

tonella muris anemia early in life, between the fourth and sixth week. It then becomes a carrier of the *Bartonella muris* and possesses an acquired immunity to the infection. The infection following splenectomy in the adult carrier rat is indicative of a depression in the acquired resistance to *Bartonella muris*. It has been further shown that the acquired resistance to *Trypanosoma lewisi* of normal rats as a result of a previous infection is uninfluenced by subsequent suprarenalectomy. These observations indicate that once a cellular or humoral immunity is established to an infection or an antigenic substance this acquired resistance cannot be broken down by subsequent suprarenalectomy. Bilateral suprarenalectomy, though markedly depressing the *natural resistance* of the adult albino rat to toxins, poisons and bacterial and protozoan infections, does not affect the *acquired resistance* resulting from previous injections of such substances. Acquired and natural resistance are dependent on different physiological processes in the organism and are not merely quantitative variations of the same process as is generally assumed.

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Effect of Injections of Cortin on Resistance of Suprarenalectomized Rats to Histamine Poisoning.

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In a previous communication¹ the protective action of injections of cortin on the resistance of suprarenalectomized rats to typhoid vaccine was reported. In these studies an extract of the cortex of the suprarenal gland, made in this laboratory according to the method of F. A. Hartman, was used. It was found that Hartman's cortin is a highly potent extract of the suprarenal cortex. It is free of toxicity and epinephrin. Repeated injections of cortin will raise the resistance of suprarenalectomized rats to several lethal doses of typhoid vaccine. It was suggested that a cortical extract may be biologically assayed by determining the minimal protecting amount to be administered within 24 hours before and after the injection of the minimal lethal dose of typhoid vaccine for suprarenalectomized adult rats on the 6th day after suprarenalectomy.

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

In the following experiments the effect of injections of cortin on the resistance of suprarenalectomized rats to histamine (ergamine acid phosphate, Burroughs Wellcome) was studied. Previous work² had shown that suprarenalectomized rats are highly susceptible to histamine poisoning. It was suggested that histamine could be used as a gauge of suprarenal insufficiency. Adult suprarenalectomized rats are killed by 100-120 mg. of histamine per kg. when administered on the 6th day after operation.^{2, 3} Normal rats survive 700-900 mg. per kg.^{4, 5, 2}

Preliminary tests in the present studies indicated that immature suprarenalectomized rats will resist larger amounts of histamine than mature suprarenalectomized rats. Six-week-old immature albino rats of Wistar stock were used. The minimal lethal dose of histamine for 6-week-old suprarenalectomized rats was determined. Twenty-four suprarenalectomized, 6-week-old albino rats were divided into 3 groups. Five received on the 6th day after operation 100 mg. per kg. of body weight of histamine, 14 received 150 mg. per kg. and 5 received 200 mg. per kg. Of those receiving 200 mg. none survived; of those receiving 150 mg., 60% survived, and of those receiving 100 mg. all survived. The minimal lethal dose of histamine for suprarenalectomized 6-week-old rats is between 150 and 200 mg. per kg. of body weight. The minimal lethal dose of histamine for suprarenalectomized adult rats is between 100 and 120 mg. per kg. of body weight. It has been found in earlier experiments that the continuous administration of epinephrin from the day of operation to the day of histamine poisoning will protect suprarenalectomized rats in about half the instances to one minimal lethal dose of histamine.⁶ In these experiments it has been found that injections of physiological salt solution did not raise the resistance to histamine poisoning.

Injections of 0.5 cc. (1 cc. is equal to 40 gm. of cortex) of cortin were made twice daily into 14 suprarenalectomized rats. On the 6th day, 6 rats received 150 mg. of histamine per kg., 3 received 200 mg. per kg., 3 received 300 mg. per kg. and 2 received 500 mg. per kg. All of these rats survived. The daily injections of cortin raised the resistance to at least 3 minimal lethal doses of histamine. The maximal amount of histamine that suprarenalectomized rats treated with cortin will survive is being determined.

² Marmorston-Gottesman, J., and Gottesman, J., *J. Exp. Med.*, 1928, **47**, 503.

³ Scott, W. J. M., *Arch. Path. and Lab. Med.*, 1927, **4**, 491.

⁴ Crivellari, C. A., *Compt. rend. Soc. biol.*, 1927, **96**, 223.

⁵ Voegtlin, C., and Dyer, H. A., *J. Pharmacol. and Exp. Therap.*, 1925, **24**, 101.

⁶ Perla, David, and Marmorston-Gottesman, J., *Am. J. Phys.*, 1929, **89**, 152.

The effect of injections of cortin during the last 24-hour period before and after the injections of histamine was determined. One cc. of cortin was administered to 6 suprarenalectomized rats twice on the 5th day and on the 6th day, 2 hours prior to the injection of histamine and 2 hours after the injection of histamine. Three of these rats were given 300 mg. of histamine per kg. of body weight and three, 500 mg. per kg. of body weight. All the rats survived. The administration, therefore, of cortin during the last 24-hour period prior to the injection of histamine will raise the resistance of suprarenalectomized rats to at least 3 minimal lethal doses of histamine. (See Table I.)

TABLE I.
Effect of Injections of Cortin on Resistance of Suprarenalectomized Rats to Histamine Poisoning at End of Second Week (6-week-old rats).

Rat No.	Cortin for 6 days after suprarenalectomy	Histamine mg. per kg. 6th day		No cortin 8-12 days after operation. Cortin given days after operation	Histamine mg. per kg. 14th day		
1	1 cc.	500	Survived	0	0	200	Died
2	"	500	"	"	"	200	"
3	"	300	"	"	"	200	"
4	"	300	"	"	"	200	"
5	"	300	"	"	"	200	"
6	"	200	"	2 cc.	1.5 cc.	300	Survived
7	"	200	"	"	"	300	"
8	"	200	"	"	"	300	"
9	0	150	"	"	"	300	"
10	"	150	"	"	"	500	"
11	"	150	"	"	"	500	"
12	"	150	"	"	"	500	"
13	"	150	"	"	"	500	"

An experiment was carried out to determine the protective action of cortin in suprarenalectomized rats when administered during 24 hours at the end of the second week after operation. Thirteen rats were used. Eight of these received daily injections of 1 cc. of cortin in 2 doses during the first 6 days after operation. Five rats received no cortin. Of the 8 treated rats, 2 were given 500 mg. of histamine per kg.; three, 300 mg., and three, 200 mg. per kg. on the 6th day after operation. All of these rats survived. The 5 untreated suprarenalectomized rats were given 150 mg. of histamine per kg. All the rats of this group survived. During the second week no cortin was administered to the rats of either group until the 13th day. The 5 rats that had received no cortin in the first week were given 2 cc. of cortin on the 13th day and 1.5 cc. on the

TABLE II.
Effect of Repeated Injections of Cortin on Resistance of 6-week-old Suprarenalectomized Rats to Histamine Administered on the 6th Day after Operation

No. of Rats	Cortin						Histamine mg. per kg. 6th day	No. of Rats Survived	No. of Rats Died
	Days after suprarenalectomy	1	2	3	4	5			
6	1 cc.	1 cc.	1 cc.	1 cc.	1 cc.	1 cc.	150	6	0
3	"	"	"	"	"	"	200	3	0
3	"	"	"	"	"	"	300	2	1
2	"	"	"	"	"	"	500	2	0
3	0	0	0	0	2 cc.	2 cc.	300	3	0
3	"	"	"	"	"	"	500	3	0
Untreated Rats									
5	0	0	0	0	0	0	100	5	0
14	"	"	"	"	"	"	150	9	5
5	"	"	"	"	"	"	200*	0	5

1 cc. extract represents 40 gm. of cortex.

*It has been previously demonstrated that adult suprarenalectomized rats are killed by 100-120 mg. of histamine per kg. on the 6th or 7th day.^{2, 3}

14th day. Three rats which had received daily injections of cortin in the first week were given 2 cc. on the 13th day and 1.5 cc. on the 14th day. On the 14th day, 4 of these rats received 300 mg. of histamine per kg. and 4 received 500 mg. per kg. All 8 rats survived. Five rats that had received cortin during the first week received no cortin in the second week. On the 14th day these rats were injected with 200 mg. of histamine per kg. of body weight. All were killed within 3 hours.

These experiments further demonstrate that repeated injections of cortin raise the natural resistance of suprarenalectomized rats to poisons as well as bacteria. It is evident that the marked susceptibility of suprarenalectomized rats to histamine poisoning is not due to epinephrine insufficiency as maintained by Wyman but to cortical insufficiency.

It is suggested that the protective action of cortical extracts against histamine poisoning in suprarenalectomized rats is a better means of biologically assaying the potency of such extracts than typhoid vaccine which we suggested in a previous communication. Ergamine acid phosphate (histamine) is a standard chemical that varies very little in toxicity. The amount of cortical extract injected intraperitoneally into suprarenalectomized albino rats on the 5th and 6th day after operation necessary to protect these rats against 200 mg. of ergamine acid phosphate (Burroughs Wellcome) may be considered as a standard unit.