jected into bilaterally adrenalectomized cats. Accordingly, the previously thyroidectomized cats used in the above experiments were bilaterally adrenalectomized in 2 stages. The respiratory exchange was measured daily. As was the case in the animals in which the thyroid was intact,[1] the metabolism fell with the development of the symptoms of adrenal insufficiency. When these symptoms became severe, injections of cortical hormone were begun. The metabolism rose promptly to a level slightly above the normal and remained there as long as the cortical hormone was administered. In other words, the changes in the respiratory exchange following bilateral adrenalectomy in cats are essentially the same, whether the thyroid is intact or totally removed.

5656

Effect of Injections of Cortin on Resistance of Suprarenalectomized Rats to Large Amounts of Histamine.

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In previous experiments it was demonstrated that repeated injections of cortin raise the resistance of suprarenalectomized rats to typhoid vaccine.[1] Similar results were obtained by Hartman and Scott.[2] In subsequent experiments we found that repeated daily injections of cortin raise the resistance of suprarenalectomized rats to 4 and 5 lethal doses of histamine (about 500 mg. of histamine per kg. of body weight).[3] In the following experiments an effort was made to increase further the resistance of suprarenalectomized rats to very large amounts of histamine, by injections of cortin. It has been demonstrated that adult suprarenalectomized rats are killed by 100 to 120 mg. of histamine per kg. when the drug is administered on the sixth day after suprarenalectomy;[4] that immature suprarenalectomized rats are killed by 150 to 200 mg. of hista-

[1] Perla, David, and Marmorston-Gottesman, J., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 648.

[2] Scott, W. J. M., and Hartman, F. A., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 649.

[3] Perla, David, and Marmorston-Gottesman, J., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 650.

[4] Marmorston-Gottesman, J., and Gottesman, J., *J. Exp. Med.*, 1928, **47**, 503.

mine[3]; that normal rats are killed by 700 to 900 mg. of histamine per kg. of body weight.[4, 5, 6] In spite of the fact that rats have accessory cortical tissue, it has been the experience in this laboratory that all rats are highly susceptible to the effects of small amounts of histamine injected after removal of the suprarenals, and that if the histamine is administered from the 6th to the 14th day, 100% of rats will succumb to less than 200 mg. of histamine per kg. of body weight. In these experiments the cortical extract used was made in the laboratory according to the method of F. A. Hartman. Cortin is a potent extract of the suprarenal cortex. It is free from toxicity and epinephrin.

It was found that a batch of cortin can be assayed by estimating the amount of cortical extract injected intraperitoneally into suprarenalectomized rats on the 5th and 6th day after operation necessary to protect these rats against 200 mg. of ergamine acid phosphate.

Suprarenalectomized adult rats were injected daily from the day of operation with 1.5 to 2 cc. daily of cortin (1 cc. was the equivalent extractive of 40 gm. of cortex). On the 6th day after operation 5 rats were injected with 600 mg., 3 with 700 mg. and 8 with 800 mg. of histamine per kg. of body weight. Three normal rats received 900 and 950 mg. of histamine per kg. of body weight. Of the 5 rats injected with 600 mg. of histamine per kg. all survived. Of the 3 rats injected with 700, 2 survived and of the 8 receiving 800, 3 survived. The normal rats were killed with 950 mg. per kg.

TABLE I.

Effect of repeated injections of cortin on resistance of adult suprarenalectomized rats to histamine administered on the 6th day after operation.

No. of rats	Cortin Days after suprarenalectomy 1	2	3	4	5	6	Histamine mg. per kg. 6th day	No. Survived	No. Died
5	2 cc.	2 cc.	2 cc.	2 cc.	2 cc.	2 cc.	600	5	0
3	"	"	"	"	"	"	700	2	1
8	"	"	"	"	"	"	800	3	5
3 normals	0	0	0	0	0	0	900	2	0
3 "	0	0	0	0	0	0	950	1	2

From these results it is apparent that it is possible to raise the resistance of suprarenalectomized rats in many instances almost to the normal level of resistance of normal rats by repeated injections of large amounts of cortin. The effect of cortical hormone on the resistance of suprarenalectomized rats is a specific

[5] Crivellari, C. A., *Compt. rend. Soc. biol.*, 1927, **96**, 223.

[6] Voegtlin, C., and Dyer, H. A., *J. Pharmacol. and Exp. Therap.*, 1925, **24**, 101.

one. Previous work has shown that large amounts of saline have no demonstrable effect on the resistance of suprarenalectomized rats. Repeated injections of epinephrin have only a very slight effect.[8] An extract of the spleen made in the exact manner as the cortical extract failed to produce any increase in resistance of suprarenalectomized rats. The female sex hormone of Doisy (Theelin, Parke, Davis and Co.) did not raise the resistance of suprarenalectomized rats. Through the kindness of Prof. Harrow of the College of the City of New York, we tested the effect of the male sex hormone on the resistance of suprarenalectomized rats with negative results. We believe, therefore, that the action of cortin on the resistance of suprarenalectomized rats to histamine and other toxins and poisons is a measure of specific activity of the life prolonging hormone of suprarenal cortex.

5657

A Substance in Urine of Normal Human Adults That Raises the Resistance of Suprarenalectomized Rats.

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Though potent extracts of the suprarenal cortex as made by F. A. Hartman[1] and Swingle and Pfiffner[2] will prolong the life of suprarenalectomized cats, enormous quantities of suprarenal glands are necessary for the recovery of small amounts of the active substance. A more efficient method should be found for obtaining the substance in larger amounts in order to make the use of cortical hormone available.

It occurred to us that the cortical hormone may be eliminated in the urine in large amounts. A lipoid extract of the urine of normal young adults, males and females, was made. The urine of young male and female adults is extracted with benzene. The benzene is allowed to separate. The benzene fractions are evaporated at 40° *in vacuo* to dryness, the residue taken up in ether, the ether evaporated off *in vacuo* and the residue taken up in water or oil. The final

[7] Hartman, F. A., *Endocrinol.*, 1930, **14**, 229.

[8] Perla, David, and Marmorston-Gottesman, J., *Am. J. Phys.*, 1929, **89**, 152.

[1] Hartman, F. A., *Endocrinol.*, 1930, **14**, 229.

[2] Swingle, W. W., and Pfiffner, J. J., *Am. J. Phys.*, 1931, **96**, 153.