Influence of Cold, Fasting and Adrenalectomy on the Blood-Fibrinogen Response to Trauma. (17761)

OLGA B. HENRIQUES,* S. B. HENRIQUES,* AND H. SELYE.

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montréal, Canada.

A reduction of the plasma fibrinogen in fasting rats exposed to cold has been previously reported(1). On the other hand a rise in plasma fibrinogen is observed after surgical trauma(2) and a wide variety of physical and chemical injuries(3,4). Hence it appeared important to determine whether cold and fasting would reverse the blood-fibrinogen rise normally induced by trauma.

As during exposure to cold important changes occur in the adrenals(5), we also studied the influence of adrenalectomy upon the fibrinogen response to injury.

Exp. I. Influence of fasting on the fibrinogen response to trauma. 74 female, piebald rats, weighing from 130 to 180 g were distributed into 8 groups. Group I served as absolute controls. Groups II, III and IV were fasted for periods of 24, 48 and 72 hours respectively, before killing. Groups V and VI were submitted to *complete* nephrectomy, the former being normally fed (Purina Fox Chow) and the latter fasted for a period of 48 hours. The operation was performed after 24 hours of fasting. Groups VII and VIII were *partially* nephrectomized, the latter being fasted for a total of 72 hours (48 hours before and 24 hours after the operation).

All operated animals were bled and killed 24 hours after the surgical trauma and the remainder at the end of the periods indicated above.

Plasma fibrinogen determinations in this and in the subsequent experiments were made by a modification of the method of Campbell and Hanna(1).

As can be seen from Table I, periods of 24, 48 and 72 hours fasting depress constantly, though not always significantly, the blood-fibrinogen concentration of intact animals.

It is also shown that the plasma fibrinogen response to the trauma of nephrectomy is unaffected by fasting periods of 48 and 72 hours.

Exp. II. Influence of cold on the fibrinogen response to trauma. 47 female piebald rats, weighing from 130 to 170 g were divided into 5 groups. Group I served as absolute controls. Group II was unilaterally nephrecto-

TABLE I.
Influence of Fasting on Fibrinogen Response to Trauma.

Groups	Treatment	No. of animals	Body wt Initial	Body wt Final	Fibrinogen mg/100 ml
I	Normal control	8	145 ± 10*	-	252 ± 13†
II	24 hr fasting	9	140 ± 10	130 ± 13*	231 ± 12
III	48 " "	8	144 ± 11	124 ± 11	203 ± 12
IV	72 " "	11	166 ± 9	136 ± 7	229 ± 9
V	24 " after complete nephrectomy	9	141 ± 7	149 ± 12	540 ± 26
VI	Complete nephrectomy 48 hr fasting	6	147 ± 12	133 ± 12	516 ± 21
VII	24 hr after partial nephrectomy	9	141 ± 7	149 ± 12	449 ± 11
VIII	Partial nephrectomy 72 hr fasting	12	166 ± 9	135 ± 8	484 ± 23

* Standard deviation.
† Standard error.

* Instituto Butantan, Sao Paulo, Brazil.

1. Henriques, S. B., Henriques, O. B., and Selye, H., PROC. SOC. EXP. BIOL. AND MED., 1949, v71, 82.

2. Chanutin, A., Hortenstine, J. C., Cole, W. S., and Ludewig, S., *J. Biol. Chem.*, 1938, v123, 247.

3. Ham, T., and Curtis, F. C., *Medicine*, 1938, v17, 413.

4. Chanutin, A., and Ludewig, S., *J. Biol. Chem.*, 1947, v167, 313.

5. Selye, H., *J. Clin. Endocrinol.*, 1946, v6, 118.

TABLE II.
Influence of Cold on Fibrinogen Response to Trauma.

Groups	Treatment	No. of animals	Body wt Initial	Body wt Final	Fibrinogen mg/100 ml
I	Normal control	10	-	149 ± 3*	243 ± 8.9†
II	24 hr cold after unilateral nephrectomy	12	153 ± 7*	146 ± 6	470 ± 12
III	24 hr cold + fast after unilateral nephrectomy	8	155 ± 7	127 ± 4	373 ± 13
IV	24 hr cold	9	146 ± 10	155 ± 14	244 ± 10
V	24 hr fast cold	8	147 ± 12	129 ± 13	190 ± 14

* Standard deviation.
† Standard error.

TABLE III.
Influence of Adrenalectomy on Fibrinogen Response to Trauma.

Groups	Treatment	No. of animals	Body wt Initial	Body wt Final	Fibrinogen mg/100 ml
I	Intact control	7	168 ± 9*	180 ± 12*	243 ± 9†
II	Adr-X + 25 days rest then unilateral nephrectomy	10	168 ± 17	176 ± 23	420 ± 22
III	Adr-X + 25 days rest	9	166 ± 11	176 ± 22	346 ± 24
IV	Adr-Xp + 25 " "	5	170 ± 10	184 ± 14	243 ± 27
V	Adr-Xp + 25 " " then unilateral nephrectomy	6	165 ± 12	176 ± 11	534 ± 26

* Standard deviation.
† Standard error.
Adr-X Complete adrenalectomy.
Adr-Xp Unilateral adrenalectomy.

mized and following operation was exposed to cold for 24 hours (1 to 5°C). Group III was similar to II but in addition was fasted during the exposure interval. Groups IV and V served as controls for cold and cold combined with fasting respectively.

Table II summarizes the results. It is to be seen that although fibrinogen is not altered by exposure to cold alone, it is markedly decreased under the combined influence of fasting and cold. On the other hand it can be seen from Experiment II that the blood-fibrinogen is only slightly diminished by fasting alone.

As regards the operated animals, it is seen that addition of fasting to exposure to cold reduces significantly the fibrinogen response to trauma.

Exp. III. Influence of adrenalectomy on the fibrinogen response to trauma. 37 piebald female rats, weighing from 140 to 200 g were distributed into 5 groups. Group I served as intact control. Groups II and III were totally adrenalectomized. Groups IV and V were unilaterally adrenalectomized. In order to control for the trauma of total adrenalectomy, a laparotomy was performed on the opposite side, although the remaining adrenal was left intact.

All animals were kept on Purina Fox Chow and an aqueous solution containing 0.97% of sodium chloride and 0.03% of sodium bicarbonate in place of drinking water, for the duration of the experiment. The adrenalectomized rats were in good condition and even gained some weight, during the experimental period. Twenty-five days after the beginning of the experiment, Groups II and V were unilaterally nephrectomized. The following day all the animals in all groups were bled and killed. Autopsy failed to reveal either detectable infection in any group or adrenal remnants in the adrenalectomized groups.

The results are summarized in Table III. It is to be noted that total adrenalectomy greatly decreases, but does not abolish, the

fibrinogen response to trauma.

It is shown that totally adrenalectomized animals, 25 days after the operation still have a blood-fibrinogen concentration higher than intact controls, while rats unilaterally adrenalectomized at the end of the same period already have normal values.

Thus total adrenalectomy while diminishing the fibrinogen response to trauma delays its return to normal values.

Discussion. The data for plasma fibrinogen of fasted non-operated animals indicate a certain correlation between the decrease in fibrinogen and in body weight. This confirms previous experiments on dogs(6) and shows indirectly the relation between increased catabolism and decrease in fibrinogen. Incidentally we should like to mention that plasma proteins are considered to be freely utilized by tissues during emergencies(7,8).

Simultaneous exposure to cold and fasting for 24 hours, while causing a greater decrease in fibrinogen, induced approximately the same loss in weight as fasting for 48 hours. However, it is to be noted that in the first case the same loss of weight occurred during a shorter period, thus indicating a greater rate of catabolism. This finding could explain the sharper decrease in fibrinogen in the first instance. The same relation between fibrinogen decrease and weight loss appears to exist after injury in animals exposed to cold and fasting.

Exposure to cold is followed by an increased production of certain hormones such as corticotrophin(9), corticoids(10), thyroid hormone(11) and epinephrine(12). None of these is known to cause any marked decrease in blood-fibrinogen. It was observed that bovine corticotrophine causes a marked increase in plasma fibrinogen while ovine corticotrophine induces a milder rise(13), this suggests a foreign protein effect(14). Preliminary experiments with prolonged thyroxine treatment did not show any influence upon plasma fibrinogen(13) while epinephrine increased it markedly(13,15).

Our experiments with adrenalectomized rats suggest that the fibrinogen metabolism is influenced by the adrenals. The delayed return of plasma fibrinogen to normal after adrenalectomy could be explained by the diminished capacity of the adrenalectomized rat to catabolize protein(16). The smaller response to a second trauma indicates a difficulty in the synthesis of new protein in the absence of the adrenals. Further work is necessary to elucidate whether this fact is dependent upon a deficiency in corticoids.

Summary. Periods of 24, 48 and 72 hours of fasting constantly, though not always significantly, depress the blood-fibrinogen concentration in intact rats.

The blood-fibrinogen response to trauma is unaffected by fasting periods of 48 and 72 hours.

Simultaneous exposure to cold and fasting significantly reduces the fibrinogen rise induced by trauma.

Total adrenalectomy greatly decreases but does not abolish the fibrinogen response to injury. However, the blood-fibrinogen increase following an operation is prolonged in totally adrenalectomized as compared to partially adrenalectomized rats.

These observations suggest that the adrenals play an important role in fibrinogen metabolism.

This work was supported by a grant of the Commonwealth Fund of New York.

6. Vars, H. M., *Am. J. Physiol.*, 1930, v93, 554.

7. Holman, R. L., Mahoney, E. B., and Whipple, G. H., *J. Exp. Med.*, 1934, v59, 269.

8. Zeldis, L. J., and Alling, E. L., *J. Exp. Med.*, 1945, v81, 515.

9. Sayers, G., and Sayers, M. A., *Endocrinol.*, 1947, v40, 265.

10. Hemphill, R. E., and Reiss, M., *Endocrinol.*, 1947, v41, 17.

11. Leblond, G. P., Gross, J., Peacock, W., and Evans, R. D., *Am. J. Physiol.*, 1943, v140, 671.

12. Hartman, F. A., and Brownell, K. A., The Adrenal Gland, Philadelphia, Lea & Febiger, 1949.

13. Henriques, O. B., Henriques, S. B., and Selye, H., unpublished results.

14. Berger, W., *Klin. Wchnschr.*, 1944, v1, 1053.

15. Cannon, W. B., Wisdom of the Body, New York, W. W. Norton, 1932.

16. Bondy, P. K., Engel, F. L., and Farrar, B., *Endocrinol.*, 1949, v44, 476.

Received March 6, 1950. P.S.E.B.M., 1950, v73.