

40% in rabbits after total removal of the thyroid and both adrenal glands.

Conclusion. White rats given large or small quantities of thallium over periods up to 9 weeks in length showed no abnormality of the estrual cycle or of the reproductive organs. The basal metabolic rate of guinea pigs did not change during administration of small or large doses of thallium, except for a rapid decrease shortly preceding death. These findings fail to support previous claims that thallium intoxication is characterized by alteration of endocrine function.

7805 C

Hemorrhagic Changes in Suprarenal Cortex of Adult Rats Following Pituitarectomy.

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Smith and many other investigators have demonstrated that removal of the pituitary gland in tadpoles and rats is followed by atrophy of the suprarenal cortex,¹⁻⁸ as well as atrophy of the gonads, thyroid and parathyroid. Similar changes have been described in the rabbit^{9, 10} and dog.^{11*} In humans, in conditions associated with hypofunction of the pituitary and in Simmond's disease the adrenal

¹ Smith, P. E., *Am. Anat. Mem.*, 1920, **11**, 151.

² Atwell, W. J., *Proc. Soc. Exp. Biol. and Med.*, 1932, **29**, 621.

³ Smith, P. E., *Anat. Rec.*, 1926, **32**, 221.

⁴ Smith, P. E., *J. Am. Med. Assn.*, 1927, **88**, 158.

⁵ Smith, P. E., *Am. J. Anat.*, 1930, **45**, 205.

⁶ Richter, C. P., and Wislocki, G. B., *Am. J. Physiol.*, 1930, **95**, 481.

⁷ Evans, H. K., Meyer, M. E., Simpson, *et al.*, *Mem. Univ. Cal.*, 1933, **2**.

⁸ Collip, J. B., Selye, H., and Thompson, D., *Nature*, 1933, **131**, 56.

⁹ Ikeda, M., *Jap. J. Obst. and Gynecol.*, 1932, **15**, 213.

¹⁰ Kusonoki, J., *Folio Endocrinol.*, Japan, 1927, **3**, 34.

¹¹ Houssay, B. A., and Sammartino, R., *Compt. rend. Soc. de Biol.*, 1933, **114**, 717.

* The atrophy of the suprarenal cortex in pituitarectomized rats may be repaired by daily homotransplants of pituitary gland,⁵ by injection of potent extracts of growth hormone,⁷ or by the adrenotropic hormone.¹⁶ The administration of cortin in pituitarectomized rats does not prevent or repair this atrophy of the cortex.¹⁷

¹⁶ Anderson, E. M., Thomson, D. L., and Collip, J. B., *Lancet*, 1933, **225**, 347.

¹⁷ Shumacker, H. B., and Firor, W. M., *Endocrin.*, 1934, **18**, 676.

glands are atrophic.¹²⁻¹⁵ The regressive changes in the suprarenal glands of immature rats are noted as early as the 7th day, are pronounced by the 15th day and reach their maximum by the 30th day, though the cortex may continue to decrease in size after this (Smith⁵).

In studies on the relation of the pituitary gland to resistance¹⁸ in adult rats, we noted the early changes preceding this involutinal atrophy of the suprarenal cortex.

Method. The rats were adults, 3 to 4 months old, of a uniform stock raised in our laboratory. The observations were made on 20 pituitarectomized rats that died spontaneously in the course of other experiments within 4 to 10 days after operation. Control observations were made on 15 rats in which large fragments of anterior lobe remained and on 20 operated controls. In a second group, 10 rats were pituitarectomized and 2 rats were killed on the 4th, 5th, 6th, 7th, and 9th day after operation. The suprarenals were immediately removed and fixed in Bouin's fluid.

Results. From 4 to 10 days after pituitarectomy the suprarenal gland showed striking changes. Hemorrhages appeared in the reticular zone of the cortex. Marked engorgement of the capillaries was noted and the cells showed evidence of vacuolization and cloudy swelling. The nuclei were often vacuolated. In other instances in which the hemorrhage was less prominent or absent the cells appeared shrunken and the cytoplasm diminished in amount. In many instances large macrophages filled with iron pigment were observed in the interstitial tissue of reticular zone and between the cortex and medulla. When sections were stained by the Turnbull method a broad blue zone of iron pigment was seen in the inner layers of the cortex. The hemorrhagic changes were observed as early as the 3rd day and as late as the 21st day after operation but apparently occur with greatest frequency about 7 to 9 days after pituitarectomy. It is probable that the hemorrhagic changes in the suprarenal cortex precede actual shrinkage and atrophy of the cells of the cortex. The presence of cortical hemorrhages was noted in rats that showed no evidence of infection and in which no other procedure had been done.

The daily administration subcutaneously of a crude saline emulsion of fresh anterior lobes of ox pituitary during a period of 2

¹² Falta, W., *Die Erkrankungen der Blutdrüsen*, Springer, Berlin, 1913.

¹³ Cushing, H., and Davidoff, L. M., *Monograph, Rockefeller Inst.*, 1927, **22**, 1.

¹⁴ Simmonds, M., *Deutsche med. Wchnschr.*, 1919, **45**, 487.

¹⁵ Erdheim, J., *Beitrage z. path. Anat. u. z. allg. Path.*, 1916, **62**, 302.

¹⁸ Perla, D., in press.

weeks prior to pituitarectomy caused marked enlargement of the suprarenal glands (as well as increasing the size of the thyroid and gonads, and the rate of growth). After operation the hemorrhagic changes were definitely delayed.

These observations are of significance in the interpretation of the spontaneous involution of the suprarenal cortex which occurs during the first month of life in human beings. The extraordinary degenerative changes which take place in the suprarenal cortex of infants soon after birth were described by Thomas,¹⁹ Elliott and Armour,²⁰ Kern,²¹ Landau,²² and in great detail by Lewis and Pappenheimer.²³ These observers noted that during the latter half of pregnancy the suprarenal is unusually large. This enlargement is due to a hypertrophy of the cortex. Shortly after birth (during the second week of extra-uterine life) according to Lewis and Pappenheimer a massive degeneration of the 2 inner layers of the cortex occurs, associated with more or less hemorrhage and fatty change of the cells. The degeneration is fully established by the end of the second week and during the next 5 weeks rapid removal of the broken down cells occurs, leaving a relatively thin glomerular layer that collapses on the medulla. Regeneration does not occur up to the third year.

The physiological significance of this degenerative involution was not clear. Marine, Lowe and Cibra noted that there is a rise in heat production in infants during the second week of life and this is associated with other signs of increased tissue activity. They believed that the rise in heat production beginning the second week of life may be related to the normal destruction of the reticular layer of the suprarenal cortex. With the newer knowledge of the interrelation of the pituitary and suprarenal glands, it would appear as Marine²⁴ suggests, that the suprarenal involution in infants was due to the sudden withdrawal of the maternal source of adrenotropic substance at birth. It is striking that the involution of the suprarenal following pituitarectomy in adult rats is preceded by hemorrhagic changes within one week of operation, analogous to those observed 8 days after birth in humans. It is obvious that the withdrawal of the adrenotropic hormone of the pituitary is responsible for the changes in the rat.

¹⁹ Thomas, E., *Ziegler's Beitr.*, 1911, **50**, 283.

²⁰ Elliott, T., and Armour, R., *J. Path. and Bact.*, 1911, **15**, 481.

²¹ Kern, H., *Deutsch. med. Wchschr.*, 1911, **37**, 981.

²² Landau, M., *Die Nebennierenrinde*, Jena, 1915, G. Fischer.

²³ Lewis, R. W., and Pappenheimer, A. M., *J. Med. Res.*, 1916, **34**, 81.

²⁴ Marine, D., *J. Am. Med. Assn.*, 1935, in press.

Summary. Within the first 2 weeks following pituitarectomy in adult albino rats hemorrhagic changes are observed in the cortex of the suprarenal which precede the atrophy of the gland. The similarity to the changes observed soon after birth in humans is pointed out.

By inference this observation tends to strengthen the hypothesis that the severe hemorrhagic involucional changes noted in early extra-uterine life may be due to the withdrawal of the maternal adrenotropic hormone of the anterior lobe.

7806 P

Enzymatic Efficiency in Malignancy.*

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Recently we have begun a detailed investigation of enzymatic efficiency of avitaminosis.¹ Being at the same time engaged in a problem on the relationship of vitamin therapy to regression of tumors in the albino rat, we had access to considerable numbers of tumor-bearing animals and had available the necessary materials and equipment to study the enzymatic efficiency of malignancy.

We found our Wistar stock of animals rather resistant to the Flexner-Jobling carcinoma; consequently, the greater portion of our work was done on animals receiving another type of transplantable tumor, in which we had from 60 to 85% takes, provided the tumor used for implantation was not too necrotic. The tumor used was furnished by Dr. Francis Carter Wood of New York City, which was designated as Walker Carcino-Sarcoma No. 256.

The experiments were conducted in pairs, and for every animal with an implanted tumor, a litter-mate control of the same sex was used, which was restricted to the same plane of nutrition as the tumor-bearing animal. The tumors were measured with a caliper in length and width, and in some cases in depth. Forty-two groups were studied in the case of most enzymes. The blood serum phos-

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¹ Sure, B., Kik, M. C., and Buchanan, K. S., *J. Biol. Chem.*, 1935, **108**, 11.