

# The relationship to age and cerebral vascular accidents of fibrin and fibrinolytic activity

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**SYNOPSIS** Three 'normal' groups of people—young, middle-aged, and old—have been investigated with regard to the fibrin content and fibrinolytic activity of the blood. The fourth group consisted of middle-aged people who had previously sustained a cerebral vascular accident matched statistically for age with the middle-aged normals. It was concluded that fibrin increases with age but there is an interaction between age and sex, the female having a higher level in the young group and the male a higher level in the middle-aged group. There was no sex difference in the levels of fibrin in the old age group. Fibrinolytic activity increases with age and there is a positive correlation between fibrin and fibrinolytic activity but no age-sex interaction. Those with cerebral vascular accidents tended to have higher fibrin levels and lower fibrinolytic activity but the differences were not statistically significant. There did, however, appear to be an increase in antifibrinolytic activity in the cerebral vascular group.

There is in blood an enzyme system which is capable of digesting fibrin, and this property of blood is called fibrinolytic activity. Although a vast literature has gathered on the biochemical investigation of the component parts of this system, less attention has been paid to relating fibrinolytic activity to vascular disease.

An increase in antifibrinolytic activity has been found in certain cases of myocardial infarction (Guest, Daly, Ware, and Seegers, 1948) and correspondingly fibrinolytic activity has been found to be depressed (Hume, 1958a; Røjel, 1959). Intermittent claudication (Nestel, 1959) and arteriosclerosis in general have been reported to be associated with depressed fibrinolytic activity (Janiakowa, Kotlarek-Haus, Potoczek, and Tkaczewski, 1958).

As there is a possible relationship between fibrin formation and vascular disease, and since there is an increase in vascular disease with age, it seemed of interest to determine whether fibrinolytic activity varied with age and whether people with cerebral vascular accidents occurring in middle life differed from normal controls in this respect. In the process of this pilot study it was found that there were differences in the fibrin levels and these observations are also reported.

## MATERIALS AND METHODS

**PATIENTS** Group I consisted of 20 (seven men and 13 women) young healthy medical students and nurses whose ages ranged from 19 to 30 years.

Group II (10 men and 10 women) consisted of 10 healthy members of the hospital staff and 10 patients attending the Department of Psychological Medicine with minor psychiatric disturbances but not thought to have any organic or vascular disease. Their ages ranged from 40 to 65 years. Although not intensively studied to exclude occult vascular disease, it was felt that for a pilot study they were reasonably normal in this respect.

Group III consisted of 20 (four men and 16 women) old people whose ages ranged from 75 to 92 years. Their admission to hospital was for the following reasons: eight were social problems, seven had had a small cerebral episode resulting in weakness of one side, one had mild iron deficiency anaemia with urinary infection, one had glycosuria (no treatment required), one had mitral stenosis with cerebral embolus, one had leg pains of a vague nature, and one had diverticulosis. It was felt that although all had some evidence of arteriosclerosis, they differed from the 'normal' population in longevity, namely 67.3 years for males and 72.1 years for females at 1 year of age (Registrar-General for Scotland, 1960), and because of the mere fact of survival were likely to differ from people dying in middle life from vascular disease. No attempt was made to eliminate all the occult diseases to which the aged may well fall heir, *e.g.*, osteoporosis, chronic renal insufficiency, etc.

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TABLE I

Group I: Young Normals					Group II: Middle-aged Normals					Group III: Old Age					Group IV: Middle-aged Cerebral Cases						
No.	Age	Sex	Total Fibrin in 1 (mg.%)	Lysis in 1 Hour	No.	Age	Sex	Total Fibrin in 1 (mg.%)	Lysis in 1 Hour	Lysis in 2 Hours	No.	Age	Sex	Total Fibrin in 1 (mg.%)	Lysis in 1 Hour	No.	Age	Sex	Total Fibrin in 1 (mg.%)	Lysis in 1 Hour	Lysis in 2 Hours
1	30	M	291	52	1	40	M	309	64	206	1	85	F	379	272	1	50	M	206	0	86
2	27	M	202	77	2	48	M	270	0	0	2	80	F	515	193	2	32	M	245	0	168
3	21	M	189	88	3	50	M	218	12	102	3	79	M	180	51	3	62	F	386	129	386
4	25	M	231	64	4	44	F	245	0	0	4	84	F	322	13	4	49	F	386	51	51
5	25	M	167	38	5	48	F	180	0	26	5	87	F	309	309	5	53	F	245	0	81
6	29	M	232	52	6	46	F	193	0	0	6	84	F	206	52	6	59	M	309	129	309
7	24	M	193	26	7	53	F	296	39	103	7	79	F	245	0	7	53	F	257	25	39
8	23	F	180	13	8	53	M	463	0	0	8	78	F	329	0	8	64	M	296	0	77
9	20	F	347	167	9	60	M	373	141	219	9	75	F	322	116	9	44	M	193	0	0
10	19	F	270	13	10	50	F	296	51	78	10	78	F	386	77	10	54	F	270	0	25
11	19	F	212	0	11	54	M	360	231	360	11	76	M	202	0	11	56	M	412	0	245
12	21	F	218	0	12	58	M	386	77	141	12	92	M	399	399	12	55	M	412	0	0
13	25	F	257	0	13	61	F	218	38	154	13	87	F	270	25	13	65	F	566	154	489
14	28	F	360	51	14	47	F	218	51	64	14	82	M	450	38	14	54	M	245	13	52
15	24	F	296	0	15	47	F	180	13	64	15	82	F	386	13	15	63	F	438	78	168
16	24	F	218	51	16	64	F	502	180	257	16	85	F	438	26	16	56	M	579	64	257
17	22	F	296	39	17	55	F	245	0	65	17	85	F	386	0	17	48	M	283	65	154
18	23	F	335	117	18	58	M	605	0	0	18	81	F	438	39	18	49	M	399	167	399
19	23	F	386	129	19	65	M	463	154	283	19	81	F	309	309	19	58	F	218	0	89
20	25	F	193	26	20	58	M	309	64	180	20	79	F	482	77	20	54	F	438	103	193

Group IV consisted of 20 patients (11 men and nine women) whose ages ranged from 32 to 65 years and who had sustained a cerebral catastrophe resulting in hemiparesis or hemiplegia. Cerebral embolism was excluded as far as was possible but it was not possible to be certain whether cerebral thrombosis or haemorrhage had been the cause. Such an accident, however, was taken to indicate cerebral vascular disease. The illness had been established between five months and eight years with the exception of two patients who had developed paralysis three weeks previously. No patient was included whose cerebral vascular accident was of recent onset because it had been noted on two occasions that the fibrin levels were very high a few days after the incident, falling to normal levels in two weeks or so. A similar phenomenon has been reported after acute myocardial infarction (Gilchrist and Tulloch, 1952; Losner, Volk, and Wilensky, 1954) and it appears to be a usual occurrence after a variety of insults including surgical, chemical, and physical injuries as well as infections (Cohen, 1953).

Fibrinolytic activity was measured by the method of partial lysis previously described (Hume, 1958b). Briefly this involves measuring the amount of fibrin digested in a given period of time. Equal amounts of diluted plasma are added to test-tubes in a water-bath at 37°C. and clotted with thrombin. The amount of fibrin present after incubating for half an hour is taken as the initial level, and the difference in the fibrin content of the remaining tubes, estimated at hourly intervals, is a measure of the fibrinolytic activity. The method employed for estimating fibrin is a colorimetric one (Ratnoff and Menzies adapted by Holborn, 1951) and the results expressed as milligrams of fibrin per 100 ml. A low temperature technique was not employed. The blood was collected into graduated centrifuge tubes at room temperature and immediately spun in a M.S.E. super minor centrifuge at 4,500 r.p.m. for five minutes. The

tubes were prepared and set up for incubation within 10 minutes after withdrawal of blood. The estimations were made between 1.30 p.m. and 2.15 p.m. in order to try and standardize the technique with regard to the effect of diet (Greig and Runde, 1957) and diurnal fluctuation (Buckell and Elliott, 1959).

## RESULTS

AGE From a consideration of the ages in terms of groups (Tables I and II) it can be seen that there

TABLE II

Group	MEAN AGE GROUPS STUDIED					
	Male			Female		
	No. of Cases	Mean Age	S.D.	No. of Cases	Mean Age	S.D.
I	7	25.9	2.4	13	22.8	1.8
II	10	54.4	6.73	10	51.5	6.38
III	4	82.3	5.3	16	81.9	2.8
IV	11	51.5	8.4	9	56.8	4.9

is no statistical difference between groups II and IV, that is, the middle aged controls and the middle aged cerebral cases, nor is there any difference between the sexes in any group with regard to age, with the exception of group I where the sex difference is statistically significant ( $P < 0.01$ ).

FIBRIN Analysis of the initial fibrin levels in groups I, II, and III (Tables I and III) shows that there is a positive correlation between age and fibrin levels for both males and females (M.r. = +0.49 F.r. =

TABLE III  
INITIAL MEAN FIBRIN LEVELS

Group	Male			Female			Male and Female		
	No. of Cases	Mean Fibrin Level (mg.%)	S.D.	No. of Cases	Mean Fibrin Level (mg.%)	S.D.	No. of Cases	Mean Fibrin Level (mg.%)	S.D.
I	7	215	37.8	13	274	65.5	20	254	67
II	10	375.6	106	10	257.3	91	20	316	115
III	4	307.8	118	16	357.6	82	20	348	111
IV	11	325.4	110	9	356	110	20	339	111

+0.47). This is illustrated in Fig. 1. However, analysis of variance yielded the fact that there was an interaction between sex and age. This was statistically significant ( $P < 0.01$ ) and is illustrated in Fig. 2. The sex differences analysed separately show that there is probably a significant difference between the means in group I ( $P < 0.05$ ) and similarly in group II ( $P < 0.05$ ). However, the results in group I are statistically suspect in the sex difference because there was a significant difference ( $P < 0.01$ ), as previously noted, between the ages of the males and females in this group. In actual fact, however, the age effect is so slight that the age difference could not explain the sex difference in this group. No significant difference was noted in group III. Although the mean fibrin level is much higher in the middle-aged females in group IV compared with that of the middle-aged females in group II (Table III), the difference between the means is not significant ( $P = 0.1$ ). Similarly there is no statistically significant difference between the means of the males in the same two groups.

LYSIS When lysis during the first hour is considered for groups I, II, and III (Tables I and IV) it can be seen that there is a positive correlation between age and lysis for both sexes (M.r. = +0.35 F.r. = +0.30) illustrated in Fig. 3. Analysis of variance revealed no sex and age interaction (Fig. 4). However, a variance ratio test shows that the difference in the variance between groups I and III is of high statistical significance ( $P < 0.001$ ), and between groups I and II and I and IV to be statistically significant ( $P < 0.01$ ). Analysis of the means revealed no statistically significant difference between the sexes in any group (Table IV), although the males had a higher mean reading and wider variation in group II. Although the mean lysis level is much lower in the middle-aged males in group IV as compared with the lysis level in the middle-aged males of group II, the differences were not statistically significant, nor was there any difference between the females of the same groups.

When lysis during the second hour was compared between groups II and IV (Table IV) again no statistically significant difference in variance or

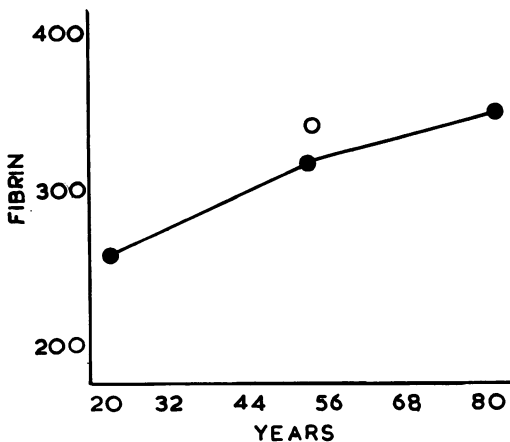


FIG. 1. The mean fibrin levels (mg.%) for each group reflect an increase with years (● = mean fibrin level for cerebral cases).

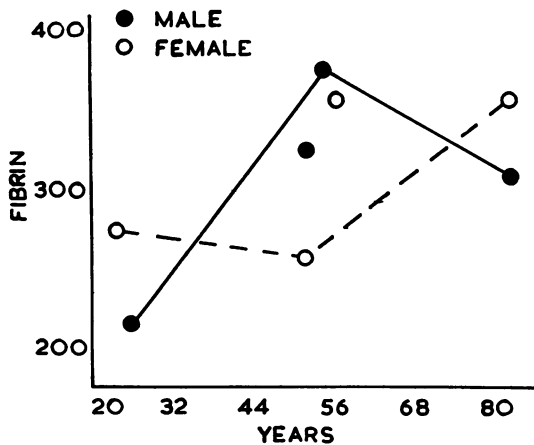


FIG. 2. The mean fibrin levels (mg.%) for each sex shows an interaction between sex and age (● = male cerebral cases and ○ = female cerebral cases).

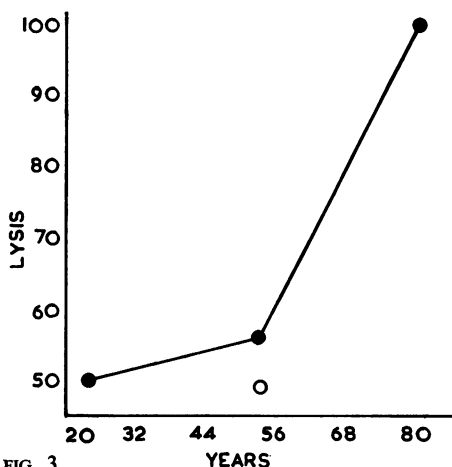


FIG. 3

FIG. 3. Mean lysis (mg. fibrin digested %) for each group reflects an increase with years (●=mean lysis level for the cerebral cases).

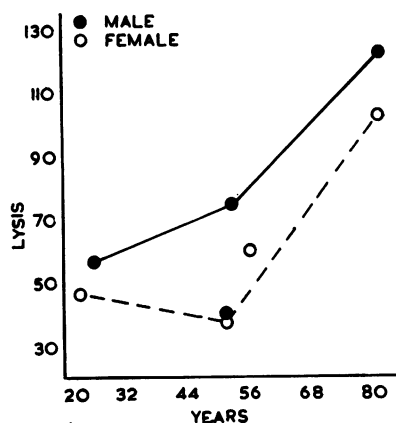


FIG. 4

FIG. 4. The mean lysis level (mg. of fibrin digested %) for each sex shows no sex-age interaction (●=male cerebral cases, ○=female cerebral cases).

means was detected. However, when the lysis was expressed as a percentage lysis in the second hour compared with the first hour, analysis of variance revealed that the difference between the two groups was probably significant ( $P < 0.05$ ) (Table IV), suggesting the presence of a retarding factor in group IV. The females in both groups showed a lower mean percentage but this was not statistically significant.

Consideration of fibrin levels and lysis together revealed a positive correlation between these two factors for both sexes (M.r. = +0.20 F.r. = +0.44).

## DISCUSSION

Analysis of the initial fibrin levels in the first three groups reveals the fact that the fibrin content of blood increases with age. However, when the sexes are analysed separately it can be seen that there is an interaction between age and sex, the female having the higher level in the young age group and the male in the middle-aged group. In the old age group there is no sex difference. This suggests that the ageing process is associated with an increase in fibrin content of the blood and that it occurs at an

TABLE IV

MEAN LYSIS LEVELS FOR TWO PERIODS OF STUDY AND PERCENTAGE LYSIS COMPARED FOR EACH PERIOD

Group	Male			Female			Male and Female		
	No. of Cases	Lysis in First Hour (mg. %)	S.D.	No. of Cases	Lysis in First Hour (mg. %)	S.D.	No. of Cases	Lysis in First Hour (mg. %)	S.D.
I	7	56.7	20	13	46.6	54	20	50	45
II	10	74.3	75	10	37.2	52	20	56	67
III	4	122	161	16	95.1	109	20	100	121
IV	11	39.8	56.9	9	60	55.8	20	49	57
Group	No. of Cases	Lysis in Second Hour (mg. %)	S.D.	No. of Cases	Lysis in Second Hour (mg. %)	S.D.	No. of Cases	Lysis in Second Hour (mg. %)	S.D.
II	10	149.1	119	10	81.1	73.4	20	115	104
IV	11	158.8	125	9	169	155	20	163	139
Group	No. of Cases	Change in % Lysis	S.D.	No. of Cases	Change in % Lysis	S.D.	No. of Cases	Change in % Lysis	S.D.
II	10	14.3	17.3	10	9.1	18.7	20	11.7	18.1
IV	11	33.4	23.9	9	18.2	26.7	20	26.6	26.4

earlier age in the male. An increase in fibrin with age has previously been described (Schultz, 1956). It is of interest to speculate on whether the high fibrin levels in middle-aged males contribute to vascular disease in this group, especially in view of the fibrin theory of the genesis of atheroma (Duguid, 1954) and as the number of deaths from myocardial infarction between the ages of 45 and 49 years is five times greater in males (Registrar-General for Scotland, 1960). When the middle-aged cerebral cases are considered, it can be seen that there is a tendency for them to have higher fibrin levels and this is especially so of the females, but the differences are not statistically significant. However, the changes are such as to merit a more intensive study of this group.

Consideration of the fibrinolytic activity shows that once more there is an increase with age and also a positive correlation with fibrin levels. There is, however, within the limits of this pilot study, no interaction between sex and age and the differences are not statistically significant in any group between the sexes with regard to fibrinolytic activity. In view of the higher fibrin levels in the males compared with the females in middle life, it could be argued that the female has relatively more fibrinolytic activity with respect to fibrin than the male and possibly less susceptibility to thrombosis as a consequence of a greater clot-dissolving potentiality. It is interesting to note too that the lytic activity of the cerebral group as a whole is less than the controls and this applies especially to the males. The differences are not statistically significant but worthy of further investigation.

Finally, although the middle-aged cerebral group have only a relatively higher fibrin level and relatively lower fibrinolytic activity than their controls, when

lysis during the second hour is expressed as a percentage of that of the first hour, it becomes apparent that the activity of the cerebral group has increased disproportionately. This could be explained by the presence of enhanced fibrinolytic inhibitor in those patients who have had cerebral vascular accidents. Antifibrinolytic activity has been described in cases of myocardial infarction (Guest *et al.*, 1948).

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