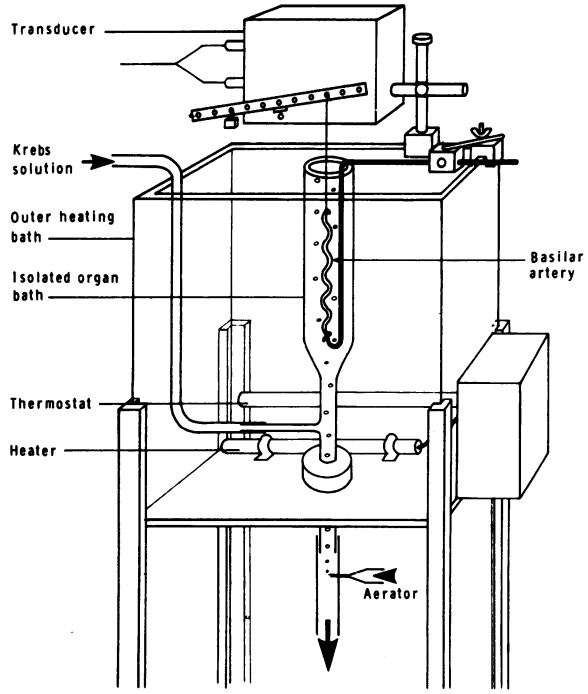


Fig 2 *Diagrammatic view of apparatus used for investigating the pharmacological effects of drugs and CSF on isolated organ model systems, which include the isolated human and baboon basilar arteries, the baboon middle cerebral artery and the rat aortic strip, by isotonic recording. For further details see text*

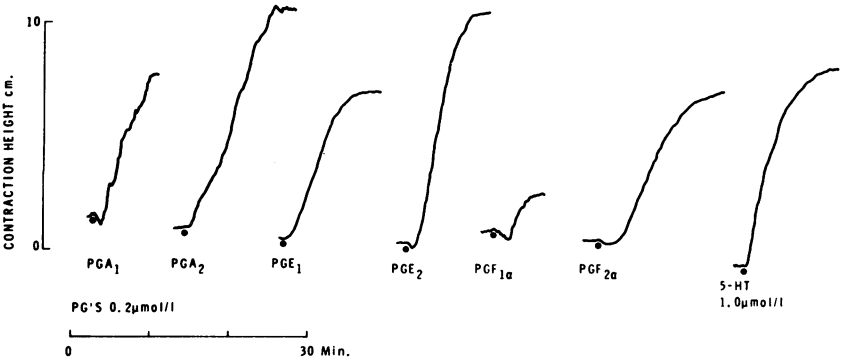


Fig 3 *Responses of the isolated human basilar artery to prostaglandins (0.2 μmol/l) and 5-hydroxytryptamine (1.0 μmol/l). Isotonic recording; arterial length, cm, ordinate, time during contraction, min, abscissa*

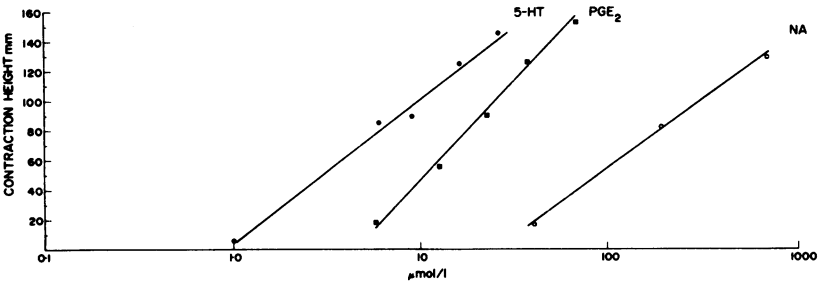


Fig 4 *Dose/response relationships for 5-HT, prostaglandin E_2 and noradrenaline upon the isolated human basilar artery*

converse is true for peripheral arteries. This is in agreement with the work of Bohr *et al.* (1961), Nielsen & Owman (1971) and Toda & Fujita (1973), using arteries of various animal species.

In addition to contracting in response to drugs, the artery is also contracted by CSF obtained preoperatively from patients with CAS (e.g. Boullin *et al.* 1975; Boullin *et al.* 1976).

Fig 5A shows an angiogram obtained in a 56-year-old female patient with an aneurysm of the vertebral artery and intense spasm of the vertebrobasilar system. CSF was obtained within four hours of angiography and applied to an isolated basilar artery. The response obtained is shown in Fig 5B. The slowly developing contraction was not blocked by 10 μmol/l 2-bromolysergic acid diethylamide (anti-5-HT), mepyramine (antihistamine), or phentolamine (adrenergic α-blocker) when added together at just over an hour's incubation.

The response illustrated is typical of our results with 34 SAH patients, which are summarized in Table 1. Of the patients with preoperative CAS 16 out of 22 (73%) had a vasoconstrictor substance in the CSF, whereas only 2 out of 12 (16.6%) SAH patients without spasm produced similar constriction. Normal CSF from 25 patients undergoing myelography for suspected prolapsed intravertebral disc did not contract the artery (results not shown).

In addition to contracting basilar arteries, CSF from patients with SAH and CAS also interacted with drugs. This CSF potentiated the contractions produced by 5-HT and prostaglandins between three and ten times (Figs 6 and 7). CSF from SAH patients without CAS did not produce this degree of potentiation of drug-induced contractions.

These initial experiments showed that the isolated human basilar artery was contracted by a variety of agents, including drugs and CSF.

In order to evaluate the effects of agents with potential clinical use for relief of postoperative CAS, we tested the effects of drugs upon basilar arteries previously contracted with the substances

Table 1

Responses of isolated human basilar arteries to CSF from SAH patients with or without arterial spasm

			Basilar artery response to CSF■		
No. of subjects	*Sex*	*Arterial spasm*●	*Contraction*	*Relaxation*	*No response*
9	Male	Yes	6	1	2
13	Female	Yes	10	1	2
6	Male	No	1	1	4
6	Female	No	1	2	3

●Arterial spasm was determined by carotid angiography
■CSF was collected within 4–18 hours, and thereafter yophilized as described by Boullin *et al.* (1976) and then applied to isolated human basilar arteries as described in the text

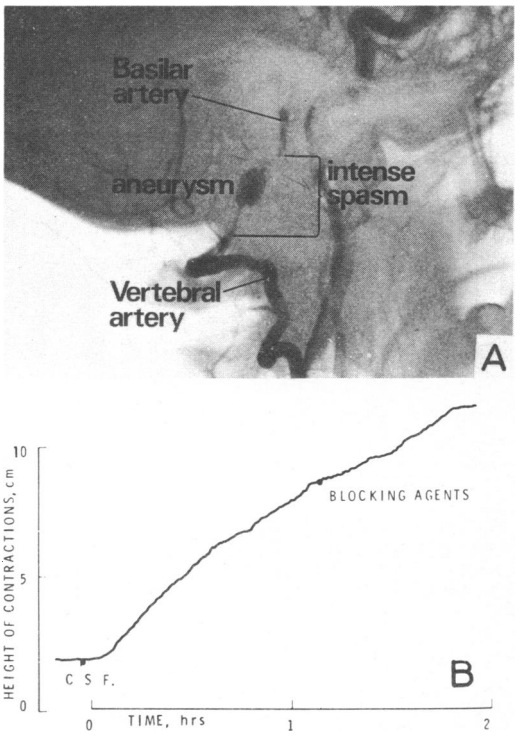


Fig 5A, *angiogram in a 56-year-old female subject showing aneurysm of the vertebral artery and intense spasm of the vertebrobasilar system.* B, *contraction of human basilar artery produced by CSF obtained within 4 hours of making the angiogram* (A)

described above. Propranolol relaxed arteries showing spontaneous contractions and also those contracted by CSF from patients with SAH (Fig 8). Papaverine also relaxed arteries in a similar fashion. Fig 9 shows papaverine-induced reversal of contractions produced by $PGF_{2\alpha}$, histamine and CSF from a patient with SAH (spasm CSF).

Dopamine is known to dilate the mesenteric and renal arteries (Goldberg 1975; Goldberg & Toda 1975). We also found that it relaxed the basilar artery in low concentrations (Fig 10) and that these relaxations were dose dependent (Fig 11). They were specifically prevented by the dopamine antagonist haloperidol (Fig 12).

In addition to relaxing arteries, high concentrations of dopamine (100–1000 μmol/l) produced biphasic effects as shown in Fig 10. The secondary small contractions were not dose dependent and were completely antagonized by 10 μmol/l phentolamine, which did not affect the initial relaxation.

It appears therefore that dopamine stimulates specific dopamine receptors on the human basilar artery which mediate relaxation and are blocked by haloperidol. In addition dopamine also has affinity for adrenergic α-receptors which produce arterial contractions blocked by phentolamine.

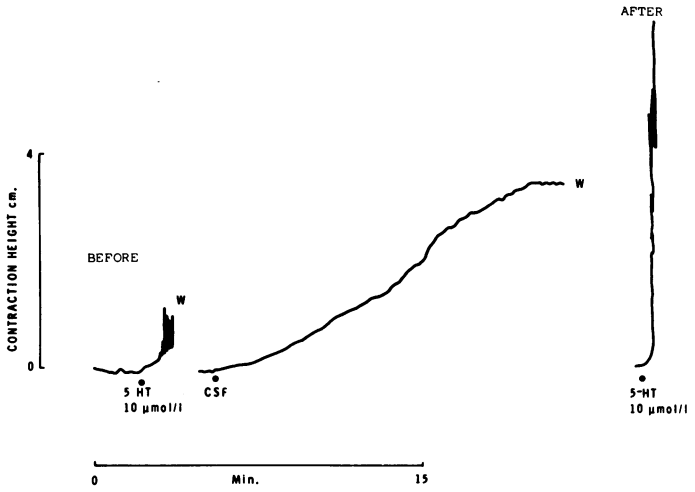


Fig 6 *Potentiation of 5-HT induced contraction of the basilar artery. The response to 5-HT after application of preoperative CSF from a patient with CAS ('after') increased 5.7 times compared to the 5-HT response prior to addition of CSF to the organ bath ('before'). The basilar artery was washed to remove the contracting agents at 'W'*

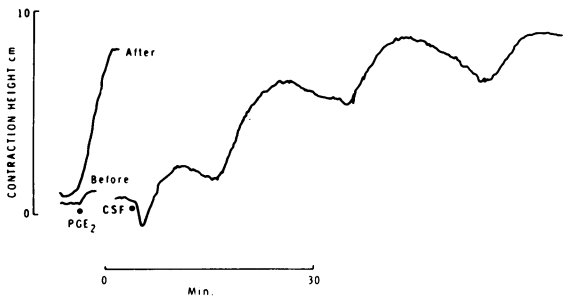


Fig 7 *Potentiation of PGE_2-induced contraction by preoperative CSF from a patient with CAS. Experimental details as for* Fig 6; *the contraction produced by PGE_2 after the artery was contracted with CSF is shown above the initial response, prior to the application of CSF. The PGE_2 response is potentiated 9.5 times*

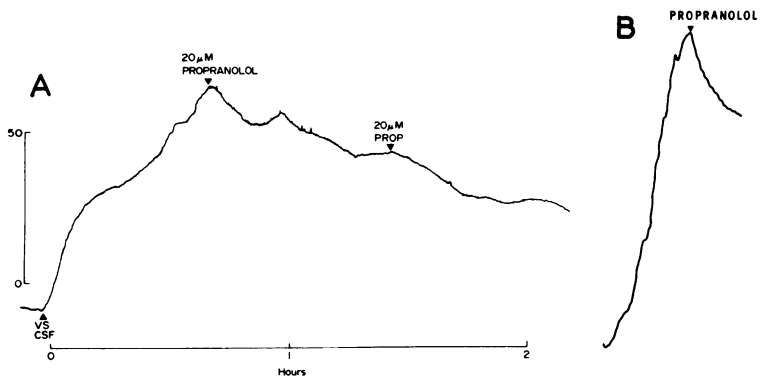


Fig 8 *Reversal of basilar artery contractions by propranolol 20 µmol/l).* A, *reversal of contraction produced by CSF from a patient with CAS (VS CSF). Ordinate, contraction, cm height.* B, *reversal of spontaneous contraction*

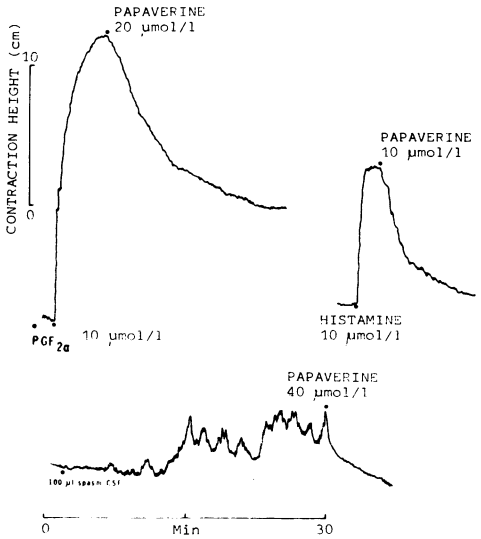


Fig 9 *Papaverine-induced antagonism of contractions of the isolated human basilar artery produced by $PGF_{2\alpha}$, histamine and spasm CSF (CSF from a patient with CAS)*

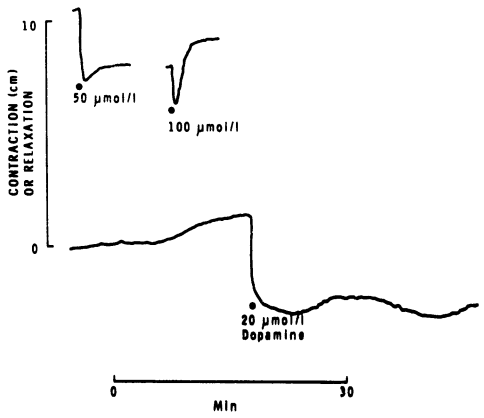


Fig 10 *Biphasic effects of dopamine on the basilar artery. Low concentrations of dopamine relax the artery (responses produced by 20 µmol/l and 50 µmol/l). A higher concentration produces a biphasic effect: relaxation followed by contraction*

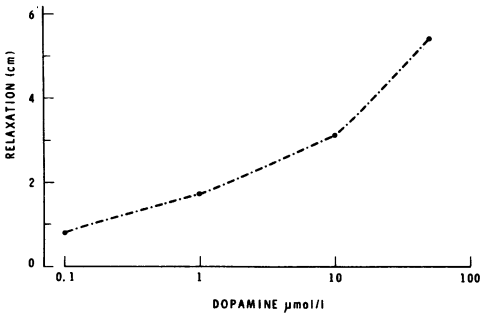


Fig 11 *Dopamine-induced relaxation of the isolated basilar artery. Arterial relaxation (isotonic) recorded on the ordinate is plotted against dopamine concentration on the abscissa. The responses were obtained in one experiment*

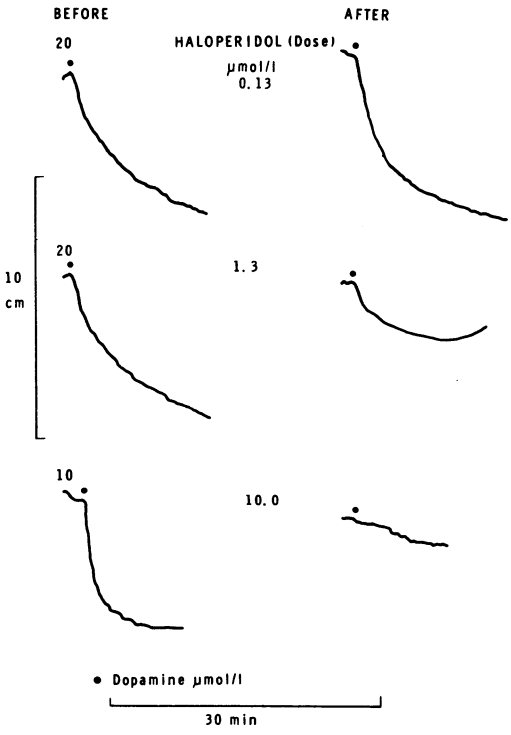


Fig 12 *Haloperidol blockade of dopamine induced relaxation. The records on the left show responses of different basilar arteries to 10 or 20 µmol/l dopamine. Various concentrations of haloperidol were added to the organ bath as stated in the centre column, and inhibition of dopamine-induced relaxation was then observed as shown on the right, when dopamine was added 3 min after haloperidol. It is evident that 1.3 and 10.0 µmol/l haloperidol prevent dopamine-induced relaxation*

Fig 12

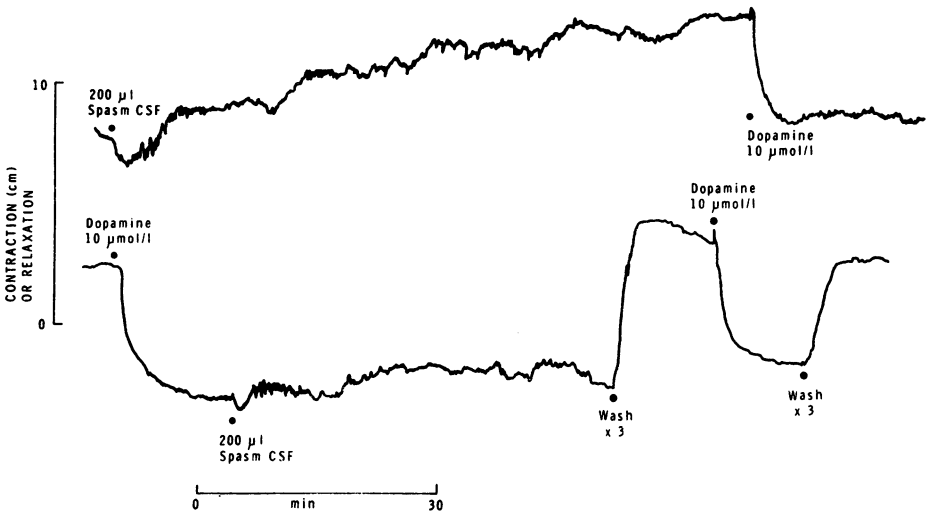


Fig 13 *Prevention and reversal of CSF-induced contractions of the isolated human basilar artery by dopamine.* Upper record: *200 µl of* spasm CSF *(freeze-dried and reconstituted 1:10 in distilled water see text) from an SAH patient with preoperative generalized CAS applied to the artery produced a slowly developing contraction over about 75 min. This was reversed by 10 µmol/l dopamine.* Lower record: *From the same experiment: Application of 10 µmol/l dopamine prevents a second dose of* spasm CSF *from producing a contraction. As a control two consecutive doses of the* spasm CSF *were applied with intervening washes in the absence of dopamine and identical contractions were obtained (not shown)*

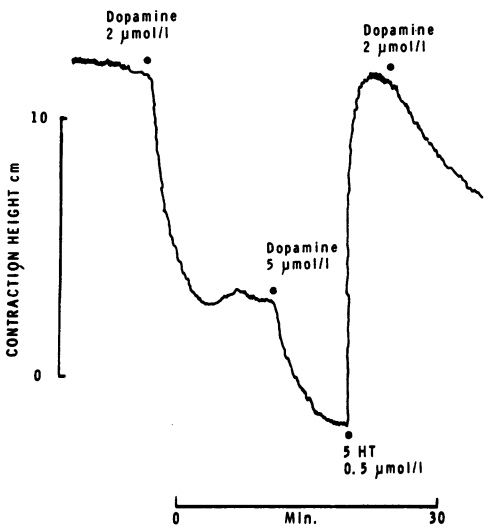


Fig 14 *Interactions between dopamine and 5-HT on the basilar artery. Dopamine relaxations are antagonized by 5-HT and in turn dopamine reverses 5-HT contractions*

Most important in regard to the etiology of CAS, dopamine both antagonized and prevented contractions produced by CSF from subjects with CAS. This is illustrated in Fig 13, where the upper record shows that dopamine antagonizes CSF-induced contractions, while the lower record shows that pretreatment of the artery with dopamine to cause an initial relaxation effectively prevents the expected contraction when CSF is applied thereafter.

5-HT has often been implicated as a causative agent in CAS (Allen *et al.* 1974; Simeone & Vinall 1975; Zervas *et al.* 1973) and Fig 14 shows that dopamine and 5-HT interact on the basilar artery. Dopamine relaxations are reversed by 5-HT and subsequently dopamine antagonizes the 5-HT contraction. Dopamine also interacts with various prostaglandins on the isolated artery in a similar way to 5-HT. Thus when arterial relaxations are produced by dopamine, the artery will then contract to any of the following prostaglandins: PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, and PGA_1. Conversely, arteries initially contracted by these prostaglandins can then be relaxed by dopamine.

It has also been proposed that numerous prostaglandins are involved in CAS (Pennick *et al.* 1972, Yamamoto *et al.* 1972). The prostaglandin antagonist polyphloretin phosphate inhibits basilar artery contractions produced by PGE_2 but not PGE_1, PGA_1, $PGF_{1\alpha}$ or $PGF_{2\alpha}$. We have no further information at present on the significance of the effects of prostaglandins or prostaglandin antagonists in relation to the etiology of CAS after SAH.

Dopamine appears to reverse the contractile effects of CSF and various drugs by activation of dopaminergic vasodilator receptors described above, rather than by any pharmacological an-

tagonism of the effect of some endogenous vasoconstrictor agent which has affinity for the same receptors as dopamine. We visualise the interactions as involving separate receptor mechanisms.

On the basis of the data described above, it appeared to us that dopamine was a suitable agent for clinical investigations, attempting to reverse CAS in patients following surgery for the clipping of ruptured cerebral aneurysms. However, in view of the spasmogenic effects of dopamine in high concentrations (100–1000 μmol/l; 19–190 μg/ml), we decided to investigate other *in vitro* model systems using fresh mammalian tissues.

Isolated Baboon Cerebral Arteries

The baboon basilar artery responds to drugs and dopamine in a similar fashion to the human artery. It is contracted by 5-HT and prostaglandins (Fig 15) and relaxed by dopamine and papaverine (Fig 16); the dopamine relaxation is blocked by 1 μmol/l haloperidol.

There was no evidence that dopamine contracted the baboon artery.

In contrast, the isolated baboon middle cerebral artery was contracted by dopamine over a range of rather high concentrations (Fig 17); relaxation was never seen. The contractions were completely blocked by 0.2 μmol/l phentolamine, indicating involvement of adrenergic α-receptors.

These experiments with isolated baboon cerebral arteries show that, like the human basilar artery, the baboon vessels have specific dopamine receptors causing relaxation and vasodilatation plus adrenergic α-receptors mediating contraction and vasoconstriction.

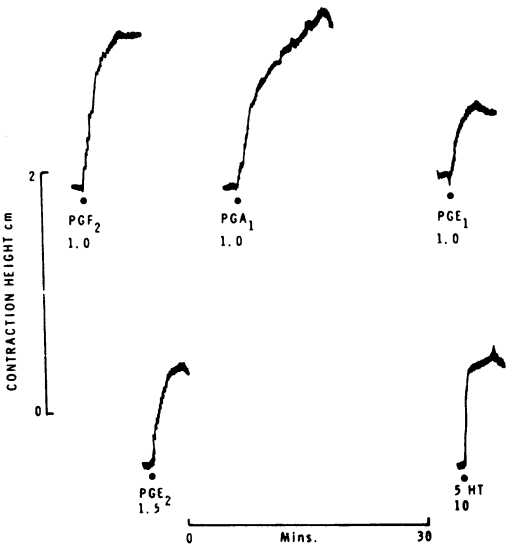


Fig 15 *Responses of the isolated baboon basilar artery to 5-HT and prostaglandins (PGs). Drug concentrations are given in μmol/l*

Both the baboon basilar and middle cerebral arteries behave in a similar way to the human basilar artery in response to CSF; CSF from patients with preoperative CAS generally contracts these arteries, while CSF from patients without CAS does not.

Rat Aortic Strip

We were also anxious to study the response of a freshly obtained systemic artery to drugs and CSF, in order to determine whether differences in its sensitivity to 5-HT and noradrenaline by com-

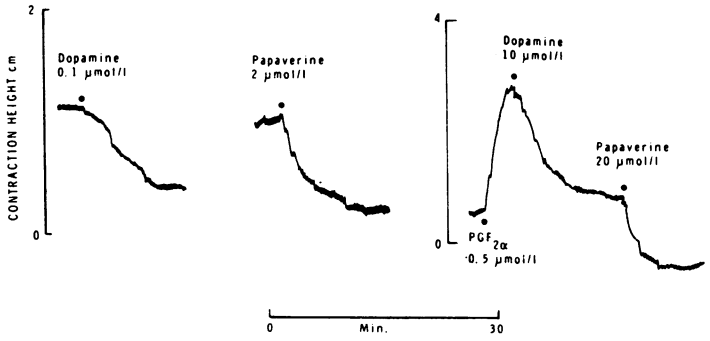


Fig 16 *Dopamine- and papaverine-induced relaxations of the isolated baboon basilar artery*

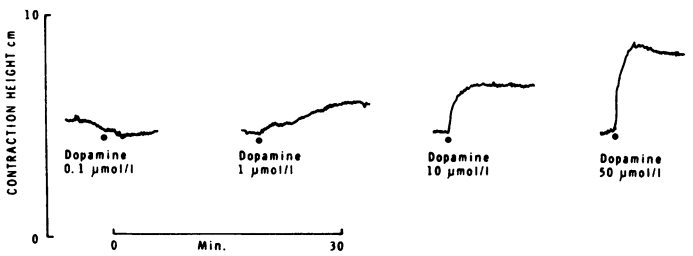


Fig 17 *Dopamine-induced contractions of the isolated baboon middle cerebral artery*

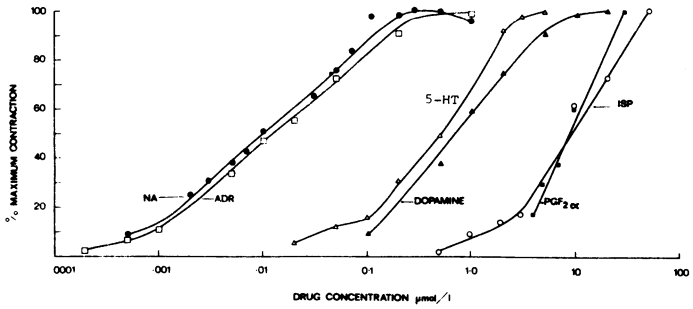


Fig 18 *Responses of the rat aortic strip to drugs. The effects of various compounds are compared with the effects of 5-HT. NA, noradrenaline; ADR, adrenaline; ISP, isoprenaline. Note that the catecholamines NA and ADR are more potent than 5-HT in contrast to the effects of these drugs on cerebral arteries* (see *Fig 4*)

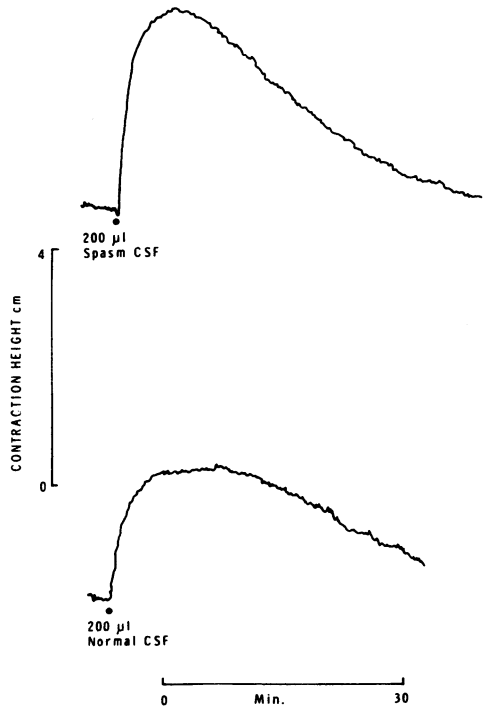


Fig 19 *Effects of normal CSF and CSF from a SAH patient with CAS (spasm CSF) on the rat aortic strip*

parison with cerebral vessels could be exploited in regard to the etiology of CAS. For example, it is known from earlier work that systemic arteries are more sensitive to noradrenaline than to 5-HT, whereas the converse is true of cerebral arteries (Toda & Fujita 1973). The rat aortic strip was found to contract to a variety of drugs, including noradrenaline, adrenaline, prostaglandins, isoprenaline and 5-HT (Fig 18). The artery was also contracted by dopamine; as with all other vessels which responded to dopamine by contracting, this response of the aortic strip was an α-effect blocked by 0.1 to 1.0 μmol/l phentolamine

The effects of CSF were also tested on the aortic strip, but as shown in Fig 19 both CSF from patients undergoing angiography for suspected prolapsed intravertebral disc (normal CSF) and CSF from SAH patients with CAS (spasm CSF) produced comparable contractions, of short duration.

Summary of in vitro *Experiments*

These results obtained with isolated model systems indicate that dopamine stimulates both specific haloperidolsensitive receptors which cause arterial relaxation, hereafter termed 'arterial dopamine receptors', and also α-adrenergic receptors which mediate contraction responses but are not specifically dopaminergic.

The data suggest that arterial dopamine receptors predominate in the human and baboon basilar arteries but that in the baboon middle cerebral artery and aortic strip of the rat the α-adrenergic receptors are dominant.

The next step in the investigation was to examine the effects of dopamine *in vivo* in a mammalian model system for human CAS. For these experiments we selected the baboon.

Investigations in vivo

Symon *et al.* (1973) showed that autologous blood injected intracisternally into the baboon caused short-lasting constriction of the major cerebral vessels, and they used this as a model system for human SAH. In this work it was found that 2 ml blood given intracisternally caused maximal arterial constriction of the internal carotid, middle and anterior cerebral arteries approximately 30 min after injection, and the effect persisted for longer than 90 min. In the current experiments 10 μg/kg dopamine was given intracisternally during the time when arterial spasm was previously found to be maximal, and the drug caused a pro-

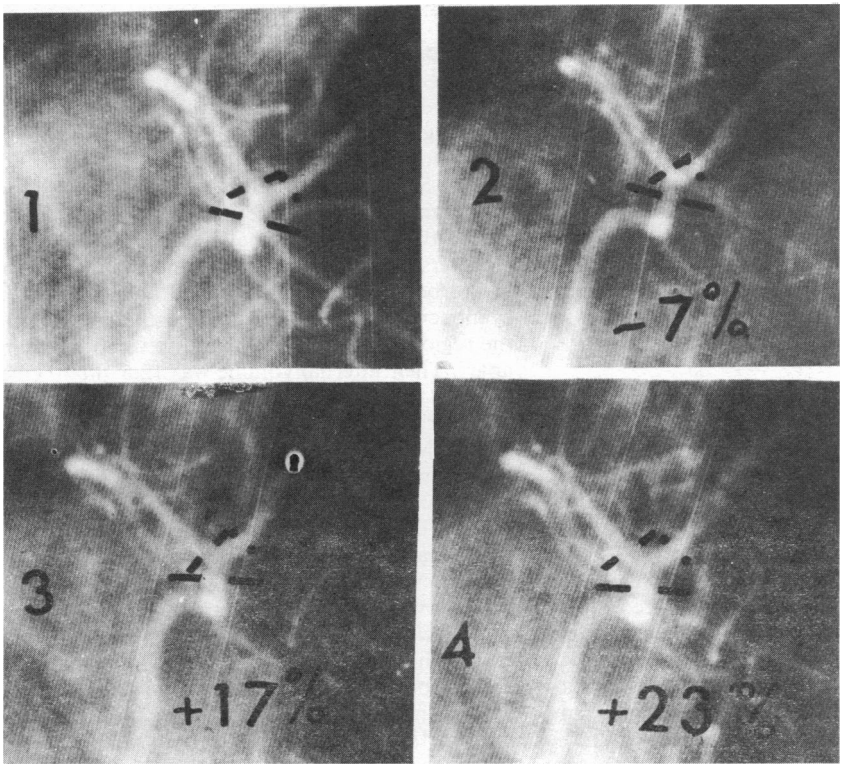


Fig 20 *Effects of intracisternal injections of autologous blood and dopamine upon the calibre of baboon cerebral arteries. Each illustration is a representative angiogram from a series of 8 carotid angiograms. The diameter of the arteries was measured at the points shown:* ▬ ▬ *internal carotid;* ▬ ▬ *middle cerebral;* ● ● *anterior cerebral. The percentage values stated on the illustrations refer to the sum of the mean changes in diameter of these arteries as measured in each angiographic series. They are expressed as percentages of the values obtained in series 1. A minus sign indicates vasoconstriction and a plus sign vasodilatation.* Series 1 *initial observations.* Series 2 *55 min after series 1 and 30 min after intracisternal injection of 2 ml autologous blood.* Series 3 *115 min after series 1; 50 min after series 2; and 10 min after 10 μg/kg intracisternal dopamine.* Series 4 *20 min after series 3 and 30 min after dopamine*

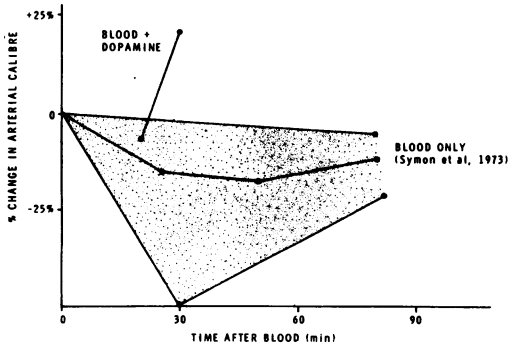


Fig 21 *Time course of cerebral arterial constriction in the baboon following the intracisternal injection of 2 ml autologous blood in replacement of 2 ml CSF removed immediately prior to injection. The data for blood alone are taken from Symon* et al. *(1973) and illustrate the mean and rauge of 3–8 observations. The blood plus dopamine results were obtained in 1976: 10 μg/kg dopamine was injected intracisternally 20 min after blood in a single experiment. The % change in arterial diameter (ordinate) is based on angiographic measurements of changes in calibre in the internal carotid middle and anterior cerebral arteries in the region of the bifurcation as described and illustrated in Fig 20*

nounced dilatation within 10 minutes as shown in Figs 20 and 21.

When dopamine was administered intracisternally without prior injection of blood, variable effects were seen. Low doses of 1 μg/kg caused moderate dilatation of the above arteries, whereas 100 μg/kg caused constriction, and 10 μg/kg had intermediate effects. In the more distal branches of these arteries, and in the pericallosal artery, dilatation predominated.

We considered that these experiments formed an adequate basis for clinical investigations attempting to relieve postoperative CAS with dopamine.

CLINICAL STUDIES

Administration of Dopamine by Intracranial Perfusion

Although the ultimate cause of CAS after SAH remains unknown, there is much experimental evidence to show that blood in the subarachnoid space is an essential factor and that arterial spasm is probably generated by substances present in the CSF. (Echlin 1971; Kapp *et al.* 1968). Accordingly it seemed most appropriate to administer dopamine as soon as possible after placing the aneurysm clip. The drug was given intracranially in the subarachnoid space, into the region of the aneurysm, so that the amine came into contact with the adventitial surface of the major cerebral arteries where aneurysms are most commonly found, that is the arteries forming or adjoining the circle of Willis.

The procedure commenced at the time of surgery for aneurysm clipping. First the patients were prepared for serial postoperative angiography by inserting a catheter down the superficial temporal artery so that the tip was in the external carotid artery. Second, the patients were prepared for intracranial dopamine perfusions. To do this we placed two 2–3 mm diameter soft silicone rubber catheters into the region of the aneurysm sac after it had been clipped (or wrapped and glued with cyanoacrylate). The tips of the catheters were in the region of the aneurysm and were about 2 cm apart. Their internal volume was 12.5 μl/cm. One catheter was used for dopamine perfusion, which was carried out with a syringe pump (Sage Instruments, Model 355, Division of Orion Research Inc, Cambridge, Massachusetts 02139, USA; UK agents Arnold H Horwell Ltd, London NW5 2BP) using a 10 or 20 ml syringe. This was termed the inflow catheter; it was 37 cm long and had an internal volume of 463 μl. The second, outflow catheter was of identical dimensions and was used to collect the dopamine perfusion medium and CSF. This mixture was assayed for biological activity on the isolated human basilar artery and for dopamine and noradrenaline by spectrophotofluorimetry (Chang 1964). Blood samples were taken from a peripheral arterial catheter for assay of dopamine and noradrenaline. A catheter was

Table 2

Results of dopamine perfusion in subarachnoid haemorrhage patients

Subject	*Age*	*Sex*	*Pre-op Botterell grade*●	*Pre-op spasm*■	*Operation days from bleed*	*Post-op spasm*■ *prior to dopamine*	*Dopamine infusion rate and duration*	*Angiographic effect of dopamine*	*CNS effect of dopamine*	*Post-op Botterell grade*●	*Time of transfer (days)*
1	39	F	I	Generalized mild	8	Generalized severe	1 mg/6 min	Slight dilatation	Moderate arousal	I	4
2	54	M	II-III	Generalized mild	8	Generalized mild	28 μg/6 min	No effect	Slight arousal	II	11
3	31	F	I	None	8	Local slight	9.5 μg/min 25 hrs	No effect	No effect	I	4
4	46	F	I	Generalized severe	8	Generalized mild	10μg/min 19 hrs	No effect	Slight arousal	I	9
5	34	M	I	Localized severe	8	Generalized mild	1 mg/5 min ×4 10 μg/min 22 hrs	Pronounced dilatation	Pronounced arousal	I	5
	52	F	II-III	Generalized mild	4	Generalized severe	210 μg/min 10 min 84 μg/min 10 hrs 42 μg/min 25 hrs	No effect	Slight arousal	Died	–
7	27	F	II	Localized mild	8	Generalized mild	200 μg/min 4 hrs	Moderate dilatation	Moderate arousal	I	6

The aneurysm sites were the anterior communicating artery in patients 1, 2, 3 and 6, the posterior communicating artery in patients 4 and 5 and the internal carotid artery in patient 7

●Neurological grading (based on the grading of Botterell *et al.* 1956) is as follows:

I Conscious with or without signs of SAH

II Drowsy, no neurological deficit

III Drowsy, neurological deficit

■Spasm was determined by angiography: 'localized' refers to spasm of one or two vessels; 'generalized' refers to spasm of three or more vessels

also placed in the lateral ventricle or subdural space for monitoring intracranial pressure (ICP).

When the catheters were all in place the wound was closed and a predopamine angiogram was undertaken to assess the degree and extent of spasm. This was invariably done within one hour of aneurysm clipping.

Dopamine perfusion was begun immediately thereafter. The drug was dissolved in sodium chloride injection BP (0.9% NaCl w/v) to give a concentration of 50 or 500 μg/ml. The fluid perfusion was varied between 19 μl/min and 0.4 ml/min so that the rate of dopamine perfusion was approximately 9.5 to 200 μg/min. A second angiogram was obtained 20 min after the first, and 15 min after starting the dopamine perfusion. Thereafter further angiography was done at varying times over the periods of perfusion and up to 14 hours after it was stopped.

The results of our investigations are shown in Table 2 and are presented in chronological order. Fig 22 illustrates the intracranial perfusion apparatus and the various catheters in patient 5.

The above protocol only refers to patients 3–7. This protocol was developed from investigations on the first two patients, in whom dopamine was injected manually via a 2 ml syringe in 0.2 ml aliquots as will be described below.

Dopamine was generally perfused at a slow rate of about 10 μg/min. During the first 15 min the rate was increased to 200 μg/min for 5 mins in subjects 5 and 6 as stated in Table 2. Subsequently patient 5 was perfused at the high rate for 3 further periods as described below (see dopamine-induced arousal).

The effects of dopamine are presented below.

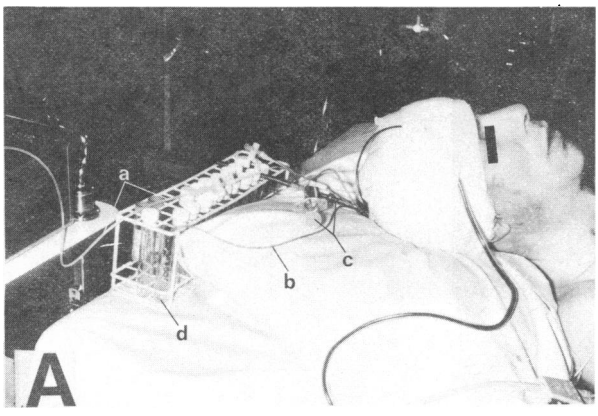
Clinical Effects of Dopamine

Intracranial dopamine perfusions produced two effects: dilatation of cerebral arteries and an arousal response.

Dilatation of cerebral arteries: Dilatation of cerebral vessels and the arousal response were observed in the first patient studied. This 39-year-old female with an anterior communicating artery aneurysm received an intracranial infusion of 1 mg dopamine in 0.2 ml aliquots over 6 min through an inflow catheter; there was no outflow catheter in this case. The infusion began immediately after taking a carotid angiogram, which showed generalized severe spasm of the middle and anterior cerebral, anterior communicating and internal carotid arteries. A second carotid angiogram was done within 3 min of the end of the dopamine infusion and there was slight dilatation of these vessels.

In the second patient, a 54-year-old male with an aneurysm on the same artery, the original procedure was repeated except that the dose of dopamine was reduced. In this case there was no arterial dilatation and only slight arousal.

Following the results with these two patients we considered that it would be necessary to give a more prolonged dopamine perfusion through 2 catheters rather than a simple infusion. Accordingly we devised the previously described protocol.



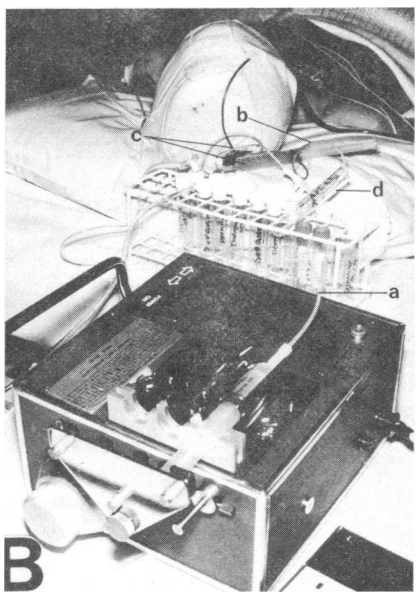


Fig 22A, *34-year-old male patient (no 5, Table 2) prepared for intracranial perfusion with dopamine hydrochloride.* B, *another view of patient showing infusion pump with infusion syringe and inflow catheter.* a *Dopamine catheter with the tip placed close to the aneurysm clip;* b *Outflow catheter with the tip approximately 2 cm from the tip of* a; c *Syringe connected to catheter in the superficial temporal artery and used for angiography;* d *Tube for collection of fluid from outflow catheter. This fluid is assayed for dopamine and vasoactivity upon the isolated human basilar artery*

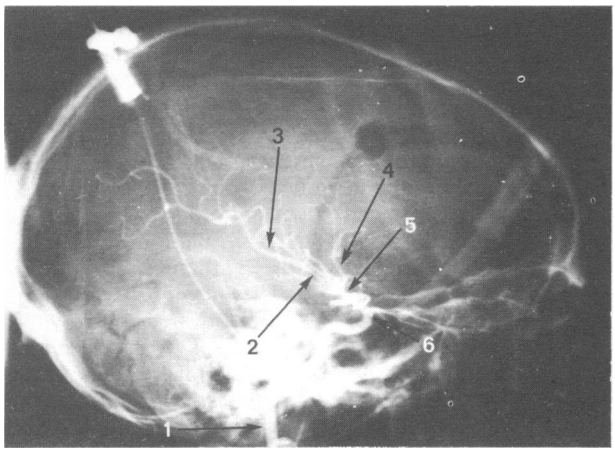


Fig 23 *Angiogram of 34-year-old male patient (no 5, Table 2) before dopamine perfusion. The various arteries are numbered as follows:* 1 *extracranial internal carotid;* 2 *middle cerebral showing spasm;* 3 *middle cerebral;* 4 *middle cerebral showing spasm;* 5 *intracranial carotid/middle cerebral in spasm;* 6 *intracranial carotid in spasm*

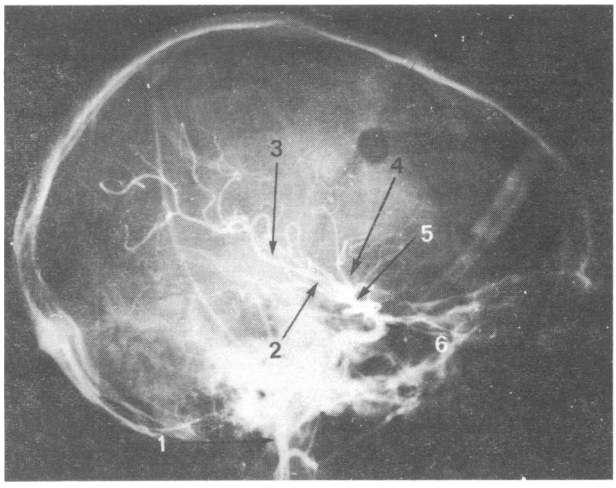


Fig 24 *Angiogram taken 20 min after Fig 23 and 15 min after starting dopamine perfusion (200 μg/min for 5 min, 10 μg/min for 10 min). Arteries labelled as in Fig 23. Note dilatation of* 4 5 6 *with no change in* 1 2 3

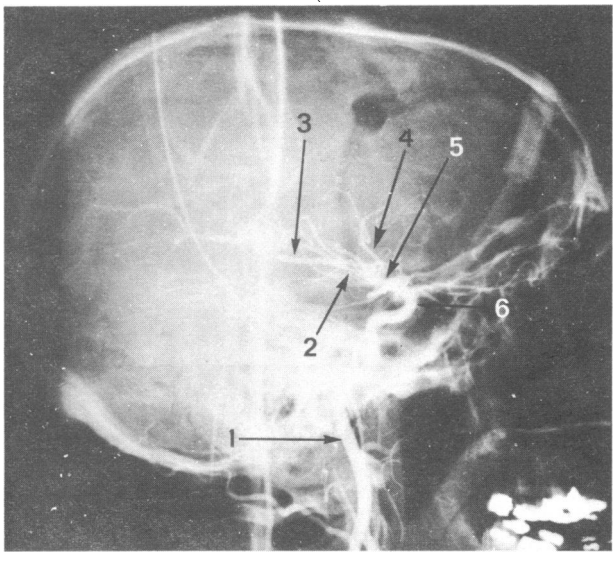


Fig 25 *Angiogram taken 165 min after Fig 23 and 160 min after commencing dopamine perfusion (10 μg/min)*

The most dramatic results were obtained in patients 5 and 7, and some of the angiograms taken in the former illustrate the qualitative effects of dopamine perfusions. Figs 23 to 25 show angiograms before, and 20 and 160 min after starting dopamine perfusion. It is clear from comparison of these illustrations of the angiograms that dopamine dilates some vessels but not others. Thus the middle cerebral artery labelled 3, which is not in overt spasm, shows little or no change after dopamine. Also a branch of the middle cerebral artery, labelled 2, is in spasm prior to dopamine perfusion and the spasm remains unchanged. On the other hand the middle cerebral and the internal carotid arteries, labelled 5 and 6, in the region of the aneurysm clip on the posterior communicating artery (not visible on the angiograms), show dilatation, as does artery 4.

Although not all the vessels were dilated by dopamine and some vessels in spasm remained so after dopamine perfusion, we have never observed a spasmogenic effect in the seven patients we have investigated. There is no vasospasm mediated by α-adrenergic mechanisms comparable to that observed in the studies with isolated organs or in the anæsthetized baboon.

Similar results to those obtained in patient 5 were also seen in patient 7. In this instance there was a particularly pronounced dilatation of the anterior communicating artery which disappeared 14 hours after termination of the dopamine perfusion, when mild spasm returned.

In patient 6 severe spasm was apparent in the immediate postoperative angiogram. Dopamine perfusions at the high rates shown in Table 2 did not affect this spasm and the patient died after 4 days.

Dopamine-induced arousal: This was observed in the first patient to receive dopamine. This 39-year-old woman was heavily sedated with diazepam for angiography, yet when the first 0.2 ml aliquot of dopamine was injected she awoke and opened her eyes, appeared alert and was talkative. The arousal effect disappeared almost immediately after the 0.2 ml aliquot was injected but reappeared at once when another 0.2 ml injection was made.

As shown in Table 2 six out of the seven patients showed this arousal phenomenon, but only when some 100–200 μg/min was perfused; lower perfusion rates did not produce any obvious arousal. The most dramatic effects were observed in the 34-year-old male patient (no. 5) previously illustrated in Fig 22. Dopamine was perfused at a rate of 10 μg/min for 22 hours, and after about 20 hours the rate was increased from 10 μg/min (19 μl/min) to 202 μg/min (0.4 ml/min) for about 5 mins. At the beginning of perfusion, which was begun at 10.00 hrs, the patient was asleep and snoring. The first signs of arousal were seen after 30 sec when the patient opened his eyes and put his hand to his head. After 50 sec he was questioned about the presence of pain and the day of the week. His reply to the first question was negative, and the day of the week was given incorrectly. There were no signs of agitation or distress and the patient replied logically and intelligently to simple questions but did not initiate conversation.

After 4 min the perfusion was stopped: within 90 sec the patient was asleep, and after 120 sec he was snoring.

The dopamine perfusions at 202 μg/min were repeated at about 30 min intervals with the same time course of arousal and deep sleep on each occasion. The patient's replies during the second and third perfusion periods were correct chronologically and on the last occasion he good-humouredly complained of repetitive questioning. When told that the Friday in question was Good Friday he replied 'What's good about it?'

This patient made a rapid and complete recovery and showed no untoward responses to dopamine either before or after the perfusions.

DISCUSSION

To our knowledge this is the first demonstration of a drug-induced reversal of CAS following the clipping of cerebral aneurysms. The use of intracranial dopamine was based on *in vitro* experiments with human and baboon cerebral vessels which indicated that these arteries may possess specific dopaminergic receptors mediating vasodilatation. Adrenergic α-receptors were also detected and predominated *in vitro* in the baboon middle cerebral artery. It is possible that dopaminergic vasodilator receptors are not evenly distributed throughout the human cerebral/arterial vasculature, and that the responses of these and of the adrenergic α-receptors are differently affected by *in vitro* conditions. This is supported by the results obtained in the baboon, in which dopamine reversed spasm of the middle cerebral artery previously produced by intracisternal blood, and yet *in vitro* dopamine stimulated only vasoconstrictor α-receptors.

In any event, in the clinical studies vasospasm was not observed with dopamine perfusions, so it is likely that at the concentrations used dopamine did not stimulate α-receptors.

In this regard, dopamine appears to be a particularly suitable drug for the type of clinical investigation described here. The plasma half-life is less than 2 min in man (Arnar-Stone Laboratories, unpublished observations) and in the cat (Boullin *et al.* 1970). In CSF the concentrations at equilibrium, which was reached within 4 hours of perfusion, were in the range 50–200 μg/ml, that is 10–40% of the perfusion concentration (Fig 26).

From calculations based upon data similar to those shown in Fig 26 we reckoned that the CSF disappearance half-time ranged from 25 to 40 min. Thus if vasospasm or other untoward effects were to be seen with dopamine perfusions they should rapidly disappear when the perfusion was stopped. Our pharmacological data indicate that any vasospasm would be effectively antagonized by phentolamine.

There are at least twenty factors which may influence the pharmacological effect of any drug administered by intracranial perfusion, and these are listed in Table 3. It is quite clear that many of these factors may influence the prognosis of SAH patients. Some of these have been mentioned previously by Allcock & Drake (1965). The factors may greatly affect dopamine responses, and it will be necessary to make an extended investigation with dopamine to see if the drug is in fact of real value in the prevention and/or relief of preoperative and postoperative spasm. The latter is obviously the easiest to attempt to treat, since the hazard of causing additional hæmorrhage with a vasodilator drug is minimal (*see* Cummins & Griffith 1971). On the other hand if it proved possible to use dopamine preoperatively then this might help to reduce the mortality of 5% per week in hospitalized patients due to recurrent hæmorrhage.

To date we have only made intracranial perfusions using dopamine concentrations in the range 50–500 μg/ml, which were based on the concentrations which effectively antagonized blood-induced CAS in the baboon. On the other hand, the concentrations producing dilatation of the isolated human basilar artery were in the range 19 ng to 19 μg/ml (0.1 to 100 μmol/l, Fig 11); however it must be borne in mind that the static conditions *in vitro* cannot be compared with the dynamic situation *in vivo* where there is continuous CSF production and dopamine may be widely diffused away from the area of immediate perfusion. Nevertheless, more prolonged results may be achieved by the use of dopamine at different concentrations. Similar remarks apply to the rates

Table 3

Factors affecting the responses of cerebral arteries to drugs given by intracranial perfusion

Drug concentration
Rate of administration and time of commencement
Rate of inflow
Rate of outflow
Relative positions pf perfusion catheters
Position of aneurysm
Rate of CSF production
Duration of perfusion
Rate of drug metabolism
Distribution of perfused drug
Distribution and extent of arterial spasm
Interactions with other drugs
Drug solubility in CSF
Protein binding of drug in CSF
Blood pressure
Heart rate
Degree of surgical trauma
Presence of blood in CSF
pH of CSF
P_{CO_2}
Intracranial pressure
Duration of intraoperative hypotension

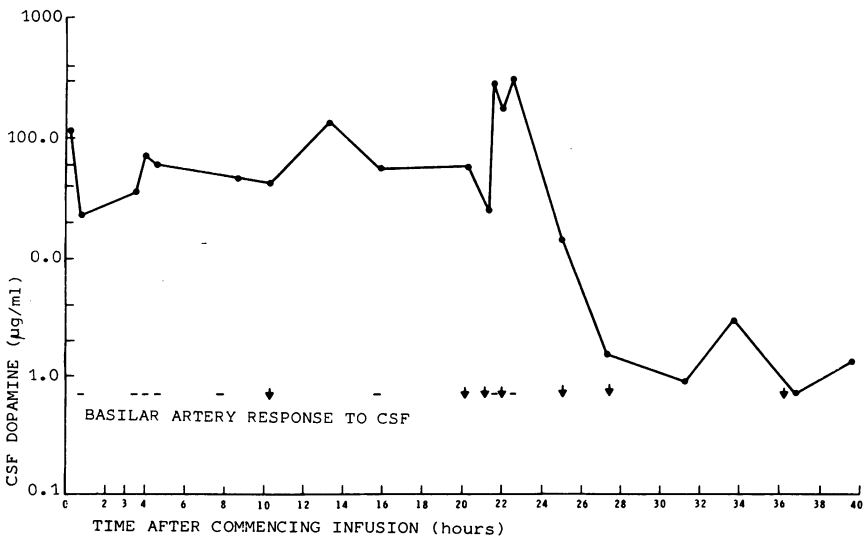


Fig 26 *CSF dopamine concentrations and response of the isolated human basilar artery to CSF during dopamine perfusion. (Data obtained from patient no 5). CSF dopamine in μg/ml (logarithmic scale ordinate) is plotted against time in hrs after commencing infusion abscissa). Basilar artery responses are indicated by —: no contraction; ↓: relaxation. Aliquots of CSF were collected at the times indicated and assayed for biological activity as described by Boullin* et al. *(1976). For further details* see *text*

of perfusion in relation to the positioning of the inflow and outflow catheters. We believe that our results should only be considered as preliminary, and we intend to make a much more extensive study of this technique.

The next question to be considered is the effect of intracranial dopamine perfusions upon the postoperative prognosis. We have no evidence that dopamine affected the prognosis in one way or the other. That is to say, it did not appear to improve the prognosis in patients expected to do well (patients 1, 3, 4, 5 and 7) and did not appear to worsen the prognosis in those predicted to do badly (patients 2 and 6); indeed patient 2 may well have benefited from dopamine. With regard to the patient who died, it is evident from Table 2 that this patient was the only one who was operated upon less than 8 days after a detectable hæmorrhage. Analysis of 100 consecutive aneurysm patients operated upon in this hospital has shown a mortality of 22% in the group that underwent surgery within 7 days of SAH in comparison to only 4.5% when the interval after hæmorrhage was 8–15 days (Adams *et al.* 1976).

In spite of the failure to alter the postoperative prognosis in this small group of subjects, there is no doubt that under certain conditions dopamine dilated some cerebral arteries in SAH patients after operation. However, optimal conditions for intracranial perfusions have not yet been established. Consequently our conclusion at this stage is that the value of dopamine in the relief of postoperative CAS following SAH is not established, but the initial results are encouraging.

Dopamine Arousal

The most dramatic effect of intracranial dopamine perfusions was the arousal or awakening effect. As we have described, dopamine appeared to be able to arouse patients from an apparently deep sleep.

To our knowledge this is the first report of an arousal effect of dopamine in man, and it is almost certainly due to an action of the amine upon neuronal pathways in the brain itself, although whether this is an effect on specific dopaminergic tracts such as the nigrostriatal pathway is another matter. The dopamine-induced arousal does not appear to involve cerebral arterial dilatation, because the arousal effect appeared and disappeared with much greater rapidity than the changes in arterial calibre.

The first reports of awakening effects caused by dopamine were reported some years ago in reserpine-sedated animals by Carlsson *et al.* (1957); Everett & Toman (1959); and Blaschko & Chrusciel (1960), following parenteral administration of the amino acid precursor of dopmaine, L-dopa.

Awakening effects were also described by Blaschko & Chrusciel (1960) in normal animals, and from their work it is almost certain that the awakening effects were due to the passage of L-dopa across the blood/brain barrier and conversion to the pharmacologically active amine dopamine. Indeed, they did find a small awakening effect of dopamine itself when administered parenterally in very large doses of 0.5 g/kg Very little dopamine can cross the blood/brain barrier, and this is the explanation for the large doses of dopamine required in the animal experiments. In our work we circumvented the barrier and therefore the concentrations of dopamine required were very much lower.

We find no evidence for acute or chronic adverse effects following dopamine-induced arousal, and therefore the possible clinical usefulness of arousal must be considered. Dopamine arousal may be valuable in comatose patients following head injuries, or in cases of overdose from anæsthetics, barbiturates or other drugs. In any case we believe that the arousal effects of intracranial dopamine like the effects of the amine on CAS, merit further investigation.

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REFERENCES

Adams C B T, Loach A B & O'Laoire S A (1976) *British Medical Journal* ii, 607–609
Allcock J M & Drake C G (1965) *Journal of Neurosurgery* 22, 21–29
Allen G S, Gold L H A, Chou S N & French L A (1974) *Journal of Neurosurgery* 40, 451–457
Allen G S, Gross C J, French L A & Chou S N (1976) *Journal of Neurosurgery* 44, 594–600
Blaschko H & Chrusciel T L (1960) *Journal of Physiology* 151, 272–283
Bohr D F, Goulet P L & Taquini A C jr (1961) *Angiology* 12, 478–485
Botterell E H, Lougheed W M, Scott J W & Vandewater S L (1956) *Journal of Neurosurgery* 13, 1–42
Boullin D J, McMahon E M & O'Brien R Z (1970) *British Journal of Pharmacology and Chemotherapy* 40, 522–523
Boullin D J, Mohan J & Grahame-Smith D G (1976) *Journal of Neurology, Neurosurgery and Psychiatry* 39, 756–766
Boullin D J, Starling L M, Grahame-Smith D G & Mohan J (1975) In: Abstracts, 5th Congress of the European Association of Neurological Societies. Department of Neurosurgery, Radcliffe Infirmary, Oxford; pp 164–166

Cameron M M & Haas R H (1975) In: Abstracts, 5th Congress of the European Association of Neurological Societies. Department of Neurosurgery, Radcliffe Infirmary, Oxford; pp 157–158
Carlsson A, Lindqvist M & Magnusson T (1957) *Nature (London)* **180**, 1200
Chang C C (1964) *International Journal of Neuropharmacology* **3**, 643–649
Cummins B H & Griffith H B (1971) *British Medical Journal i*, 382–383
Echlin F A (1971) *Journal of Neurosurgery* **35**, 646–656
Everett G M & Toman J E P (1959) In: Recent Advances in Biological Psychiatry. Ed. J Wortis. Grune and Stratton Inc, New York; pp 75–81
Goldberg L I (1975) *Biochemical Pharmacology* **24**, 651–653
Goldberg L I & Toda N 1975) *Circulation Research* **36/37**, Suppl. 1, I97–I102
Kapp J, Mahaley M S & Odom G L (1968) *Journal of Neurosurgery* **29**, 331–338
Malec D & Kleinrok Z (1971) *Neuropharmacology* **11**, 331–336
Nielsen K C & Owman C (1971) *Brain Research* **27**, 33–42
Odom G L (1975) *Clinical Neurosurgery* **22**, 29–58
Pennick M, White R P, Crockarell J R & Robertson J T (1972) *Journal of Neurosurgery* **37**, 398–406
Simeone F A & Finall P (1975) *Journal of Neurosurgery* **43**, 37–46
Starling L M, Boullin D J, Grahame-Smith D G, Adams C B T & Gye R S (1975) *Journal of Neurology, Neurosurgery and Psychiatry* **7**, 650–656
Sundt T M, Onofrio B M & Meredith J (1973) *Journal of Neurosurgery* **38**, 557–560
Symon L, Du Boulay G, Ackerman R H, Dorsch N W C & Shah S H (1973) *Neuroradiology* **5**, 40–42
Toda N & Fujita Y (1973) *Circulation Research* **33** 98–104
Yamamoto Y T, Feindel W, Wolfe L S, Katoh H & Hodge C P (1972) *Journal of Neurosurgery* **37**, 385–397
Zervas N T, Kuwayama A, Rosoff C B & Salzman E W (1973) *Archives of Neurology* **28**, 400–404

DISCUSSION

Professor Goldberg (*Chairman*): That was a fascinating paper. I was most interested in your isolated blood vessel work. I think that is the first demonstration I have seen of haloperidol block. We tried this in isolated vessels in Japan, but we had to use phenoxybenzamine to block constriction and the haloperidol relaxed the vessels, so this may be the first true demonstration of dopamine receptor blocks.

Dr Boullin: We have tried both pure haloperidol and the commercial product in a solvent (Serenace) and found that it specifically inhibits dopamine-induced relaxation of the basilar artery. On some occasions both haloperidol and Serenace actively produce contractions, but this was rare and was independent of the inhibitory actions against dopamine.

Dr H Hoyt (*Chicago*): As to whether haloperidol blocks dopamine's activity, we have had several cases reported in which patients were inadvertently receiving haloperidol and dopamine concomitantly; there was no clinical need to increase the dopamine dose, and no other evidence of dopamine being blocked.

Professor Goldberg: I think the normal clinical dose is probably not high enough to block dopamine. Do you have any comment about that?

Dr Boullin: Yes. We have seen no evidence of this clinically and I agree with Dr Goldberg. I think the concentrations are higher in these experiments than would be obtained with clinical doses.

Professor J B Brückner (*West Berlin*): In clinical anæsthesia we are using haloperidol-like compounds in neuroleptanalgesia very often. I should like to ask whether you have any experience of the amount of dopamine antagonism induced by droperidol.

Dr Boullin: No, I am afraid we have not tried it.

Professor G Milhaud (*Paris*): You have eight patients now. Do you have the feeling that what you did was of benefit to the condition of your patients?

Dr Boullin: We do not think that dopamine infusions have affected the overall outcome of surgery, one way or the other. They certainly have not caused any dramatic clinical improvement, nor have they been responsible for any dramatic deterioration. Two patients out of the eight have died, but then their clinical condition prior to operation was not very good and the interval between bleed and operation was shorter than we normally like to have, so their prognosis was not good. In any event we do not think we significantly altered this.