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The production of the adiposogenital syndrome in the rat, with preliminary notes upon the effects of a replacement therapy.

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The answer to the question whether the genital atrophy, skeletal undergrowth, and excessive adiposity of the adiposogenital syndrome are due to a pituitary deficiency or to an injury of the hypothalamus without pituitary involvement has rested heretofore upon observation made in two closely allied ways, (1) the extent of the injury inflicted as determined at the time of operation, (2) the extent of the injury as determined by autopsy and a study of sections. Both of these methods are open to the objection that the most careful study may fail to reveal the extent of damage done.

Another method is available for determining the significance of the pituitary and brain injury in the genesis of this syndrome, namely, that of a replacement therapy. If we have any confidence in the functional specificity of the endocrine glands, it follows that we must admit the significance of a pituitary impairment as the causative factor if the adiposogenital syndrome or any of its components can be corrected by pituitary administration. This point has been previously discussed (Smith and Smith) in connection with reports upon a replacement therapy in the hypophysectomized tadpole, in which it was shown that

the enlargement of the fat organ, and the pigmentary, growth, and endocrine disturbances which invariably follow hypophysectomy in the tadpole, can be corrected by pituitary administration. It is our intention to use this method to make an analysis of the part played by the pituitary in the adiposogenital syndrome of the mammal.

A considerable number of rats (seven) which display Frölich's syndrome together with several others which display an upset in the reproductive mechanism have been secured by a rather simple procedure. By removing one parietal bone together with a part of the caudal and ventral walls of the orbit a good view is secured of the stalk of the pituitary. A fine hypodermic needle is then inserted into the gland and 0.01 to 0.013 cc. of a 10 per cent chromic acid solution injected with a syringe fitted with an attachment by means of which amounts as small as 1/600 cc. can be accurately injected. The spread of the injected fluid through the gland appears to be aided by the rich vascular network, while injury to adjoining structures is hindered by the capsule.

An experiment upon one animal has been finished to date. This animal, a female, operated upon February 17, failed to show the usual sex cycles, although displaying no adiposity. On May 22 one ovary and a part of the corresponding horn of the uterus were removed for diagnosis. These structures were found to be much smaller than normal. The ovary contained no corpora and no follicles approaching maturity. There was considerable interstitial tissue. After allowing a few days for recovery from the operation a daily injection of anterior hypophysial substance by the method of Evans and Long was begun on May 28. Ovulation as revealed by the vaginal smears took place on June 10 and June 14, the usual four day cycle thus being displayed. Autopsy on June 17 revealed a normal sized ovary with many corpora and large follicles. The uterus had become normal in size. No pituitary could be distinguished with the binocular. A study of serial sections revealed the presence of apparently normal neural and intermediate lobes but no typical anterior lobe cells.

It thus seems clear that in this case we had caused the ovaries to become structurally atrophic and functionally inactive by injuring the pituitary body, and that a repair was effected by

the administration of anterior lobe substance, a result which it would seem removes in this case the possibility of a brain lesion being the causative factor except in so far as such a lesion might have directly contributed to the impairment of the hypophysis. This result we realize must be confirmed by other instances before generalizations can be ventured upon.

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The synthesis of hippuric acid by jaundiced animals.

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Experiments were carried out to determine the proportion of benzoic acid which dogs and rabbits whose common bile ducts had been ligated can conjugate with glycocoll to form hippuric acid. Two rabbits whose bile ducts had been ligated excreted only 40 per cent of the amount of hippuric acid which was synthesized by normal rabbits of the same weight, the remainder of the benzoic acid being eliminated uncombined. It was found that a normal dog which was maintained on a constant diet was able to conjugate 95 per cent of a dose of benzoic acid but after ligation of the bile duct the amount of hippuric acid which was synthesized dropped to about 60 per cent. A similar result was obtained with another jaundiced dog. The results are contrary to the work of Kühne,[1] who found no hippuric acid synthesized by a jaundiced dog, but are essentially in accord with those of Folwarczny[2] and others[3] who studied human cases, and the experiment of Lewis[4] on a rabbit. The results of this and other work on jaundice will be published in detail in the near future.

1 Kühne, W., *Virchow's Arch.*, 1858, xiv, 310.

2 Folwarczny, *Z. Kais. König. Gesellschaft der Aertzte zu Wien*, 1859, xv, 225.

3 Neukomm, J., *Klin. der Leberkrankh.*, 1861,ii, 537. Schultzen, *Dubois Arch.*, 1868, 719. Baumstark, F., *Ber. klin. Woch.*, 1873, xliii, 41. These references are quoted from C. von Noorden, "The Pathology of Metabolism," Chicago, 1907, 268.

4 Lewis, H. B., *J. Biol. Chem.*, 1921, xlvi, 73.