

COMPENSATORY HYPERTROPHY OF THE ADRENAL CORTEX.*

By EATON M. MacKAY AND LOIS LOCKARD MacKAY.

(From the Department of Medicine of Stanford University Medical School, San Francisco.)

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Experimental evidence concerning hypertrophy of the adrenal cortex and medulla following the removal of one gland is conflicting and uncertain. The results of previous workers have been summarized by Boycott and Kellaway (1), who, from a series of carefully controlled experiments, concluded that destruction of one adrenal in the rabbit is not followed by hypertrophy of either the cortex or the medulla of the other gland. Close inspection of their figures however leads one to think that these investigators were over-conservative in the interpretation of their results and that in reality some hypertrophy did take place. It is true that there is a large per cent of variability in their figures but this appears to be due to the small number of animals used rather than to highly variable results. In the rat neither Harley (2) nor Poll (3) found compensatory hypertrophy. Wiesel (4) and Scott (5) both affirm the existence of compensatory hypertrophy of the cortical accessory adrenals following the removal of both glands in this animal. The data in each case were based upon doubtfully controlled experiments. Elliott and Tuckett (6) made careful weighings but only upon four rats and found no compensatory hypertrophy.

Methods.

Fifty albino female rats of exactly the same age were divided into a control group and an operated group, each of equal number. 14 days before these ani-

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mals became 90 days of age both groups were placed upon a special¹ diet which was maintained until the end of the experiment. The daily food intake, which was determined for cage units of five rats each, has been charted in Fig. 1. Each rat was weighed daily and the average weight curves of the two groups, which are shown in Fig. 1, are nearly alike.

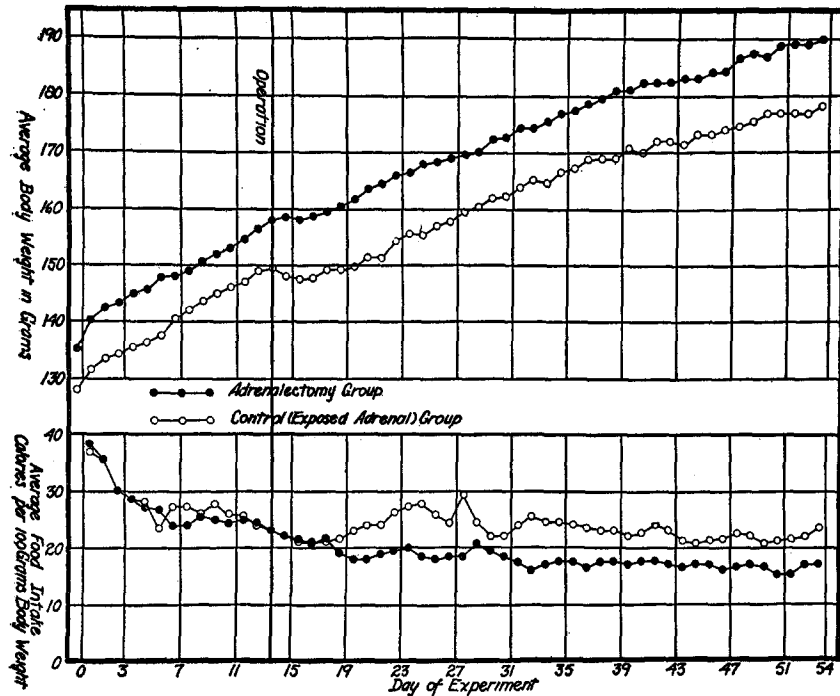


FIG. 1. Average daily body weight and average daily food intake.

¹ Adequate for growth and reproduction. The composition is as follows:

	per cent
Corn-starch.....	41.0
Casein.....	15.0
Lard.....	15.0
Cod liver oil.....	9.0
Wheat germ.....	10.0
Osborne and Mendel salt mixture.....	4.0
Dried yeast.....	4.0
Agar-agar.....	2.0

This contains 17.8 per cent protein, 24.9 per cent fat, and 42.2 per cent carbohydrate.

TABLE I.

No.	Control group.				Operated group.		
	Actual weight.		Weight of adrenal per 100 gm. body weight.		Actual weight.		Weight of adrenal per 100 gm. body weight.
	Left.	Right.	Left.	Right.	Removed.	Hyper-trophied.	Hyper-trophied.
	mg.	mg.	mg.	mg.	mg.	mg.	mg.
1	25	22	18.3	16.1	33-L.	40-R.	23.0
2	29	27	19.0	17.7	26-R.	29-L.	16.7
3	26	23	15.9	14.0	17-L.	52-R.	28.0
4	25	30	15.2	18.3	29-R.	41-L.	22.9
5	27	35	15.9	20.6	30-L.	39-R.	24.4
6	26	27	15.0	15.6	35-R.	50-L.	30.9
7	19	18	9.6	9.1	18-L.	41-R.	23.2
8	27	20	17.5	13.0	19-R.	38-L.	25.2
9	18	23	11.4	14.5	24-L.	37-R.	23.3
10	24	15	15.4	9.6	23-R.	48-L.	29.1
11	17	28	10.9	18.0	24-L.	36-R.	22.0
12	32	17	18.1	9.6	25-R.	32-L.	17.6
13	23	15	15.8	10.3	28-L.	32-R.	16.5
14	42	19	26.9	12.2	35-R.	44-L.	24.7
15	19	23	12.2	14.7	20-L.	45-R.	23.1
16	21	19	14.8	13.4	25-R.	46-L.	22.9
17	24	19	16.2	12.8	19-L.	43-R.	22.6
18	19	25	11.9	15.6	30-R.	43-L.	25.7
19	26	23	16.6	14.7	29-L.	40-R.	23.8
20	26	18	15.9	11.0	23-R.	38-L.	19.3
21	24	31	13.5	17.4	19-L.	42-R.	24.6
22	30	35	17.0	19.8	29-R.	33-L.	20.4
23	26	27	16.8	17.3	22-L.	39-R.	22.7
24	28	20	17.9	12.8	25-R.	31-L.	17.8
25	27	29	12.3	13.2	26-L.	36-R.	21.4
26	29	32	16.4	18.1	30-R.	39-L.	21.1
27					21-L.	35-R.	20.6
Average . .	25.3	23.8	15.6	14.6	25.3	39.6	22.7
	24.6		15.1				
					Control group.	Operated group.	
	Standard deviation				5.44	5.48	
	Probable error of the average				0.51	0.71	
	Coefficient of variability				22.09	13.84	

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The stimulus to compensatory hypertrophy was given by the removal of one adrenal from each rat of the operated group. This was done 14 days after the start of the experiment; that is, when each rat was exactly 90 days old. At this age it has been shown (7) that the histological structure and the volume relations of the adrenal cortex and medulla have reached the adult condition. In the control group one adrenal was exposed. In both groups alternate glands were chosen on each successive rat for either exposure or removal under ether anesthesia. After removal each gland was freed of any adherent tissue or fat, with the aid of fine eye forceps, and the glands removed were weighed immediately on a torsion² balance to within 0.5 mg. They were then fixed in 10 per cent neutral formalin.

40 days was arbitrarily chosen as the period of time in which to determine the ability of the adrenal gland to undergo compensatory hypertrophy. At the end of this period all of the animals of both groups were killed with ether, quickly opened, and the adrenals removed and carefully weighed as before. In the case of the rat adrenal volume changes have been found comparable (8) to results expressed by weight.

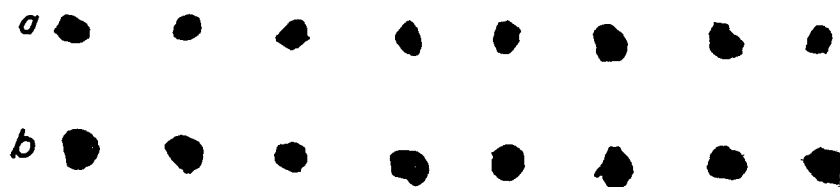


FIG. 2. Gross appearance of adrenals selected at random from each group. (a) Normal adrenals from control group. (b) Hypertrophied adrenals from operated group.

RESULTS.

The results are given in Table I. These give indisputable evidence of adrenal hypertrophy following unilateral adrenalectomy, either of the cortex, medulla, or the whole gland. This is shown visually in Fig. 2. The actual difference between the averages of the adrenal weights of the control and operated groups is 15.0 mg., while the probable difference of the averages determined by the usual method is only 0.88 mg. The degree of compensatory hypertrophy, that is the difference between the average value of the single control adrenals and the average value of the hypertrophied adrenals, is expressed as the percentage of the average value of the single control adrenals. In this experiment, 40 days after the removal of one adrenal, the

² Hartmann-Braun torsion balance of 500 mg. capacity.

compensatory hypertrophy of the other gland amounted to 61 per cent. Since the average body weights of the control and operated groups were practically alike (Fig. 1) the results in Table I determined from actual weights and adrenal weight in relation to body weight are essentially the same. Actual weights only are therefore considered here.

A comparison of the average value of the adrenal weights of the control group with that of the adrenals removed from the operated group at 90 days of age makes it evident that little if any growth of the glands of the control group took place during the course of the experiment. From Donaldson's table (9) an average adrenal weight increase of 8 mg. might be expected during this 40 day period. Even though this growth had taken place a large degree of hypertrophy

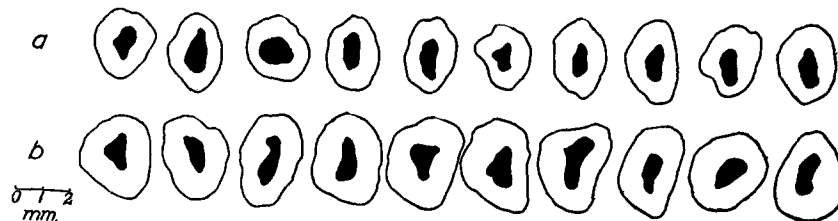


FIG. 3. Camera lucida outlines of adrenal medulla and cortex. (a) Normal adrenals of control group. (b) Hypertrophied adrenals of operated group.

would still exist. In order to obviate the necessity of considering the right and left glands separately alternate glands were used for exposure in the control group and removal in the operated group. This was not absolutely necessary for no difference has been found between the right and left adrenals of the control group. The probable difference of the average weights of the two sides is 0.97 mg. and the actual difference is only 1.50 mg.

The only compensatory adrenal hypertrophy which has been found in the rat, that of accessory adrenals following total adrenalectomy (4, 5), consisted of an increase in cortical tissue. In our experiment likewise the hypertrophy was limited to the cortex. Ten unselected glands from each group were available for histological examination. Fig. 3 shows camera lucida outlines of the medulla and cortex of central sections of all twenty glands as determined by serial section.

The area of the whole section and of the medulla was determined in each case and then, treating these as center sections of spheres, the average volume of cortex and of medulla was determined for the ten glands of each group. The results form Table II. The relative volume of cortex and medulla, that is cortex 93 per cent and medulla 7 per cent, as determined from the average figures for the control group agree very well with similar figures of other observers determined by accurate reconstruction methods. In adrenals of female rats of the same age Jackson (7) found that the cortex comprised

TABLE II.
Cortex and Medulla Volumes in C. Mm. of Ten Adrenals from Each Group Calculated from the Area of the Central Section of Each Gland Treated as the Midplane of a Sphere.

	Control group.			Hypertrophied group.		
	Total gland.	Medulla.	Cortex.	Total gland.	Medulla.	Cortex.
Average.....	5.99	0.42	5.58	11.15	0.46	10.69
Standard deviation.....	0.74	0.11	0.69	1.37	0.10	1.32
Probable error of average.....	0.16	0.02	0.15	0.29	0.02	0.28
Coefficient of variability.....	12.50	26.20	12.36	12.29	21.73	12.34
		Whole gland.	Medulla.	Cortex.		
Actual difference of the averages.....		5.16	0.04	5.11		
Probable difference of the averages.....		0.33	0.03	0.32		
Per cent compensatory hypertrophy.....		86.0	0.0	91.0		

about 93 per cent and the medulla 7 per cent of the total gland volume. Another investigator (8) found 93.5 and 6.5 per cent respectively.

It is evident from Table II that the hypertrophy is limited to the cortex as there is no appreciable difference in the medulla volumes of the control and hypertrophied glands. When considered as hypertrophy of the entire gland the increase in tissue as we have already shown amounted to 61 per cent. This is due to a 91 per cent hypertrophy of the cortex. The irregular form of the adrenals lends a large degree of inaccuracy to this method of determining the region of hypertrophy. However, further evidence of the limitation of hypertrophy to the cortex is offered in cell measurements to follow.

It is conceivable that the increase in adrenal cortex is a result not of hypertrophy but of stimulated growth. In this case an increase in the number and not in the size of cells would be expected. Measurements of cell areas have been made in sections of normal and hypertrophied glands. Areas of every twentieth 6 micron section from ten adrenals of each group were counted. The number of nuclei in two areas 0.01 mm. square were determined in three parts of each section. The cells comprising the various cortical layers differ greatly in size. The zona glomerulosa is very narrow and no measurements were made of these cells. The cells of the zona fasciculata

TABLE III.

Average Number of Nuclei in 0.01 Sq. Mm. of a 6 Micron Section Determined from Measurements of Every Twentieth Section of Ten Glands from Each Group.

Area of gland.....	Control group.			Hypertrophied group.		
	Cortex— zona fascicu- lata.	Cortex— zona reticu- laris.	Medulla.	Cortex— zona fascicu- lata.	Cortex— zona reticu- laris.	Medulla.
No. of areas counted.....	75	52	39	108	66	41
Average number of cells.....	124	330	144	63	202	145
Standard deviation.....	26.44	50.89	30.59	20.03	75.02	31.85
Probable error of the average.....	2.06	4.76	3.30	1.30	6.23	3.36
Coefficient of variability.....	21.32	15.42	21.23	31.80	37.13	21.97
		Cortex—zona fasciculata.	Cortex—zona reticularis.			Medulla.
Actual difference of the averages.....		61.00	128.00			1.00
Probable “ “ “ “		2.44	7.84			4.71

are normally larger and more variable in size than those of the zona reticularis adjoining the medulla and are considered separately. Two areas each were taken of the middle cortical zone, of the cortex adjoining the medulla, and of the medulla cells. The results in Table III show a definite increase in the size of the cortical cells, or at least a decrease in the number of nuclei per unit volume, and evidence of cortical hypertrophy which is not accelerated growth.

It is of great interest that no increase in the size of the medulla or its cells was found. No hypotheses are offered here relative to the failure of the medulla to hypertrophy as we propose carrying out further experiments in an endeavor to explain this finding.

SUMMARY.

1. Removal of one adrenal in the albino rat is followed by hypertrophy of the remaining gland. In the case of female rats 90 days of age this compensatory hypertrophy amounted to 61 per cent.

2. The increase in size of the whole gland is due entirely to hypertrophy of the cortex. This increase in cortical tissue amounted to approximately 91 per cent and was due in large part if not entirely to an increase in the size of the cells.

3. No increase in the size of the medulla or its cells was found.

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