

**Effect of Pituitary Substances on Adrenalectomized Rats.**

C. J. CAVANAUGH AND ROBERT GAUNT.

*From the Department of Biology, Washington Square College, New York University.*

It has been shown that either the condition of pseudopregnancy or the administration of anterior pituitary substances will in certain instances extend the lives of adrenalectomized animals.<sup>1,2,3</sup> Among those who have used pituitary implants and extracts in adrenalectomized rats only Emery and Schwabe have found a life-sparing effect. In earlier experiments we gave large daily doses of various pituitary extracts, and of beef and rat pituitary implants (one to 2 rat pituitaries per day and similar or larger volumes of beef pituitary tissue), to partially and completely adrenalectomized rats in attempts to stimulate adrenal accessory tissue. This treatment failed to increase the percent of adrenal accessories, distinguishable by gross or histological observation, and also failed to ameliorate the symptoms of adrenal insufficiency. The substances administered were on the contrary somewhat toxic to adrenalectomized animals.

In the meantime Emery and Schwabe showed that homo-implants in smaller doses (one pituitary per week) would extend life markedly in female salt-treated adrenalectomized rats. We have confirmed their findings, using for treated and control animals the low salt diet of Weiser and Norris,<sup>4</sup> a diet which makes the test considerably more exacting and which has the advantage of reducing somewhat the variability in life span of adrenalectomized rats.

Adrenalectomy was performed in female rats at approximately 30 days of age. Three intramuscular implants of a whole male rat pituitary each were given in a 5-day period before adrenalectomy. Two rat pituitary implants per week were given after adrenalectomy. In all experiments litters were divided and the survival of treated animals compared to that of untreated littermate controls. Animals given implants lived twice as long as controls and during the period of their survival showed considerable weight increment (Table I). Death eventually ensued in nearly all cases despite the continuance

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<sup>1</sup> Rogoff, J. M., and Stewart, G. N., *Am. J. Physiol.*, 1928, **96**, 20.

<sup>2</sup> Swingle, W. W., Parkins, W. M., Taylor, A. R., Hays, H. W., and Morrell, J. A., *Am. J. Physiol.*, 1937, **119**, 675.

<sup>3</sup> Emery, F. E., and Schwabe, E. L., *Endocrinology*, 1936, **20**, 550.

<sup>4</sup> Weiser, R. S., and Norris, E. R., *Endocrinology*, 1936, **20**, 556.

of treatment, a fact which suggests that the value of the therapy did not lie in its stimulation of accessory cortical tissue. The treatment was non-effective under sub-optimal living conditions as demonstrated in 35 cases subjected to a low and fluctuating temperature soon after operation (due to loss of the thermostatic control of the animal room) in which both treated and control animals showed an average survival of 6 days. The replacement value of the therapy is therefore not complete.

TABLE I.  
Survival of Adrenalectomized Female Rats Receiving Pituitary Implants.

| No. of Animals | Treatment               | Aver. Survival, days | Range, days | No. living indefinitely | Aver. wgt. diff. between operation and death<br>gm. |
|----------------|-------------------------|----------------------|-------------|-------------------------|---|
| 36             | Male pituitary implants | 18.0                 | 6-30        | 2                       | +12   |
| 37             | None                    | 9.7                  | 6-15        | 1                       | - 1   |

Negative results have been obtained with the following materials\*: 1, beef anterior lobe implants given bi-weekly in amounts approximately the same as the effective doses of rat pituitary tissue (27 cases); 2, daily doses of pregnancy urine extracts (Follutein or Antuitrin-S) in amounts varying from 15 to 50 R.U. per day (44 cases); 3, anterior pituitary extract (Squibb), found effective in cats,<sup>2</sup> in doses of 0.5-0.75 cc. per day (10 cases); 4, progesterone in doses of 0.15 I.U. per day, preceded in part of the cases before operation by estrogenic or pregnancy urine extracts (15 cases). The importance of dosage and optimal mode of administration is such, however, as seen in the rat implant results, that the negative findings above cannot be considered final.

Many workers have reported previously the non-beneficial effects of estrogens in adrenalectomized animals.<sup>2, 3, 5, 6</sup> In our experience the estrogens were distinctly toxic. A series of 17 adrenalectomized rats given a normal diet lived for an average of 7.9 days while receiving 25-50 R.U. of Progynon-B daily, whereas untreated controls lived for an average of 14.7 days. Somewhat similar results have

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<sup>5</sup> Martin, S. J., *Am. J. Physiol.*, 1932, **100**, 180.

<sup>6</sup> Grollman, A., *The Adrenals*, Williams and Wilkins Co., Baltimore, 1936, p. 148.

been observed by Schacher, *et al.*,<sup>7</sup> and Nelson<sup>8</sup> has found estrin toxic in hypophysectomized male rats.

Large doses of pituitary implants are therefore perhaps toxic rather than life-sustaining because of the high estrogen production induced. In any case the beneficial effect of pituitary therapy is not because of its estrin stimulating effects. Emery and Schwabe's interpretation that pituitary stimulation was effective because of its luteinizing effect was satisfactory for their data and for most of ours on the rat, but the non-effect of progesterone and pregnancy urine extract administration as seen here and in work on dogs,<sup>2</sup> and the effectiveness of pituitary extracts in castrate and male cats,<sup>2</sup> point to the inadequacy of this explanation for all conditions in various species.

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### Comparison of Pituitary Gonadotropic Extract and Prolan on Ovarian and Uterine Response in Immature Rats.

S. K. CHOU AND S. H. LIU.

*From the Department of Medicine, Peiping Union Medical College, Peiping, China.*

Aschheim and Zondek<sup>1</sup> emphasized the similarity of prolan to anterior pituitary implants or extract in its effects on the genital tract of immature mammals. Later work of other authors demonstrated several important differences, which have been summarized in recent reviews.<sup>2, 3</sup> Evans and Simpson<sup>4</sup> and Evans, Meyer, and Simpson<sup>5</sup> observed that prolan, in contrast to anterior pituitary extract, did not cause increasing ovarian hypertrophy with markedly increasing dosage. Similar observations were reported on placental extract by Collip, *et al.*,<sup>6</sup> and on extract from blood of pregnant

<sup>7</sup> Schacher, J., Browne, J. S. L., and Selye, H., *PROC. SOC. EXP. BIOL. AND MED.*, 1937, **36**, 488.

<sup>8</sup> Nelson, W. O., *Cold Spring Harbor Symp. Quant. Biol.*, 1937, **5**. In press.

<sup>1</sup> Aschheim, S., and Zondek, B., *Klin. Wschr.*, 1927, **6**, 1322.

<sup>2</sup> Evans, H. M., *J. A. M. A.*, 1935, **104**, 464.

<sup>3</sup> van Dyke, H. B., *The Physiology and Pharmacology of the Pituitary Body*, Chicago, 1936.

<sup>4</sup> Evans, H. M., and Simpson, M. E., *Am. J. Physiol.*, 1929, **89**, 381.

<sup>5</sup> Evans, H. M., Meyer, K., and Simpson, M. E., *Am. J. Physiol.*, 1932, **100**, 141.

<sup>6</sup> Collip, J. B., Thomson, D. L., McPhail, M. K., and Williamson, J. E., *Canad. M. A. J.*, 1931, **24**, 201.