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Some Experimental Evidence of Production of Adrenotrophin by the Fetal Hypophysis.*

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The relatively enormous size of the suprarenals in the human fetus raises the question as to whether the growth of these structures is normally governed in part by the action of adrenotrophin. Assuming that there might be more than one source of the adrenotrophin of pregnancy, it still remains to be shown whether the fetal hypophysis is a source. Accordingly, it was decided to approach the problem through experiments in rats.

Fifteen accurately timed fetuses with placental circulation intact were given a series of subcutaneous injections¹ of adrenotrophin† (Group A), 23 were deprived of the hypophysis by decapitation² (Group B) and 6 were subjected to both treatments (Group C). Near term they were taken by Caesarian section, weighed and autopsied. After each partially eviscerated body had been fixed in Bouin's solution, the lumbar region with the adrenals *in situ* was serially sectioned, and the sections stained either with hematoxylin and eosin or by the method of Dominici. Sections through adrenals of experimental fetuses were compared with those of controls by means of a microcomparator attached to two microscopes placed side by side. Thereafter, in each case, the volume of one adrenal was determined from the serial sections, using the paper-weight method, and the relative volume was calculated as follows:

$$\text{Rel. vol. adr.} = \frac{\frac{\text{Vol. adr. experimental fetus, mm}^3}{\text{Body wt experimental fetus, g}}}{\frac{\text{Vol. adr. littermate control, mm}^3}{\text{Body wt littermate control, g}}}$$

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¹ Wells, L. J., *Anat. Rec.*, 1946, **94**, 530.

The fetuses of Group A received a total of 0.05 to 0.8 mg of hormone, in 1 to 5 individual injections made about 12 hours apart, and were killed 14 to 54 hours after the initial injection. The relative volume of the adrenal was 1.08 to 3.36, the median being 2.34. Especially in those fetuses that received the larger doses, the cortical cells were exceedingly hypertrophic. The nuclei were significantly larger than in the controls, and the cytoplasm showed such increased granulation and vacuolation that it looked like fine foam. The outer zone of the adrenal, that of cellular proliferation and metamorphosis, showed many mitoses but was thin, giving the impression of having been rapidly "used up."

Fetuses of Group B, after having been deprived of the hypophysis, were either left inside the uterus or transferred to the maternal abdominal cavity, and were killed 47 to 102 hours later. In the 9 cases uncomplicated by any knowingly introduced variable,† the relative volume of the adrenal, in terms of headless body weight of controls, was 0.39 to 0.80 (median, 0.60). The adrenal cortex was abnormally thin and failed to show the usual pattern of sinusoids and cellular cords, the cells being more tightly packed and much smaller than those of controls. Nuclei were abnormally small and the cytoplasm gave the impression of having been "washed out." The outer proliferative zone was relatively thick

† Generously supplied by the Armour Research Laboratories, Chicago (their Sample No. 32-D).

² Wells, L. J., *Anat. Rec.*, 1947, **97**, 409.

‡ In the other 14 cases, all complicated by the fact that a littermate had received injections of adrenotrophin or of gonadotrophin (Upjohn's Gonadogen), the volumetric data were less consistent; thus in these cases it is necessary to consider the possibility that some injected hormone had actually crossed the placental barrier.

but quite condensed and its occasional mitotic figures were usually abortive.

The fetuses of Group C were operated and then given 0.25 to 0.5 mg adrenotrophin, in 4 to 5 divided doses, and were killed 49 to 54 hours after the first injection. Microscopically, the adrenal cortex resembled that of the fetuses of Group A. The relative volume of the adrenal, using operated littermates as controls, was 1.01 to 3.21, the theoretical median being 2.35. Also, the adrenals were much larger than those of normal littermates of the same sex (relative volume, up to 2.29).

In considering all aspects of the study, the

data show that injected hypophyseal adrenotrophin causes the fetal adrenal to grow more rapidly than in controls. They suggest that removal of the fetal head (hypophysis) inhibits growth of the adrenal and causes abnormal changes in the cortical cells. They indicate that this inhibition and these changes may be prevented by giving a series of injections of adrenotrophin.

In conclusion, these observations may be taken as experimental evidence of the production of adrenotrophin by the hypophysis of the fetal rat.

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Effect of Sulfamethazine on the Testes and Accessory Glands of Normal and Hypophysectomized Rats.

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Asplin and Boyland¹ have reported that chronic administration of sulfamethazine (4,6-dimethyl-2-sulfanilamidopyrimidine) causes a hyperplasia and increase in the weight of the testes and some increase of weight of the seminal vesicles and prostate in male rats receiving the drug from birth to a weight of about 50 g. In older males an increase in weight of only the seminal vesicles and the prostate was noted. They found that the drug had no effect on the seminal vesicles and prostate of castrated rats and postulated that sulfamethazine causes hyperplasia of the seminal vesicles and the prostate by stimulation of the testes.

Since the accessory glands of male rats are normally maintained and stimulated by androgen secreted by the interstitial tissue of the testes under the influence of the anterior pituitary gland, it seemed of interest to investigate whether the effects reported by Asplin and Boyland in young rats could be

secondary to the stimulating effect of the drug on the anterior pituitary gland. If that were the case, the ablation of the anterior pituitary gland would nullify the reported hypertrophy of the seminal vesicles and prostate in rats receiving sulfamethazine.

Experimental. Forty-one immature rats of weaning age (21-day old) of the same inbred stock were divided into 2 groups of 20 and 21 each. The hypophysis of the rats in the first group* was removed by the parapharyngeal approach according to the technic of Smith.² Half of the rats in both the hypophysectomized and the unoperated groups was placed on a stock laboratory diet. The other half of each group was fed on a similar diet to which 0.2% by weight of sulfamethazine† was added. The rats were weighed at the beginning of the ex-

* Four rats in this group died within one week after hypophysectomy.

² Smith, P. E., *Am. J. Anat.*, 1930, **45**, 205.

¹ Asplin, F. D., and Boyland, E., *Brit. J. Pharm. and Chemother.*, 1947, **2**, 79.

† Sulfamethazine was kindly furnished by Mr. W. A. Lott of the Squibb Institute for Medical Research.