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Influence of Acute Changes in Blood Pressure on the Distribution of Fibrinogen.*

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Observations on fibrinogen completed in the course of studies on histamine shock previously reported[1] are included in the communication that follows. The acute fall and rise in the fibrinogen level of plasma, as will be seen, does not parallel those of other plasma proteins[2] but conforms to the acute pressure changes. The evidence indicates that the fibrinogen content of the circulating blood is coordinated with the sudden change in size of the smaller vessels.

Material and methods. Dogs anesthetized with 25-30 mg of nembutal per kg of body weight, rarely with morphine—amytal, received intravenously 2-6 mg of histamine dihydrochloride. The blood pressure was recorded from the femoral artery with a mercury manometer. Hematocrit readings were made on 10 ml samples of blood rendered incoagulable by addition of 20 mg of solid sodium oxalate and centrifuged for 25 minutes at 2000 r.p.m. Total plasma proteins were estimated by the Kjeldahl method. Fibrinogen values were determined in duplicate as fibrin by the Cullen-Van Slyke method[3] and as fibrinogen by the protamine precipitation method.[4] Both methods were carried out in standardized dilutions of 1 ml of plasma in 25 ml of saline. Albumins and globulins were calculated by deducting the protamine precipitable fibrinogen values from the total plasma protein values.

Changes in the level of fibrinogen in the femoral vein. The averaged results of 28 experiments are compiled in Table I. Concomitant with, but lagging somewhat behind the falling blood pressure a marked absolute as well as a relative decrease of fibrinogen occurs. The maximal loss per unit of plasma is reached in about 3-5 minutes after the administration of the drug and amounts to an average of 49.2% for fibrin and 30.1% for protamine precipitable fibrinogen. With slight delay as compared to the climbing arterial pressure the fibrinogen tends to return toward the preinjection level. But like the pressure it usually does not quite reach this height. During the same interval the plasma albumins and globulins show only minor change. In column 6 of Table I the fibrin values are expressed in relation to the albumin and globulin values. This index shows a 48.1% decline at the peak of the fibrinogen loss. When the plasma fibrinogen level has reached a postinjection maximum at around 30 minutes, there is a secondary progressive decline that is paralleled by a similar fall in albumins and globulins. Reinjection of histamine, on the other hand, is followed by the same marked loss in fibrinogen as compared to other plasma proteins.

Columns 3 and 4 of Table I show the fibrinogen values as estimated by the two methods to follow the same trend. Quantitatively the protamine precipitation method yields higher absolute values than the fibrin method. The difference reaches a maximum with the peak of the fibrinogen loss, to be reduced again toward the end of the experiment. The loss in fibrinogen is consequently more pronounced by the fibrin method.

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TABLE I.
Changes in Plasma Protein Constituents of Dog After Intravascular Administration of Histamine. The figures are computed from 28 identically arranged experiments.

Time, min	Mean arterial blood pressure, mm Hg	Fibrinogen as fibrin, %	Fibrinogen as protamine precipitate, %	Albumins and globulins, %	Fibrinogen as fibrin × 100 / Albumins and globulins, %
0	136	0.459	0.485	4.96	9.25
	Intravascular administration of 2-6 mg of histamine dihydrochloride.				
1½-2	40	0.303	0.377	4.90	6.18
4-5	45	0.233	0.339	4.84	4.81
10	87	0.307	0.362	4.83	6.85
30	102	0.378	0.401	5.00	7.56
60	103	0.338	0.365	4.70	7.19

TABLE II.
Effect of Epinephrine on the Blood Composition of the Dog.

Time, min	Mean arterial blood pressure, mm Hg	Fibrinogen as fibrin, %	Fibrinogen as protamine precipitate, %	Albumins and globulins, %	Hematocrit, %
0	105	0.158	0.172	4.58	51.5
	Intravascular administration of 0.5 ml of 1:10,000 epinephrine solution.				
3	165	0.278	0.245	3.87	42.7
6	105	0.236	0.222	4.45	51.5

Changes in fibrinogen content of blood from different vessels and under different experimental conditions.

Fibrinogen, albumin-globulin and hematocrit estimations were made from samples of blood obtained simultaneously from femoral vein and aorta, carotid and femoral arteries, inferior vena cava, jugular and portal veins. The fibrinogen changes are similar in the blood from all these vessels.‡

The characteristic fall and rise of fibrinogen after histamine injection is uninfluenced by anesthesia and splenectomy.

After cord transsection usually there is a trend towards hemodilution. This trend is temporarily interrupted by histamine. Concomitant with the ensuing hemoconcentration an increase in plasma albumins and globulins actually may occur. In spite of this the fibrinogen decreases with the pressure fall.

The effect of other vasodepressors and a vasopressor on the fibrinogen level. The changes described above for fibrinogen are not specific for histamine. Similar changes follow when vasodepression occurs from other cause, like intravascular injection of peptone,[5, 6] thromboplastic substance,[1] acetylcholine,[7] acute hemorrhage.[6]

With vasopressor substance, like epinephrine, the resultant rise in pressure is accompanied by elevation of plasma fibrinogen[7, 8] that disappears with the return of the pressure to normal. As is seen in Table II the peak of the rise in arterial pressure is reached in about 3 minutes after the injection of 0.5 ml of a 1:10,000 solution of epinephrine. This is associated with marked rise in fibrinogen, amounting to 76% and 42.4%, respectively. A 23% hemodilution, on the other hand, is followed by a 15.5% decline of the plasma albumin and globulin level. The fibrinogen trend as estimated by the two methods is similar but the difference between corresponding values is not constant. The increase in fibrinogen is more pronounced by the fibrin method. The fibrin value in the preinjection sample is 8.7% lower, in the 3 minutes sample 13.5% higher than the protamine precipitable fibrinogen value. At the termination of the experiment it is still higher

‡ Consecutive preinjection samples from different vessels show variations in fibrinogen content of blood.

6 Unpublished observations.

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8 Cannon, W. B., *The Wisdom of the Body*, W. W. Norton, New York, 1932.

but the difference has diminished. On the return of fibrinogen to preinjection level the usual relationship is restored.

Summary. The fibrinogen level of plasma and blood of large veins and arteries declines sharply and then gradually returns toward the preinjection level immediately after intravascular injection of histamine. The quantitative changes in fibrinogen are independent of those in other plasma proteins. They parallel the acute drop and gradual return in blood pressure referable to peripheral capillary alterations. This movement of fibrinogen is independent of anesthesia, splenectomy and cord transsection. It is not specific for histamine but occurs with other vasodepressors as well. With vasopressor agents a reversed movement of fibrinogen follows. The sudden changes in size of the capillary bed seem to be coordinated with the fibrinogen content of the circulating blood.

The two methods used for the estimation of fibrinogen yielded qualitatively similar but quantitatively differential values.

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Prophylactic and Curative Effects of Certain Sulfonamide Compounds on Exoerythrocytic Stages in *Plasmodium Gallinaceum* Malaria.

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The discovery by Raffaele[1] of a hitherto unrecognized form in *Plasmodium relictum* malarial infections has aroused considerable interest. They are non-pigmented and develop outside the red cell. They have been seen in *Plasmodium gallinaceum* infections by James and Tate[2] who called them exoerythrocytic schizonts. More recently these forms have been recognized in several other avian malarial infections, but with doubtful exceptions they have not been encountered in monkey or human malaria. A complete summary of recent literature has been compiled by Porter and Huff.[3]

The chief interest in these forms from the standpoint of chemo-therapy has been their refractoriness to quinine or atebrin. It is possible to obtain a marked therapeutic effect on the circulating *Plasmodium gallinaceum* parasites in young chicks by administering quinine or atebrin, yet death usually ensues, and at autopsy overwhelming numbers of exoerythrocytic forms can be found. For this reason it has been postulated by some that they are responsible for initiating relapses since they are not destroyed by the accepted antimalarial drugs. According to Kikuth and Mudrow[4] plasmochin possesses slight activity on the exoerythrocytic stages but no other drug has been shown to affect them.

Since these stages are found rarely in the circulating blood it has been difficult to study their development and to determine their response to chemo-therapy. This handicap has been overcome by perfecting a simple biopsy technic which permits multiple examination of brain tissue in individual animals and thus enables one to follow the course of development in treated and control chicks. The purpose of this preliminary report is to describe the methods used and to show that

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2 James, S. P., and Tate, P., *Nature*, 1937, **139**, 545.

3 Porter, R. J., and Huff, C. G., *Am. J. Trop. Med.*, 1940, **20**, 869.

4 Kikuth, W., and Mudrow, L., *Z. f. Immun.*, 1939, **95**, 285.