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Increased Plasma Prothrombin Activity after Epinephrine Injections; Relation to Hyperglycemia.

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Hypercoagulability of the blood often accompanies the hyperglycemia produced in dogs by epinephrine.[1] Similar changes observed in cats after acute hemorrhage, rage and pain were attributed by Cannon and coworkers[2, 3, 4] to the action of epinephrine on the liver. The evidence here presented in preliminary form, indicates that the hypercoagulability brought about by epinephrine is the result, in part at least, of an increase in the prothrombin activity of the plasma.

Prothrombin activity was measured by the method of Quick[5] with minor modifications[6] and the following precautions: (a) All thromboplastin solutions used were potent enough to produce coagulation of undiluted recalcified dog plasma in 8-10 seconds, and of human plasma in 15 to 18 seconds. (b) Dilutions (1-2, 1-4) of each plasma were made and their times compared with that of undiluted or similarly diluted control plasma. (c) Heparin (4 Toronto units) was added to 1 cc of each of the plasmas and the respective prothrombin times compared. (d) Determinations were carried out simultaneously with solutions of thromboplastin of slightly different potency. The percent cell volume of the blood was measured in each specimen. Variations were generally slight. In most instances the coagulation time of venous blood was also measured.

1. Epinephrine and the prothrombin activity of dog plasma (12 experiments on 4 dogs).

Dog S-10. Weight 15.7 kg, fasting; 0.055 mg of epinephrine intravenously over a 2 min. interval. (See Table I.)

2. Epinephrine and the prothrombin activity of normal human plasma (7 experiments on 6 normal men): (See Table II.)

Intramuscular injections of the drug (0.01 mg-0.005 mg per kilo

1 Vosburgh, C. H., and Richards, A. N., *Am. J. Physiol.*, 1903, **9**, 35.
2 Cannon, W. B., and Gray, H., *Am. J. Physiol.*, 1914, **34**, 232.
3 Cannon, W. B., and Mendenhall, W. L., *Am. J. Physiol.*, 1914, **34**, 251.
4 Gray, H., and Lunt, L. K., *Am. J. Physiol.*, 1914, **34**, 332.
5 Quick, A. J., *Am. J. Physiol.*, 1937, **118**, 260.
6 Hause, W. A., and Tocantins, L. M., *Am. J. Clin. Path.*, 1941, **11**, 54.

TABLE I.

April 16, 1941	Before	Time after epinephrine 9′	19′	79′	150′	281′
Blood coagulation time (min)*	10½	8	5	5	3	4½
Plasma Proth. (sec)	9.2	8.6	8.2	7.9	8.6	8.7
Plasma + 4 units of heparin (sec)	16.6	15.3	14.9	lost	15.5	15.5

*1 cc of venous blood at 38°C in paraffined tubes, 17 mm diameter.

TABLE II.

			Epinephrine 0.0025 mg/kg body wt intraven. (2′ for injection)				
	Apr. 14, 1941	Control	Before	27′	60′		
T.	Bl. Coag. time (min)*	29	22	10	15		
	Plasma Proth. time (sec)	16.5	16.5	15.2	16.5		
		Control	Before	22′	80′	135′	195′
J.N.	Bl. Coag. time (min)	27	32	20	21	19	6½
	Plasma Proth. time (sec)	15	15.3	14	14.5	14.4	14

*1 cc of venous blood at 38°C in paraffined tubes, 17 mm diameter.

body weight) followed by observations at 30, 60 and 120 minutes gave only slight and inconstant results in 3 normal men. Judging from the doses employed by Cannon and Gray[2] in cats our intramuscular doses were probably too small.

3. Epinephrine and the prothrombin activity of abnormal human plasma:

(a) In patients with various types of hepatic disease (11 experiments in 10 patients). In 6 instances there was an increase in prothrombin activity within 1 hour after injection (0.0025 mg epinephrine per kilo body weight, intravenously over a 2-minute period), in 4 there was no change and in 1 there was a slight decrease.

April 7, 1941. B.C., fem., 29. Widespread metastatic carcinoma of the liver. For 2 days before experiment patient received 2 mg of 2-methyl-1,4-naphthoquinone by mouth.

TABLE III.

	Before Epinephrine	Min after injection 20	60	150	300	Control
Prothrombin time (sec)	20.6	18.9	19.9	20.2	19	17.5
% prothrombin	55	80	67	65	78	100

(b) In patients with hemophilia (5 experiments, 4 patients). In 3 instances a significant increase in prothrombin activity was observed, in 2 the change was insignificant. There were no significant changes in the coagulability of whole blood.

S.M., male, age 23. Epinephrine (0.0025 mg per kg body weight) injected intravenously over a 2-minute period.

TABLE IV.

		Min after injection				
	Before	5	60	184	274	Control
Prothrombin time (sec.)	17.8	15.3	16.8	16	17.9	18
% prothrombin	110	400	155	250	110	100
Blood coagul. time (min)	84	75	74	74	54	

Comment. Current work on variations in prothrombin has dealt mostly with diminutions in this substance. Quantitative fluctuations in prothrombin must, however, be found obviously in either direction from normal values, as with other components of the plasma. Observations to be reported elsewhere point to the occurrence of pronounced increases in prothrombin activity of the plasma after a meal especially rich in protein, after emotional excitement and during parturition. In all of these states variable degrees of hyperglycemia may be found. Attention has been drawn[7] to an as yet unexplained relationship between sugar metabolism and coagulation of the blood. Removal of liver tissue is followed by a rapid decrease in blood prothrombin[8] and, likewise, by a profound hypoglycemia.[9] The common nature of the forces that lead to hyperglycemia and increased coagulability of the blood has led Stuber and Lang[7] to attribute to glucose an important rôle in blood coagulation. Perhaps a more likely interpretation is that both glycogenolysis and prothrombin production or liberation into the blood are functions of the liver affected in a common manner by identical forces.

Summary. Epinephrine, by slow intravenous injection, increases the prothrombin activity of human and dog plasma. An identity of type seems to exist between the forces capable of exciting hyperglycemia and increases in plasma prothrombin activity.

[7] Stuber, B., and Lang, K., *Physiologie und Pathol. der Blutgerinnung*, Berlin und Vienna, 1930.

[8] Warner, E. D., *J. Exp. Med.*, 1938, **68**, 831.

[9] Mann, F. C., and Magath, T. B., *Arch. Int. Med.*, 1922, **30**, 73.