

Denny-Brown,⁹ Hinsey,¹⁰ Hines and Knowlton,¹¹ Tower,¹² and many others.

Summary. Starvation of the albino rat is fatal within 8 to 15 days and produces a structural detachment of about 20% of the motor nerves in skeletal muscle, morphologically manifested by: (1) progressive retraction and eventual uprooting of the hypolemmal end plate from within the atrophic muscle fiber and loss of the granular sole plate of Kühne, and (2) enormous distention of the epilemmal axons which stain very intensely with gold chloride.

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Age Factor in Responsiveness of Pituitary and Adrenals to Folliculoids.

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Several early investigators reported hypophyseal and adrenal enlargement following treatment with impure folliculoid preparations and Hohlweg¹ showed for the pituitary and Selye, *et al.*,² for both pituitary and adrenals that even crystalline estrone elicits these effects in the rat. Selye, *et al.*,² expressed the view that the adrenal enlargement is due to an increased secretion of the corticotropic hormone of the pituitary since it could not be obtained after hypophysectomy. Adrenocortical enlargement is a characteristic symptom of the alarm reaction and hence can be elicited by any nonspecific damaging agent. Histologically the cortical enlargement caused by folliculoids resembles that which appears during the alarm reaction,³ yet it can hardly be regarded merely as a response to nonspecific damage as it is elicited by comparatively small doses of folliculoids which are not very damaging.

The observation that folliculoids enlarge the hypophysis and ad-

⁹ Denny-Brown, D., *Proc. Roy. Soc. B*, 1929, **104**, 371.

¹⁰ Hinsey, J. C., *Physiol. Rev.*, 1934, **14**, 514.

¹¹ Hines, H. M., and Knowlton, G. C., *J. Physiol.*, 1939, **128**, 97.

¹² Tower, S. S., *Physiol. Rev.*, 1939, **19**, 1; *Arch. Neurol. Psychiat.*, 1939, **42**, 219; *J. Neurophysiol.*, 1941, **4**, 398.

¹ Hohlweg, W., *Klin. Wschr.*, 1934, **13**, 92.

² Selye, H., Collip, J. B., and Thomson, D. L., *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 1377.

³ Selye, H., Harlow, C. M., and Collip, J. B., *Endokrinologie*, 1936, **18**, 81.

renal cortex has repeatedly been described.^{4, 5, 6} The following experiment confirms this fact and shows the intensity of the changes produced in this manner. Twelve male albino rats weighing 105-130 g were castrated and immediately afterwards 6 of them were injected subcutaneously once daily with 200 γ of estradiol in 0.1 cc of peanut oil while the remaining 6 acted as controls. After 20 days of treatment all animals were sacrificed and their adrenals and pituitaries weighed after fixation in "Susa" solution. The adrenals in the controls averaged 36 mg (range: 31-41 mg) and the pituitaries 8.4 mg (range: 7.5-8.8 mg). In the estradiol injected group the adrenals weighed 54 mg (range: 51-66 mg) and the pituitaries 15.9 mg (range: 14.8-16.9 mg). Both the enlargement of the adrenals and that of the pituitaries proved statistically highly significant ($P < 0.01$).

Since this type of response is invariably observed in adult rats, we were surprised to note that in a recent experimental series, in which immature rats were used, even very high doses of estradiol failed to cause pituitary or adrenal enlargement, indeed, they appeared to induce adrenal involution. Perusal of the literature indicates that only Clausen and Freudenberger⁷ obtained a similar inverse response to folliculoids. They made no comment upon this finding, which was in apparent contradiction to all previously observed facts, but their protocols indicate that they also used immature animals. We felt that the age factor may be of great importance in determining the reaction of the hypophysis and adrenals to folliculoids since this factor proved to play a prominent rôle in other hormone-conditioned reactions, *c. g.*, the response of the ovaries to gonadotropic hormones,⁸ the response of the uterus to testosterone,^{9, 10} and the response of the male accessory sex organs to testoid compounds.¹¹

Ten immature male albino rats weighing 40-60 g were gonadectomized. Five of them received 1 mg of α -estradiol in 0.1 cc of peanut oil subcutaneously bidaily on 10 consecutive days. The remaining 5 animals acted as controls, receiving only 0.1 cc of peanut oil subcutaneously bidaily given during the same period. On the

⁴ Ellison, E. T., and Burch, J. C., *Endocrinology*, 1936, **20**, 746.

⁵ Diaz, J. T., Phelps, D., Ellison, E. T., and Burch, J., *Am. J. Physiol.*, 1938, **121**, 794.

⁶ Albert, S., *Endocrinology*, 1942, **30**, 454.

⁷ Clausen, F. W., and Freudenberger, C. B., *Endocrinology*, 1939, **25**, 585.

⁸ Selye, H., and Collip, J. B., *Proc. Soc. Exp. Biol. and Med.*, 1933, **30**, 647.

⁹ Selye, H., *Anat. Record*, 1940, **76**, 145.

¹⁰ Selye, H., *Endocrinology*, 1940, **27**, 657.

¹¹ Selye, H., and Albert, S., *Proc. Soc. Exp. Biol. and Med.*, 1942, **49**, 361.

11th day all animals were killed and their adrenals and pituitaries weighed after fixation in "Susa" solution. The adrenals in the controls weighed 22 mg on the average (range: 18-25 mg) and the pituitaries 5 mg (range: 4-6 mg). In the estradiol-injected group the adrenals weighed 16 mg (range: 15-19 mg) and the pituitaries 4 mg (range: 3-5 mg). While the decrease in the size of the adrenals proved statistically significant ($P < 0.01$) the apparent decrease in pituitary weight was not statistically significant ($P = 0.1$). Histologically the decrease in adrenal weight proved to be due to atrophy of the cortical cells. A repetition of this experiment under similar experimental conditions, but adding 2 groups of mature animals, one control, one estradiol-treated, yielded essentially similar results for the immature males, namely, a statistically highly significant ($P < 0.01$) adrenal involution without any significant change in pituitary weight. In the adults, on the other hand, estradiol elicited the usual statistically significant adrenal and pituitary enlargement. It appears that the responsiveness to folliculoid compounds is fundamentally different in immature and adult animals. Even such enormous doses as 2 mg of estradiol daily fail to cause adrenal or pituitary enlargement in the prepubertal rat while in the adult they always cause hypertrophy of these organs. This difference in responsiveness is not dependent upon the presence of an immature or mature gonad as it is demonstrable even in castrates.

Summary. Unlike in the adult animal, estradiol in high doses causes no pituitary or adrenal cortical hypertrophy in the immature rat, in fact it tends to decrease the size of these organs. This difference in hormone responsiveness is not due to the presence of a mature or immature gonad respectively since it is demonstrable even in castrates.

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