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Regulatory Effect of Adrenal Cortical Extract on Elaboration of Pituitary Adrenotropic Hormone.*

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Following a 24-hour fast male rats (225-300 g) of the Sprague-Dawley strain were placed in a refrigerator (3°-5°C) for one hour. The adrenals were removed under pentobarbital anesthesia and analyzed for total ascorbic acid.[1] A total dose equivalent to 4 ml of cortical extract (Upjohn)† was injected subcutaneously at 3 sites. Adrenotropic hormone[2] was injected intraperitoneally in 0.9% NaCl solution.

Alterations in adrenal ascorbic acid have been used as a measure of elaboration of adrenotropic hormone by the pituitary because (1) the reduction in content of ascorbic acid in the adrenal which follows subjection of an animal to stress does not occur in the absence of the pituitary,[3] and (2) as can be seen from Table I the administration of a preparation of adrenotropic hormone, free of other pituitary activities,[2] reduces the concentration of ascorbic acid in the adrenal of the hypophysectomized rat.

After one hour in the refrigerator, the content of ascorbic acid in the adrenal of the intact rat was decreased (Table II), indicating that the pituitary was activated to increase its elaboration of adrenotropic hormone. Pretreatment with cortical extract prevented this decrease in adrenal ascorbic acid. Cortical extract does not interfere with the action of adrenotropic hormone on the adrenal cortex since administration of cortical extract did not prevent an exogenous source of adrenotropic hormone from bringing about a reduction in adrenal ascorbic acid (Table II). The dose of adrenotropic hormone selected produced a decrease in adrenal ascorbic acid equivalent to that produced by exposure to 3°-5°C for one hour and therefore approximates the amount elaborated by the pituitary of the exposed animal.

These results strongly suggest that the rate of production of adrenotropic hormone by the pituitary is regulated by the concentration of cortical hormone(s) in the blood and tissues. It may be a direct effect of the cortical hormone(s) on the anterior pituitary cells or it may be an indirect effect brought about by an increase or decrease of some regulatory substance in the tissues, the concentration of which is dependent in turn upon the level of cortical hormone(s). Ingle, Higgins, and Kendall[4] found adrenal cortical atrophy in rats after cortical hormone administration but

TABLE I.
Effect of Adrenotropic Hormone on Ascorbic Acid Content of Adrenals of Rats Three Days Following Hypophysectomy.

	No. rats	Adrenal ascorbic acid mg per 100 g fresh tissue
Hypophysectomized controls	6	326 ± 14.8*
1 hour after admin. of adrenotropic hormone (200 μg/ 100 g body wt)	5	156 ± 9.2

* Mean and standard error.

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1 Roe, J. H., and Kuether, C. A., *J. Biol. Chem.*, 1943, **147**, 399.

† We are grateful to Dr. Wilfred N. Sisk of the Upjohn Company, Kalamazoo, for a supply of this material. Alcohol was removed under reduced pressure at 50° to 60°C.

2 Sayers, G., White, A., and Long, C. N. H., *J. Biol. Chem.*, 1943, **149**, 425.

3 Sayers, G., Sayers, M. A., Liang, T. Y., and Long, C. N. H., *Endocrinology*, 1945, **37**, 96.

4 Ingle, D. J., Higgins, G. M., and Kendall, E. C., *Anat. Record*, 1938, **71**, 363.

TABLE II

	No. rats	Adrenal ascorbic acid mg per 100 g fresh tissue
Controls	18	419 ± 8.2*
1 hr after admin. of 4 ml cortical extr.	6	423 ± 8.4
1 hr at 3 to 5°C	9	314 ± 18.0
1 hr at 3 to 5°C pretreated with 4 ml cortical extr.	9	415 ± 10.1
1 hr after admin. of adrenotropic hormone (10 μg/100 g body wt)	4	314 ± 12.1
1 hr after admin. of adrenotropic hormone (10 μg/100 g body wt) pretreated with 4 ml cortical extr.	6	310 ± 7.3

* Mean and standard error.

their experiments were chronic and did not concern the physiological response to acute stress reported here.

Summary. Administration of cortical extract prevents the decrease in adrenal ascorbic acid which accompanies exposure to cold but does not prevent the decrease which results from administration of exogenous adrenotropic hormone. Since reduction in adrenal ascorbic acid is initiated by pituitary adrenotropic hormone, cortical extract must act to inhibit elaboration of this tropic hormone by the pituitary. These results have been interpreted to mean that rate of release of adrenotropic hormone from the pituitary is regulated by the concentration of adrenal cortical hormones in the blood and tissues.

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Combined Anesthesia and Hyperimmune Serum Therapy in the Treatment of Experimental Western Equine Encephalomyelitis.

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Once the symptoms of a virus disease have become evident, the virus is well established in the host cell. For this reason, it is assumed that antibodies are unable to gain access to the virus, with the result that antiserum therapy is ineffective. The close association between the virus and the host cell likewise renders chemotherapy difficult, for an agent in concentration sufficient to destroy the virus would probably injure the host cell. The ideal therapeutic agent would bring about a reversible change in the metabolism of the host cell sufficient in degree and duration to cause destruction of the virus without injuring the cell. Such an agent should have the same tissue predilection as the virus. Studies on the treatment of neurotropic virus diseases have been discouraging. The results of experiments with hyperimmune serum therapy have been contradictory, probably because of variations in the virulence and incubation period of the virus strains employed and differences in the potency of antisera.[1,2,3] Reports with chemotherapeutic agents have likewise been discouraging.[4,5] Similarly, certain antibiotics have proved ineffective in

1 Zichis, J., and Shaughnessy, H. J., *J. A. M. A.*, 1940, **115**, 633.

2 Olitsky, P. K., Schlesinger, R. W., and Morgan, I. M., *J. Exp. Med.*, 1943, **77**, 359.

3 Zichis, J., and Shaughnessy, H. J., *Am. J. Pub. Health*, 1945, **35**, 815.

4 Kramer, S. D., Geer, H. A., and Szobel, D. A., *J. Immunol.*, 1944, **49**, 273.

5 McKinstry, D. W., and Reading, E. H., *J. Franklin Inst.*, 1944, **237**, 422.