Fibrinolysis in subarachnoid haemorrhage

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RECURRENT subarachnoid haemorrhage from intrachanal aneurysms most commonly occurs during the 2nd, 3rd and 4th weeks after the initial ictus, and after 8 weeks the recurrence rate, approaching 50% in untreated cases, falls sharply (Hamby, 1948; Walton, 1952; Holmes, 1957; McKissock, Paine & Walshe, 1958).

For those patients having no surgery who survive 6 weeks after subarachnoid haemorrhage, the chances of surviving 1 year or longer are 82% (Locksley, 1966).

The anatomical pattern of saccular aneurysm is too often repeated, at each of the common sites, for any one to be recognized as more vulnerable to recurrent bleeding than others. Mechanical factors such as the size of aneurysm, streaming, or width and configuration of the neck, do not in general influence the recurrence rate; and our attention is necessarily directed towards variations in the natural physico-chemical processes believed first to seal, and then to repair, a rent in a blood vessel.

The primary sealing of the hole in an aneurysm wall by a platelet plug, at first permeable to red cells, may be assumed responsible for the initial stemming of the leak within, say, 4 min. Cells infiltrate the plug and the complex process of building a clot commences.

What happens to this clot during the next 8 weeks determines whether the patient suffers recurrent haemorrhage. In about half such patients the seal remains viable; good firm adherent clot becomes organized, and the repair may last for many years. In a conservatively treated series of cases there must be a very fine dividing-line between the mechanism of blood clotting in these patients, and in the other 50% whose aneurysms bleed again within a few weeks.

This does not mean that there is any recognizable abnormality in the maturation of the clot in those cases that bleed again. Clotting and bleeding times in both groups are within normal limits; but the balance is so delicate that either variations within the norm are decisive, or some

other factor is operative in the maturation of clot, which we have not been able to measure sufficiently accurately. Platelet adhesiveness, blood viscosity, local fibrinogen concentration, fibrinolysis—any or all of these may be relevant. It seems certain, however, that there is both continual building up and absorption of clot going on simultaneously—the laying down of fibrin and formed elements on the one hand, and fibrinolysis with digestion on the other. Perhaps one of these processes ceases too soon, or another too late. Hellem (1960) says that 'the fact that Factor R is inactivated in plasma (*in vitro* and probably *in vivo*) may, with the fibrinolytic system, explain why a thrombus does not grow indefinitely'.

Two considerations prompted the investigation in this paper: in the first place the development of accurate methods of fibrinolysis assay *in vitro*, and secondly the marketing of epsilon aminocaproic acid (EACA), known to inhibit fibrinolysis and almost harmless when given orally.

Between November 1963 and March 1965 assay of plasminogen activator and of fibrinogen was performed in 109 cases of subarachnoid haemorrhage admitted to the South East Regional Neurosurgical Centre. A clinical trial of the effects of administering EACA was continued until the end of the year.

Methods

The large number of patients in the series and the length of the chemical estimations precluded their use for the assay of both fibrinogen and plasminogen.

Fibrinogen was therefore measured by the fibrinogen titre, using doubling dilution of plasma clotted with 50 units/ml thrombin. Preliminary experiments showed that a titre of 1/128 corresponded to more than 100 mg of fibrinogen.

Plasminogen was assayed by the streptokinase activated fibrinolysis time, using the method of Innes & Seivitt (1964). The normal range is 1-2½ hr. Comparison of this method and a caseinolytic method showed that this range corresponded to

about 40–140 mg/100 ml plasminogen, with close correlation between the methods.

The dilute whole blood clot lysis time described by Fearnley, Balmforth & Fearnley (1957) was measured. This is mainly an estimate of plasminogen activator. The normal range is between 2 and 7 hr.

The lysis times of the clots in the latter two methods were recorded by an automatically re-wound camera triggered at hourly intervals.

Excluding those cases in which the investigation was pursued for less than 3 days, and cases of aneurysm treated by definitive surgery to the sac itself, the series concerns fifteen cases in which no cause for the haemorrhage was discovered on angiography, eight vascular malformations and eighty-six cases of proved intracranial aneurysm.

Subarachnoid haemorrhage, 'cause not proved'

In fifteen cases in which angiography failed to demonstrate aneurysm, all the lysis times fell within normal limits. Such negative findings on angiography are known to carry a good prognosis after the first haemorrhage, rarely suffering recurrence; and one possibility to explain their safety is that a (small) aneurysm clotted completely after bleeding. If this is so, clotting mechanisms with subsequent repair must be very

efficient in such patients; but the present investigation shows that they do not have unusually long lysis times *in vitro*.

Vascular malformations

In eight cases of this group also, lysis times were, as expected, unremarkable.

Intracranial aneurysms

The investigation as far as aneurysms are concerned is divided into two parts: *Part I*—The relation between lysis times and the predictability of recurrent haemorrhage. *Part II*—The effects of administration of EACA on the diluted whole blood clot lysis times and on the frequency of recurrent haemorrhage. Sixty-four patients were given 12 g EACA three times daily for a maximum of 28 days. The intravenous route was employed in a few instances, in unconscious patients.

Results

Part I

There were studied twenty-two patients with berry aneurysms, to whom no EACA was administered. Twelve of these had aneurysms of the internal carotid artery, treated successfully by permanent carotid occlusion. The lowest lysis times recorded were 3.5 hr (one case) and 3.8 hr (two cases). The remaining nine cases had com-

TABLE 1

Analysis of ten of the twenty-two control patients to whom no EACA was administered. Surgical treatment was 'non-definitive'—closure of an anterior cerebral or cervical carotid artery, or both. Treatment by carotid closure was withdrawn because of hemiparesis.

Case No.	Sex Age	BP	Aneurysm	Surgical treatment on: (days)	Average lysis times (hr)	Duration of tests (days)	Remarks
1	M 51	125/65	Anterior communicating	On s.a.h. +7	2	4	r and R observed through ventricular drainage tube, on s.a.h. +15.
2	F 49	210/110	Posterior communicating	None—hemiplegia	2.3	42	O. Died hemiplegic and akynetic 6 months later. No obvious recurrence.
3	F 55	130/80	Anterior communicating	None—hemiplegia	2.5	5	r on s.a.h. +10, R on s.a.h. +14.
4	F 56	220/130	Anterior communicating	None—too ill	2.6	28	Stupor, hemiparesis. Became ambulatory, then R on s.a.h. +56.
5	M 52	170/110	Anterior communicating and middle cerebral	On s.a.h. +7	3	50	r on s.a.h. +12, again on s.a.h. +41, R on s.a.h. +45. Died akynetic 2 months later.
6	F 50	210/160	Middle cerebral	None—too ill	3.1	9	Almost blind from vitreous haemorrhages. Well s.a.h. +2 years.
7	F 58	160/90	Anterior and posterior communicating	On s.a.h. +10	3.9	13	r on s.a.h. +25, R on s.a.h. +38, dying of akynesia 3 months later.
8	F 45	230/150	Bilateral middle cerebral	On s.a.h. +11	3.9	6	r on s.a.h. +7, with hemiparesis. R on s.a.h. +16.
9	M 49	150/100	Middle cerebral	On s.a.h. +8	4	4	Necropsy—intracerebral clot (? partly fresh) and infarction. ? R., ? H.
10	M 49	170/80	Middle cerebral	On s.a.h. +8	4.6	5	R on s.a.h. +33.

s.a.h. +7 = 7 days after subarachnoid haemorrhage.

R = recurrence responsible for death

O = death from original haemorrhage.

r = minor recurrent haemorrhage, not fatal.

H = hemiplegia due to infarction, responsible for death.

paratively high times, averaging between them 6.6 hr measured over a minimum period of 8 days and over an average of 16 days. No case had significantly accelerated fibrinolysis. In none of these has there been recurrent haemorrhage to date.

Ten other patients, with less favourable or multiple aneurysms, to whom no EACA was administered, had their lysis times examined. They are analysed in Table 1. Seven of them, possibly eight, died of recurrent haemorrhage, and it may be significant that the lysis times in this group are considerably shorter than in the twelve cases mentioned above treated by carotid ligation. Only four of them at any stage had times significantly less than the normal range. Times of 1 hr were

recorded in cases 2, 5 and 7, all of whom survived akynetic for 14 weeks or longer. A time of $\frac{3}{4}$ hr was recorded in case 1, who died 5 hr later.

No fibrinogen deficiency was found in any of these thirty-two patients, a fibrinogen titre of 1/64 being found once in two patients, all other titres being 1/128 or greater. Similarly, prolonged streptokinase activated clot lysis times, evidence of plasminogen deficiency, were not found. In all, we have little evidence of accelerated fibrinolysis in these patients.

Part II

Of thirty-two patients with aneurysms to whom EACA was administered and who had no sur-

TABLE 2
Deaths among the thirty-two patients to whom EACA was administered but who had no surgery

Case No.	Sex Age	Aneurysm	Administration of EACA		Whole blood clot lysis times		Cause and date of death	Remarks
			Commenced on: (days)	Duration of treatment (days)	Range (hr)	Average (hr)		
11	F 47	Bilateral middle cerebral	s.a.h. + 6	16	6-30	19	Akynetic mutism; H on s.a.h. + 14	Had had small intracerebral recurrence, date uncertain, at necropsy.
12	M 29	Bilateral middle cerebral	s.a.h. + 4	21	12-48	26.6	H on s.a.h. + 31	Hemiplegia on admission. Had mild r on s.a.h. + 22.
13	M 43	Anterior communicating	s.a.h. + 1	28	7-48	27	O on s.a.h. + 39	Akynetic mutism.
14	F 68	Anterior communicating	s.a.h. + 6	2	10-48	29	O on s.a.h. + 9	Coma throughout.
15	M 56	Anterior communicating	s.a.h. + 11	20	11-48 +	31 (over 48 four times)	R on s.a.h. + 31	Craniotomy cancelled—collapse on operating table.
16	M 59	Basilar	s.a.h. + 16	28 + 7 on $\frac{1}{2}$ dose	29-48 + 5-12	38 (over 48 seven times)	R on s.a.h. + 57	Alcoholic. Found dead in bed after party. Necropsy.
17	M 57	Posterior communicating	s.a.h. + 3	5	10-48	38.5	R on s.a.h. + 8	Very ill on admission.
18	F 42	Internal carotid	s.a.h. + 8	2	Not examined		H on s.a.h. + 10	Hemiplegic on admission.
19	F 45	Anterior communicating and middle cerebral	s.a.h. + 6	2 oral 1 intravenous	Not examined		R on s.a.h. + 9	
20	F 68	Middle cerebral and basilar	s.a.h. + 3	18	Not examined		R on s.a.h. + 22	Middle cerebral aneurysm treated. Basilar, not recognized on angiography, found responsible at necropsy.
21	M 45	Anterior communicating	s.a.h. + 6	225 g over 8 days, half intravenously	Not examined		R on s.a.h. + 14	Too ill for surgery.
22	F 43	Posterior communicating	s.a.h. + 10	1	Not examined		O on s.a.h. + 12	Coma, refrigeration.
23	M 67	Middle cerebral	s.a.h. + 6	Intravenous 60 g for 5 days then 36 g for 19 days orally	Not examined		O on s.a.h. + 91	Feeble, chest infection, akynesia.

Symbols as in Table 1.

TABLE 3

The eleven patients who had lysis times examined, to whom EACA was administered but who had no surgery, and survived

Case No.	Sex Age	Aneurysm	Administration of EACA		Whole blood clot lysis times		Remarks
			Commenced on: (days)	Duration of treatment (days)	Range (hr)	Average (hr)	
24	M 17	Anterior communicating	s.a.h. + 9	28	25-48+	36.5 (over 48 five times)	Well at s.a.h. + 5 months.
25	F 47	Anterior cerebral	s.a.h. + 2	28	25-48+	35 (over 48 five times)	r on s.a.h. + 7, with hemiplegia which persisted, otherwise well at s.a.h. + 8 months.
26	M 64	Middle cerebral	s.a.h. + 6	28	27-48+	40 (over 48 eleven times)	Original hemiparesis, chest infection. Well at s.a.h. + 1 year.
27	F 61	Bilateral middle cerebral, right posterior communicating	s.a.h. + 21	28	27-48+	42 (over 48 twelve times)	Well at s.a.h. + 1 year except for slight dysphasia following mild r on s.a.h. + 10 months. Mild coronary infarct at s.a.h. + 8 months.
28	F 52	Anterior communicating	s.a.h. + 16	28	26-48+	43 (over 48 fourteen times)	Average times before starting EACA were usually high—averaging 14 hr over 3 days. Well at s.a.h. + 1 year.
29	F 63	Middle cerebral	s.a.h. + 3	28	18-48+	35 (over 48 six times)	Well at s.a.h. + 8 months.
30	M 53	Anterior communicating	s.a.h. + 3	36 g daily for 12 48 g daily for 18	17 17-48	17 37 (over 48 four times)	Pulmonary embolus on s.a.h. + 26. Anticoagulants on s.a.h. + 40. Dose of EACA increased because of low lysis times. Well s.a.h. + 6 months.
31	F 47	Bilateral middle cerebral	s.a.h. + 8	28	26-48	40 (over 48 twelve times)	Conscious on admission. Well at s.a.h. + 15 months. Proved lupus erythematosus, on steroids for 10 years.
32	F 34	Anterior communicating	s.a.h. + 5	28	8-48	25 (over 48 twice)	Dysphasia, paresis of leg, incontinent. Slow recovery. Well s.a.h. + 2 years.
33	M 34	Anterior communicating	s.a.h. + 9	36 g daily for 10 48 g daily for 21	6-28 9-48	19 25 (over 48 twice)	Stuporose, incontinent, epilepsy, gradual recovery. Dose of EACA increased because of low lysis times. Well s.a.h. + 9 months.
34	F 60	Bilateral posterior communicating	s.a.h. + 16	18 g daily for 8 36 g daily for 28	15-24 15-48	18 37	Akynetic. Dose of EACA increased after r on s.a.h. + 24. Well s.a.h. + 10 months.

Symbols as in Table 1.

gery, thirteen died (Table 2). Eleven of the survivors had lysis times examined (Table 3).

Of thirty-two patients to whom EACA was administered and who had 'non-definitive' surgery, ten died (Table 4). Of the twenty-two survivors, twelve had their lysis times examined. Six of these had internal carotid aneurysms and tolerated permanent carotid occlusion; none had recurrent haemorrhage, and their lysis times averaged between 32 and 40 hr with the exception of one ill young man who had average times of only 8 hr on 36 g daily for 5 days, rising to 31 hr on 48 g daily.

The remaining six survivors on EACA who had non-definitive surgery and who had lysis times examined are summarized in Table 5.

With the exception of the one case mentioned above, the lysis times were all prolonged when EACA was being given, usually to more than 24

hr and often to 48 hr; the time rapidly returned to normal if the patient vomited the drug. The streptokinase-activated lysis times were all prolonged, but this was only a reflection of the inactivation of the streptokinase by EACA. Fibrinogen was present in normal quantities in all cases.

Complications

Patients experience some difficulty in tolerating the drug in any form by mouth, in doses of 36 g daily. Much the commonest complication was nausea, which inconvenienced about three-quarters of the patients, and occasionally led to loss of a dose by vomiting. Few patients prefer chewing the granules to a watery solution, and all said that the syrup was sickly. The watery solution was best tolerated taken during a meal. Diarrhoea was slightly less common and may follow or

accompany nausea; but both usually resolved in spite of maintenance of the dosage, especially with the help of a chalk and opium mixture. In one patient, already nauseated, administration had to be stopped after 19 days because of an ulcerative stomatitis, which resolved within 4 days of cessation of treatment. No case of venous or coronary thrombosis, or of pulmonary embolism, could be ascribed to use of the drug.

Conclusions

Part I

The possible inference from Table 1 that recurrent bleeding is more likely if the lysis times approach 2 hr is not sufficient evidence for ascribing value to it as a prognostic test.

Part II

Here also we have been able to arrive at only tentative conclusions, chiefly because of the notorious difficulty in assessing results in subarachnoid haemorrhage. Examples of particular difficulties in the present investigation are cases 16 and 27. EACA may have in fact protected case 16 (Table 2) from recurrence during the

early weeks in which the clot was organizing, for haemorrhage recurred at s.a.h. + 57. Similarly case 27 (Table 3) had a recurrent haemorrhage at s.a.h. + 10 months, in spite of having satisfactory lysis times. At this interval viability of clot is no longer relevant.

Of special interest should be the lysis times of those patients who have several haemorrhages within a few weeks. Cases 1, 3 and 8 all had three haemorrhages within 16 days, but only in the first was the lysis time very short ($\frac{1}{2}$ hr before death).

Though no unequivocal evidence emerges that treatment by EACA alone protects aneurysms from repeated bleeding, recurrence may prove to be less likely if the whole-blood-clot lysis times can be raised consistently to the level of 40 hr (Tables 2-5).

The extended clinical trial provided no conclusive evidence that the administration of EACA in the doses given alters the prognosis in subarachnoid haemorrhage.

In spite of the equivocal findings in this preliminary investigation, we are convinced that the

TABLE 4

Deaths among the thirty-one patients treated by non-definitive surgery, with EACA. In all cases treatment was withdrawn because of hemiparesis, except in case 36, who tolerated permanent carotid occlusion.

Case No.	Sex Age	Aneurysm	Administration of EACA		Whole blood clot lysis times		Surgery on:	Remarks
			Commenced on: (days)	Duration of treatment (days)	Range (hr)	Average (hr)		
35	F 41	Middle cerebral	s.a.h. + 2	28 (+7)	16-48+	34 (over 48 five times)	s.a.h. + 5	R on s.a.h. + 43.
36	M 59	Posterior communicating	after r on s.a.h. + 22	18 (40 g i.v.)	5-14 before EACA	7-46	s.a.h. + 6	Common and internal carotid thrombosed. Enormous R on s.a.h. + 24.
37	M 54	Anterior communicating	s.a.h. + 11	15	7-46	22	s.a.h. + 9	R on s.a.h. + 26.
38	F 62	Internal carotid	s.a.h. + 7	28	13-48	30	s.a.h. + 10	Died of repeated pulmonary embolism on s.a.h. + 60.
39	M 39	Anterior communicating	s.a.h. + 1	7	Not examined		s.a.h. + 3	? R. ? H. on s.a.h. + 8.
40	M 59	Posterior communicating	s.a.h. + 8	2	Not examined		s.a.h. + 7	R on s.a.h. + 11.
41	F 68	Middle cerebral	s.a.h. + 3	23	Not examined			R atherosclerotic haemorrhage on s.a.h. + 32. At necropsy aneurysm had never ruptured.
42	F 29	Anterior communicating	s.a.h. + 3	39 (9 of them intravenously)	Not examined		s.a.h. + 6	r on s.a.h. + 9, on s.a.h. + 20, on s.a.h. + 40, and R on s.a.h. + 46. Akynetic mutism early.
43	F 54	Middle cerebral	s.a.h. + 7	28	Not examined		s.a.h. + 1	R on s.a.h. + 41.
44	F 43	Anterior communicating and middle cerebral	s.a.h. + 21	6	10-48	35 with none over 48	s.a.h. + 7	r on s.a.h. + 5, on s.a.h. + 7, R on s.a.h. + 25.

Symbols as in Table 1.

TABLE 5

Survivors among those treated by non-definitive surgery and EACA who had lysis times examined. Cases of internal carotid aneurysm tolerating permanent carotid closure are excluded.

Case No.	Sex Age	Aneurysm	Administration of EACA		Whole blood clot lysis times		Surgery on:	Remarks
			Commenced on: (days)	Duration of treatment (days)	Range (hr)	Average (hr)		
45	F 78	Posterior communicating	s.a.h. + 6	28	15-48	34 (over 48 six times)	s.a.h. + 6	Hemiparesis 5th day of carotid closure—carotid released, recovery. Well s.a.h. + 9 months.
46	F 46	Anterior communicating	s.a.h. + 12	28	17-48	33.9 (over 48 ten times)	s.a.h. + 1	No filling of opposite anterior cerebral artery. Tolerated permanent carotid closure. Well s.a.h. + 16 months.
47	F 48	Anterior communicating	s.a.h. + 1	28. 50 g intravenously for 3 days after r	For 4 days before r, 5-28 After r, averaged 33 hr with over 48 six times	20	s.a.h. + 2	r on s.a.h. + 6. Well s.a.h. + 16 months.
48	F 64	Middle cerebral	s.a.h. + 2	28	26-48	43 (over 48 eighteen times)	s.a.h. + 4	Well s.a.h. + 10 months.
49	F 41	Anterior communicating and middle cerebral	s.a.h. + 4	28	3-48	27 (over 48 twice)	s.a.h. + 7	Tolerated permanent carotid closure. Well s.a.h. + 15 months.
50	M 58	Anterior communicating	s.a.h. + 7	28	26-48	40 (over 48 seven times)	s.a.h. + 8	Well s.a.h. + 15 months.

Symbols as in Table 1.

future early management of bleeding intracranial aneurysms will involve biochemical control of changes within them, surgery receding more and more into the background.

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