normally present fat in the liver. The lesion is prevented by simultaneous administration of methionine.

1. Farber, E., Simpson, M. V., and Tarver, H., *J. Biol. Chem.*, 1950, v182, 11.
2. Farber, E., Koch-Weser, D., and Popper, H., *Endocrinology*, 1951, v48, 205.
3. Koch-Weser, D., Farber, E., and Popper, H., *Arch. Path.*, 1951, v51, 498.
4. Farber, E., *Thesis*, 1949, University of California.
5. Wachstein, M. and Meisel, E., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 648.
6. Farber, E. and Popper, H., PROC. SOC. EXP. BIOL. AND MED., 1950, v74, 838.
7. Goldberg, R. C., and Chaikoff, I. L., *Arch. Path.*, 1951, v52, 230.
8. Wachstein, M., and Meisel, E., PROC. SOC. EXP. BIOL. AND MED., 1951, v77, 569.

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Potentiation by Adrenaline of Protective Effect of Cortisone* on Histamine Toxicity in Adrenalectomized Mice. (19264)

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It is well known that mice are relatively insensitive to histamine. According to Halpern and Wood(1) the lethal dose of histamine dihydrochloride, injected intraperitoneally, is for normal mice 50 mg per 20 g‡ of body weight. Adrenalectomy renders the mice considerably more sensitive to histamine so that it requires only 0.5 mg per 20 g of histamine to kill the adrenalectomized mice (2). It has been shown by the same authors that pretreatment with Promethazine increases the resistance of the adrenalectomized mice to histamine and brings it up to that of the normal mice. In the same conditions adrenaline increases also the resistance of the adrenalectomized mice to histamine, but in this case the toxicity of histamine is not reduced to normal; the lethal dose of histamine is brought up from 0.5 mg to 5 mg per 20 g. Adrenaline therefore does not seem to be the only factor responsible for the high resistance of normal mice to histamine.

It is the purpose of this study to investigate whether cortisone increases the resistance of adrenalectomized mice to histamine. It has been reported by various authors that cortisone can protect this species of animals against anaphylaxis(3,4). It should be noted, however, that cortisone does not protect other species of animals either against histamine or anaphylactic shock(5-7).

Experimental. Technic. 112 adult mice (female) weighing about 20 ± 5 g were used. Bilateral adrenalectomy was performed under light ether anesthesia and the animals allowed access to normal diet with plenty of fluid. Right after the operation, the animals received subcutaneously 250 γ of desoxycorticosterone, and 0.5 ml of isotonic saline. The animals treated with cortisone were injected with 0.5 mg of the drug twice a day for 3 doses, the last dose was given 4 to 5 hours before the injection of histamine. The doses of histamine dihydrochloride were administered intraperitoneally in 0.5 ml of normal saline per 20 g of body weight 48 hours after the operation. In some animals, hemoconcentration was measured by the change of the hemoglobin concentration of the blood. Blood samples were obtained by puncture of the ophthalmic venous plexus through the inner anode of the eye with a capillary glass pipette (8), before injection and again 20 minutes after injection of histamine. A group of adrenalectomized animals treated with cortisone was also treated with adrenaline. To these

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‡ It is considered that the average weight of an adult mouse is 20 g.

TABLE I. Effect of Cortisone and Adrenaline on Histamine Toxicity in Adrenalectomized Mice.

Histamine, mg/20 g	Control animals		After cortisone		After cortisone and adrenaline	
	Mortality	Avg haemo., %	Mortality	Avg haemo., %	Mortality	Avg haemo., %
.25	3/9	31				
.5	5/5	65	0/10	12		
2.5			5/14	31		
5			10/15	50		
10					0/6	2
25					2/15	8
50					7/7	

TABLE II. Effect of Cortisone and Adrenaline on Histamine Toxicity in Normal Mice.

Histamine, mg/20 g	Control animals, mortality	After cortisone, mortality	After cortisone and adrenaline, mortality
50	10/10	7/10	10/11

animals 20 γ per 20 g of adrenaline were injected subcutaneously 30 minutes before the injection of histamine. The results of these experiments are presented in Table I. The effect of cortisone and of adrenaline on histamine toxicity in the normal mouse was also investigated using a small number of animals. The results of these experiments are presented in Table II.

Results. The data presented in Table I show that cortisone can increase from 0.5 to 2.5 mg per 20 g the tolerance of adrenalectomized mice to histamine without restoring to the animals the ability to withstand doses of histamine tolerated by the normal mouse. However, treatment with both adrenaline and cortisone enables adrenalectomized mice to withstand the same doses of histamine as normal mice. The degree of tolerance to histamine afforded by these drugs is reflected in the degree of hemoconcentration. As the animals are protected with cortisone, or cortisone and adrenaline, the degree of hemoconcentration usually caused by the injection of histamine diminishes. Thus, the degree of hemoconcentration observed in adrenalectomized control animals which received 0.5 mg per 20 g of histamine was 65%. In animals treated with cortisone, the same dose of histamine produced an increase of hemoconcentration of 12%; when treated with cortisone, a dose of histamine as high as 2.5 mg per 20 g determined in the adrenalectomized mice an increase of hemoconcentration of 31%. However, after pretreatment with cortisone and adrenaline which enables the mice to tolerate as high a dose as 25 mg per 20 g of histamine, the average hemoconcentration observed is only 8%. The data presented in Table II show that neither cortisone nor cortisone and adrenaline afford much protection to the normal mouse against histamine toxicity.

Discussion. The data presented show that cortisone affords some protection to the adrenalectomized mice against histamine toxicity; the treated animals can tolerate a dose about 5 times larger than the control animals. In this respect cortisone behaves much like adrenaline alone for these adrenalectomized animals. None of these substances can alone restore normal tolerance to a single injection of histamine as is done by promethazine. However, treatment by adrenaline in animals receiving cortisone for 24 hours confers the ability to the adrenalectomized mice to withstand the high doses of histamine tolerated by normal mice. What may be the mechanism of this phenomenon? Levine and his co-workers (8) have observed with adrenalectomized animals that treatment with cortisone increases the vascular effect of nor-adrenaline. According to these authors, cortisone improves the ability of the vascular bed to respond to vasoconstrictor agents.

The experimental data reported here indi-

cate that the decreased tolerance to histamine of the adrenalectomized mouse is directly related to the increase of hemoconcentration caused by the drug. It appears that the angiotoxic effect of histamine is potentiated by the removal of the adrenals. But, as the animals are protected with cortisone and adrenaline, they show a lower degree of hemoconcentration when injected with histamine. It seems that these hormones protect the animals by increasing the resistance of the vascular bed to the toxic effect of histamine on small vessels. This interpretation is consistent with the results obtained either with adrenaline alone, or with the anti-histaminic drugs, which, as it is admitted by certain authors(10), have a definite effect on the small vessels. The fact that neither cortisone nor cortisone and adrenaline afford any protection to the normal mice is consistent with the results obtained with promethazine. In the normal mouse, the toxicity of histamine may be due to a different mechanism.

Summary. (1) When injected into adrenalectomized mice, cortisone enables these animals to tolerate 5 doses of histamine, which are usually lethal for the adrenalectomized animals. (2) Under the same conditions, adrenaline enables adrenalectomized mice to tolerate 5 to 10 lethal doses of histamine. When, however, adrenalectomized mice are treated with both cortisone and adrenaline, they are able to tolerate 50 to 100 lethal doses of histamine, and their resistance to the drug is brought back to the normal level. (3) The relationship between increased tolerance to histamine and lowering of the hemoconcentration effect of histamine caused by cortisone and adrenaline in adrenalectomized mice suggests that these hormones exert their protective effect against the angiotoxic action of histamine on the small vessels. (4) Contrasting with this remarkable action of cortisone and adrenaline in adrenalectomized mice, these hormones do not modify the toxicity of histamine in normal animals.

1. Halpern, B. N., and Wood, D. R., *Brit. J. Pharm. and Chem.*, 1950, v5, 510.

2.———, *Compt. Rend. Acad. des Sci.*, 1950, v230, 138.

3. Nelson, C. T., Fox, C. L., and Freeman E. B., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 181.

4. Dews, P. B., and Code C. F., *J. Pharm. and Exp. Ther.*, 1951, v101, 9.

5. Leith, L. J. W., and Rose, B., PROC. SOC. EXP. BIOL. AND MED., 1948, v69, 465.

6. Friedlander, S., and Friedlander, A. S., *J. Allergy*, 1950, v21, 203.

7. Benacerraf, P. G. B., and Biozzi, G., *Ann. Inst. Pasteur*, 1951, v81, 187.

8. Halpern, B. N., Biozzi, G., Mené, G., and Benacerraf, B., *Ann. Inst. Pasteur*, 1951, v80, 582.

9. Ramey, E. R., Goldstein, M. S., and Levine, R., *Am. J. Physiol.*, 1951, v165, 450; Fritz, I., and Levine, R., *Am. J. Physiol.*, 1951, v165, 456.

10. Halpern, B. N., and Briot, M., *Arch. Int. Pharmacodyn. et Therap.*, 1950, v82, 247.

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Choline Oxidase Activity in Young Rats.* (19265)

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The low activity of choline oxidase in several rat liver tumors(1-3) as compared with normal rat liver, made it of interest to study the activity of this enzyme in the livers of young rats. The succinoxidase system, which is chiefly associated with the large granule (mitochondrial) fraction of rat liver, had been shown earlier(4) to increase rapidly from low levels in newborn rats to the normal adult level in 12-15 days. As choline oxidase has also been shown to be largely associated with the large granule fraction of rat liver(5), in the present study both succinoxidase and choline oxidase activity were measured. The results obtained with succinoxidase are in agreement with the earlier study(4). Choline

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