CONNECTION BETWEEN THE INCREASED FIBRINOGEN CONCENTRATION IN DOGS WITH RADIATION SICKNESS AND THE FIBRINOGENASE ACTIVITY

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Various workers have shown that when the animal organism is exposed to ionizing radiation an increase takes place in the plasma fibrinogen concentration [4, 8]. A considerable increase in the fibrinogen concentration in man has been observed during roentgen therapy [6]. An increase in the plasma fibrinogen concentration was observed in dogs with a severe form of radiation sickness in our researches as a constant and regular finding (Table 1).

TABLE 1. Plasma Fibrinogen Concentration in Dogs with Radiation Sickness (in g%)

Animals	No. of dogs	Statistical indices				
		N	V	M	±σ	±m
Healthy (before irradiation)	25	79	0.14-0.51	0.23	0.071	0.0009
With a severe form of radiation sickness (20th day)	13	19	0.29-1.47	0.74	0.083	0.005
With moderately severe radiation sickness (10th-20th day)	9	18	0.17-0.94	0.38	0.061	0.0004
The same, on the 40th-50th day	9	16	0.15-0.72	0.30	0.004	0.0003

The fibrinogen concentration rose sooner in the experimental dogs in which the manifestations of the hemorrhagic syndrome were particularly well marked. From the coincidence between the times of increase of the fibrinogen concentration and of development of hemorrhages, it may be assumed that the increase in the plasma fibrinogen in radiation sickness is an active reaction of the body to the development of this syndrome. At the same time, it may be assumed that the increased fibrinogen concentration is the result of a decreased activity of the enzyme causing deaggregation of fibrinogen, namely fibrinogenase.

According to Vol'fson [1, 2], fibrinogenase is one of a comparatively small number of enzymes catalyzing the reorganization of protein molecules without splitting them radically, and acts on both fibrinogen and fibrin on the same functional groups. Under the influence of fibrinogenase, fibrinogen is converted into another proetin which does not clot with fibrin. Some writers therefore ascribe to fibrinogenase the role of a regulator of the fibrinogen concentration in the blood. It has been considered for a long time that active fibrinogenase is not present in the healthy organism, and that it appears only in pathological states (shock, sudden death). V. S. Il'in [5], however, accepts that fibrinogenase is also present in the body during life, but the action of this enzyme is inhibited by certain regulating mechanisms or is masked by processes operating in the opposite direction, for example, by the constant production of fibrinogen. The regulating role of fibrinogenase in the intact organism has been demonstrated by Z. A. Chaplygin [7], who produced hemophilia experimentally by injecting preparations of active globulins (i.e., of active fibrinogenase) into the blood stream.

We have studied the changes in fibrinogenase in acute radiation sickness accompanied by a hemorrhagic diathesis.

TABLE 2. Changes in the Rate of Fibrinolysis under the Influence of Fibrinogenase from the Blood Plasma of Dogs before and after Irradiation (substrate: fibrin obtained by coagulation of an isolated preparation of fibrinogen)

Experimental dog	Degree of radiation sickness	Time (in days)																
		before irradiation								after irradiation								
		30	25	20	15	10	5	2	2	5	10	15	20	25	30	35	40	45
		rate of fibrinolysis (in minutes)																
Anchar	Severe	25	20	22	33	–	–	–	–	50	70	–	–	–	–	–	–	–
Tol	"	22	–	15	28	26	24	–	–	–	–	41	55	–	–	–	–	–
Bor	"	–	145	125	131	105	–	110	–	110	66	–	–	–	–	–	–	–
Lyutik	"	85	85	80	100	108	–	–	80	185	140	70	73	100	95	111	–	118
Bosyi	Moderately severe	–	–	102	–	105	95	–	160	80	95	110	112	163	100	172	206	–

TABLE 3. Comparison of Fibrinogenase Activity with Fibrinogen Concentration

Experimental dog	Indices	Time after irradiation (days)								
		5	10	15	20	25	30	35	40	45
Lyutik	Plasma fibrinogen (in g%)	0.18	0.33	0.26	0.32	0.48	0.3	0.23	–	0.36
	Fibrinogenase activity (min)	185	140	70	73	100	95	111	–	118
Bor	Plasma fibrinogen (in g%)	0.66	0.87	–	–	–	–	–	–	–
	Fibrinogenase activity (min)	100	66	–	–	–	–	–	–	–
Bosyi	Plasma fibrinogen (in g%)	0.37	0.37	0.15	0.17	0.22	0.37	0.21	0.21	0.23
	Fibrinogenase activity (min	80	95	110	112	163	100	172	202	–

EXPERIMENTAL METHOD

Experiments were carried out on dogs. The fibrinogenase activity was determined by a method based on estimating the excess of fibrinogen or fibrin, i.e., on the study of the velocity of the process of fibrinogenolysis and fibrinolysis [3]. Fibrinogenase inhibitors were extracted from the blood plasma (by treatment with chloroform), and after evaporation of the chloroform the plasma was put in contact with the substrate (fibrinogen) and also with fibrin, and the rate of fibrinogenolysis and fibrinolysis was determined. The velocity of the former was measured by the time taken for the whole of the fibrinogen to lose its ability to coagulate under the influence of active thrombin; the velocity of fibrinolysis was determined by the time taken for complete liquefaction of a fibrin clot. The source of fibrinogenase in our experiments was the citrated blood plasma of the experimental dogs. The plasma was treated with chloroform in a graduated flask at room temperature for 24 h. The substrate for the active fibrinogenase were fibrinogen and fibrin from human, ox, and dog plasma, and also fibrin obtained by coagulation of citrated plasma from a healthy donor dog. In the last case, the fibrin clot was freed from inhibitors by repeated (up to 20 times) washing with physiological saline.

EXPERIMENTAL RESULTS

Four of the irradiated dogs developed a severe degree of radiation sickness and one a moderately severe degree. After irradiation, none of the animals showed any change in the rate of fibrinogenolysis. When treated with fibrinogenase from both healthy and irradiated dogs, the fibrinogen lost its clotting power equally after 20 sec.

It will be clear from Table 2 that the fibrinolysis time increased after irradiation, indicating a lowering of the fibrinogenase activity. The slowing of fibrinolysis in severe radiation sickness could be detected in the initial period of the disease. At the height of the severe radiation sickness, a further inhibition of fibrinolysis took place. Similar changes were observed when the substrate for the fibrinogenase was fibrin obtained by coagulation of the plasma of a healthy donor dog. Acceleration of fibrinolysis was found in only one animal at the height of severe radiation sickness. It is clear from the results shown in Table 3 that no correlation was found between the changes in the fibrinogen concentration in the blood plasma of the irradiated dogs and the changes in the fibrinogenase activity. The increase in the fibrinogen concentration in irradiated dogs cannot therefore be regarded as the result of the lowering of the fibrinogenase activity.

SUMMARY

A study was made of the concentration of blood plasma fibrinogen in relation to the changes of fibrinogenase activity. Dogs with radiation sickness (severe, moderately severe, and mild) served as experimental animals. A rise of the blood plasma fibrinogen content was observed in dogs with severe and moderately severe radiation sickness. This phenomenon is especially pronounced at the height of radiation sickness. The activity of fibrinogenase in severe radiation sickness was considerably decreased at the initial period and at the height of the disease. The rise of fibrinogen content in severe and moderately severe radiation sickness should be regarded as an adaptive reaction directed to control hemorrhages, not as the sequence of reduced fibrinogenase activity.

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