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Effect of Adrenotropic Hormone on the Natural Resistance of Hypophysectomized Rats.

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In the present communication the protective effect of the adrenotropic fraction of anterior hypophysis on the natural resistance of hypophysectomized rats to histamine poisoning is reported.

We were unable to obtain the adrenotropic fraction prepared according to Collip's method[1] and as a source of this material we used an acid extract of the anterior hypophysis boiled for 20 minutes. Such a heated acid extract still contains adrenotropic activity, but the thyrotropic hormone and gonadotropic and growth factors are destroyed (Spence[2]). Preliminary experiments showed that such heated extracts still possess varying degrees of adrenotropic effect in hypophysectomized rats.

The acid extract of dried anterior hypophysis was prepared by the method of Loeb.[3] Ten grams of the powder was extracted with 100 cc. of ½% acetic acid overnight. The fluid was brought to pH 6.6, centrifuged and then brought to pH 7.8 and filtered through a Seitz filter. The heated fraction was prepared by suspending the extract in boiling water for 20 minutes.

Seventy-seven rats of Wistar stock, free from *Bartonella muris,* were used in these experiments. Of these, 14 were normal unoperated controls; 19 were completely hypophysectomized but untreated; 23 were hypophysectomized and injected with 1 cc. of acid extract of anterior hypophysis daily from the day of operation to the day of the test; 21 were hypophysectomized and injected daily with 1 cc. of the heated acid extract of anterior hypophysis.

Ten days after the operation the rats were injected intraperitoneally with amounts of histamine varying from 300 to 1600 mg. per kg. of body weight as indicated in Table I.

The minimal lethal dose of histamine in the control rats of Wistar stock* was about 1400 mg. per kg. The hypophysectomized rats untreated were killed in all instances by amounts of histamine greater than 400 mg. per kg. and only half the number of rats survived this dose. Hypophysectomized rats repeatedly injected

1 Anderson, E. M., Thomson, D. L., and Collip, J. B., *Lancet,* 1933, **2**, 347.

2 Spence, A. W., *Saint Bartholomew's Hospital Reports,* 1935, **67**, pt. 6.

3 Loeb, L., and Bassett, R. B., PROC. SOC. EXP. BIOL. AND MED., 1929, **27**, 490.

*This was somewhat higher than in the rats of our stock previously used.

TABLE I.

The Effect of Repeated Injections of Unheated and Heated Acid Extracts* of Anterior Hypophysis on the Natural Resistance of Hypophysectomized Rats to Histamine Poisoning.†

No. of rats	Amt. histamine per kg. body weight, mg.	No. of rats survived	No. of rats died
Hypophysectomized rats treated with acid extract of anterior hypophysis.			
3	300	3	0
3	400	3	0
2	500	2	0
2	600	1	1
4	700	2	2
4	800	3	1
4	900	2	2
1	1000	0	1
Hypophysectomized rats treated with a heated acid extract of anterior hypophysis (adrenotropic fraction).			
2	300	2	0
3	500	2	1
4	600	4	0
5	700	3	2
5	800	0	5
2	900	0	2
Hypophysectomized rats untreated.			
2	200	1	1
3	300	1	2
7	400	2	5
3	500	0	3
2	600	0	2
2	700	0	2
Normal control rats.			
2	1000	2	0
3	1100	2	1
4	1200	4	0
2	1400	1	1
2	1600	0	2
1	1800	0	1

*The extract was injected during a period of 10 days after operation in amounts of 1 cc. per rat per day.

†All the rats were 3 to 4 months of age at time of hypophysectomy.

with an acid extract of desiccated anterior hypophysis from the day of operation survived in some instances 900 mg. of histamine per kg. When treated with the adrenotropic fraction (the heated acid extract) hypophysectomized rats survived as great an amount as 700 mg. per kg. All succumbed to amounts in excess of 700 mg. per kg. of body weight.

The heated acid extract was not as effective as the unheated extract in raising resistance. This may be due to the fact that boiling partly destroys the adrenotropic fraction or that other hormonal factors present in the acid extract may influence the resistance of the hypophysectomized rat.

Since the heated acid extract is apparently free from all factors

except the adrenotropic hormone it is probable that the protective effect of the acid extract is due to the adrenotropic fraction.

The evidence reported in this paper further supports the hypothesis that the decrease in natural resistance in the rat that follows hypophysectomy is in part an expression of insufficiency of the suprarenal cortex, due to withdrawal of the adrenotropic hormone.

The experimental evidence for this hypothesis may be summarized as follows:

(1) The removal of the suprarenal glands of rats is followed by a marked depression in the natural resistance to various toxins, poisons and bacterial and protozoan infections.† The depression is associated to a greater degree with the loss of cortical than with that of medullary substance. This conclusion is based on the fact that the administration of epinephrine to suprarenalectomized rats influences the resistance only to a slight degree,[5] whereas the administration of the suprarenal cortical hormone may raise the resistance almost to the normal level.[6]

(2) The natural resistance of completely hypophysectomized rats to histamine poisoning is depressed during a period of one to ten weeks after operation and this decrease in resistance is associated with involutional changes of the suprarenal gland, such as hemorrhage into or atrophy of the inner zones of the cortex. Rats in which the posterior lobe and a large portion of the anterior lobe are removed show a similar drop in resistance and atrophic changes in the suprarenal cortex occur, but when a large fragment of anterior lobe remains no depression in resistance to histamine occurs and the suprarenal glands are normal.[7, 8]

(3) Repeated injection of large amounts of suprarenal cortical hormone raises the natural resistance of totally hypophysectomized adult rats to histamine poisoning.[9] This is particularly marked during the first 2 weeks after operation, the period during which the most severe depression in natural resistance occurs.

(4) The natural resistance of hypophysectomized rats can be raised by the administration of (a) emulsions of fresh anterior hy-

† For a review of this subject, see Perla and Marmorston.[4]

4 Perla, David, and Marmorston, J., *Arch. Path.*, 1933, **16**, 379.

5 Perla, D., and Marmorston-Gottesman, J., *Am. J. Physiol.*, 1929, **89**, 152.

6 Perla, D., and Marmorston-Gottesman, J., PROC. SOC. EXP. BIOL. AND MED., 1931, **28**, 1022.

7 Perla, D., and Rosen, S. H., *Arch. Path.*, 1935, **20**, 222.

8 Perla, D., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 655.

9 Perla, D., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 797.

pophysis of cattle,[10] (b) acid extracts of dried anterior hypophysis rich in adrenotropic factor, and (c) heated acid extracts of anterior hypophysis containing only active adrenotropic hormone (present communication).

The decrease in natural resistance that follows hypophysectomy in the rat to a poison such as histamine may be due to withdrawal of the adrenotropic hormone and the consequent insufficiency of the suprarenal cortex.

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Functional Pituitary Grafts in Rats.

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Recent experiments by Hohlweg and Junkmann,[1] Haterius, Schweizer and Charipper,[2] and Hill and Gardner[3] have indicated quite conclusively that pituitary tissue will function as a graft.

It is the purpose of this report to present summarily a series of experiments in which the empty sellae of hypophysectomized 28-day-old male and female rats were utilized immediately after the operation as sites for grafting pituitary tissue. The types of grafts included: 1. male hosts bearing (a) their own pituitaries as grafts and (b) the pituitaries of 28-day-old female rats; 2. female hosts bearing (a) their own pituitaries as grafts (b) the pituitaries of other 28-day-old female rats (c) the pituitaries of 1 to 5 newborn male rats; (d) the pituitaries of male rats 20 to 40 days old. Hosts and donors were taken from an intensively inbred strain of rats. In a group of 37 such hosts (5 males and 32 females) which were observed for 14 weeks, 73% takes occurred as judged by marked body growth and attainment of a functional sexual capacity.† The growth curves of these animals ascended much

10 Perla, David, PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 121.

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1 Hohlweg, W., and Junkmann, *Klin. Wchnschr.*, 1932, **11**, 321.

2 Haterius, H. O., Schweizer, M., and Charipper, H. A., *Endocrinology*, 1935, **19**, 673.

3 Hill, R. T., and Gardner, W. U., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**, 78.

† In a group of 70 operative controls 69 proved to be completely hypophysectomized as determined by growth stasis, severe cachexia and macroscopic examination of the sella.