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Effect of Extract of Adrenal Cortex upon Thymic Weight and Resistance to Bacterial Intoxication in Chronic Adrenal Insufficiency.

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Extirpation of both adrenal glands is rapidly fatal in most laboratory animals. However this operation seems to have little effect for several weeks upon the physical condition of the majority of rats submitted to it. But such apparently healthy survivors manifest at least 2 important differences from normal rats, an increased susceptibility to bacterial intoxication,[1] and hypertrophy of the thymus.[2] In each instance the variation has been correlated with a functional deficiency of the adrenal cortex rather than of the medulla.

It is our purpose to report the effect of an extract of the adrenal cortex upon this chronic type of adrenal insufficiency, using as criteria the resistance of the animals to bacterial intoxication and the size of the thymus.

Fifty-eight rats from 5 litters born on the same day were used. These were divided into 3 groups and sampled for the different groups according to the method adopted by Dr. Luce Clausen,[3] insuring equal distribution of weight and equal representation of the different litters in each group. At the beginning of the experiment the mean actual weights of the 3 groups were as follows:

Group 1—97 gm. ±1.7.
" 2—95 " ±1.4.
" 3—95 " ±2.2.

Each of the first 2 groups contained 19 members. Group 3 was used for control determinations of body weight and thymus weight and was subdivided into 2 similar parts of 10 members each, one of which (A) received the injection of typhoid vaccine and the other (B) did not. All members of Groups 1 and 2 were doubly adrenalectomized on the same day and were injected subcutaneously with ½ cc. of fluid twice daily for 2 weeks after operation. Group 2 received an extract of the adrenal cortex made and kindly supplied to us by Drs. W. W. Swingle and J. J. Pfiffner,[4] while in Group 1

[1] Scott, W. J. M., *J. Exp. Med.*, 1924, **39**, 457.
[2] Jaffe, H. L., *J. Exp. Med.*, 1924, **40**, 325, 619, 753.
[3] Clausen, E. Luce, *J. Nutrition*, 1929, **2**, 125.
[4] Swingle, W. W., and Pfiffner, J. J., *Science*, 1930, **71**, 321.

the same amount of Ringer's solution was used. Two weeks after operation all surviving members of Groups 1, 2 and 3 A were injected intraperitoneally with 1½ cc. of standard typhoid vaccine. (One billion killed typhoid bacilli per cc.; no preservative.) This dose has previously been shown to be usually fatal to bilaterally adrenalectomized rats 2 weeks after operation (Jaffe[5]). All surviving rats were sacrificed 48 hours after the injection of the bacterial vaccine. Four of Group 1 (saline injected) and 3 of Group 2 (extract injected) died in the first week. All of these had profound infections of the respiratory tract, (pneumonia, etc.) except one of the former that apparently died of uncomplicated adrenal insufficiency. In the second week, 10 rats of Group 1 died. All except one of these fatalities occurred one day when the temperature of the animal room by accident fell several degrees over night. Only one rat in Group 2 died in the second week although this group was exposed to the same unfavorable low temperature that proved so disastrous in Group 1. This animal escaped from his cage on to the floor of the room where the temperature was several degrees cooler and remained there over night. He was in a moribund condition when found in the morning.

The gain in weight in the 3 groups was as follows:

		%			%
For the first week	Group 1	1	For the second week	Group 1	7
	" 2	4		" 2	16
	" 3	17		" 3	20

Fifteen of the 19 rats in Group 2, and 5 of the 19 rats in Group 1 were surviving in good condition 2 weeks after operation and were injected with 1½ cc. of the typhoid vaccine at that time. All of the animals in Group 1, and 12 of the 15 animals in Group 2 succumbed to the bacterial intoxication within 36 hours. Three animals in Group 2 survived the injection and had recovered a normal appearance. Forty-eight hours after the injection of bacteria they were sacrificed.

At autopsy the thymus in all animals was carefully dissected out and weighed. In Table I the mean weight of the thymus with the probable error of the mean is given for each group. In the last

TABLE I.

Group	Mean Weight of Thymus, mg.	T/BW
I	392±.0265	3.9±.0001
II	389±.0183	3.2±.0001
IIIa	250±.0139	2.1±.0001
IIIb	294±.0124	2.1±.0001

[5] Jaffe, H. L., *Am. J. Path.*, 1926, **2**, 421.

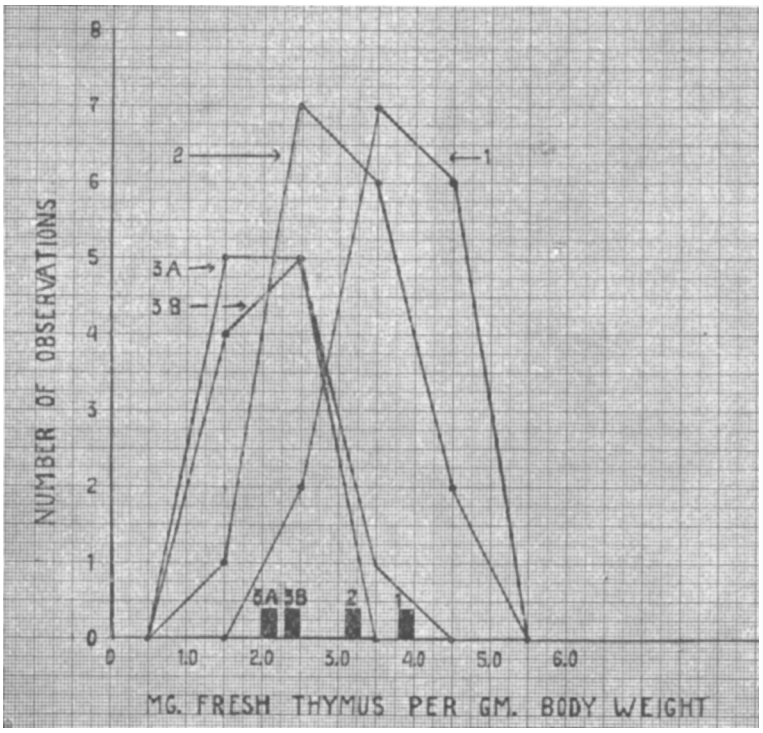

FIG. 1.

column this has been expressed in terms of mg. of fresh thymus per gm. of body weight. In order to show graphically all the observations in the 4 groups, Fig. 1 gives the data expressed in the form of frequency polygons. It is evident from this data that the size of the thymus per unit of body weight is greatest in Group 1 (saline injected), intermediate in Group 2 (cortical extract injected), and least in Group 3 (control). The difference between sub-groups IIIa (control receiving typhoid vaccine) and IIIb (control receiving nothing) is too slight to be of significance.

Two rats were found at autopsy to possess gross fragments of adrenal tissue and consequently were not classified in the above groups. One had received cortical extract injections and the other saline. They had both survived in good condition the injection of 1½ cc. of typhoid vaccine. They constitute another type of control, as they possessed functioning adrenal cortical cells. The weights of the thymus were 318 and 193 mgm. with body weights of 122 and 116 gm. respectively or 2.6 and 1.7 mgm. per gm. of body weight. These correspond closely to the greatest frequency of thymic weights in the control groups IIIa and IIIb.

The cortical extract used seemed definitely to produce an effect upon the chronic form of adrenal insufficiency in rats. The mortality occurring about 3 or 4 days after operation, due chiefly to respiratory infection, did not appear to be much affected. However, the mortality of the second week, augmented in this case by accidental chilling was largely prevented by the extract. Its beneficial effect was also shown by the resumption of practically a normal growth curve in the second week, while the saline injected control animals gained less than half as much in this period. The weight of the thymus per gm. of body weight in the extract injected group was intermediate between that of the saline injected group and that of the controls. The extract seemed also to decrease slightly the susceptibility of the adrenalectomized rats to killed typhoid bacilli.

We are of the opinion that a more complete protection in this chronic form of adrenal insufficiency can be demonstrated by pushing the administration of extract just before and during the bacterial intoxication. Such an attempt is now in progress.

We want to thank Drs. Swingle and Pfiffner for furnishing us with the extract of the adrenal cortex used.

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Relation of Various Substances Used in the Artificial Feeding Mixtures of Infants to Nutritional Anemia.

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The investigation made for the purpose of determining the influence on the hemapoietic system of various substances commonly used in infant feeding included a study of both rats and infants.

In the work with rats, substances recommended for infant feeding: carbohydrate milk modifiers, orange juice, tomato juice, autolyzed yeast, liver, egg yolk, Vitamin B containing extracts, and various iron and copper additions, were tested. These were fed in conjunction with milk in proportions comparable to those used in infant feeding. Unmodified milk diets including both boiled and pasteurized were included, also, for comparison. Fifty-seven animals were fed, 2 to 3 on each diet, for 6 to 18 weeks. Hemoglobin determinations (Newcomer method) were made at the beginning of experimental diet and after 7 weeks of the diet. Records of