Antuitrin G. Six rats were injected subcutaneously with ¼ cc. per day. Blood sugars determined on the 3rd and 8th days were normal. The dose was then stepped up to ½ cc. Two days later the blood sugars were normal. Injections were continued but by the intraperitoneal route for 3 more days after which time the blood sugar level was still normal.

Theelin. Five rats were injected subcutaneously with ¼ cc. per day. The blood sugars were determined on the 3rd, 4th and 8th days. All were normal. The injections were continued, but with ½ cc. per day. Blood sugars determined on the 10th and 13th days were normal.

Growth Hormone, Squibb. Ten rats were given 1 cc. daily, subcutaneously, for 9 days. Blood sugars were determined on the 3rd and 4th days after the injections were discontinued. All were normal. Five rats injected subcutaneously, daily, with ¼ cc. showed no change in the blood sugar level on the 3rd and 8th days. On the 8th day the dose was increased to ½ cc. daily, but no changes were observed 2 and 5 days later.

The totally negative results were surprising. We endeavored in every case to give doses within the physiological range. In one case we deviated from the dosage used. Houssay and Biasotti[7] injected 10 cc. intraperitoneally into 200 gm. rats, a volume which we considered sufficient to distend the abdomen of the animal.

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Effect of Hypothyroidism on Antidiuretic Action of Pressor Principle of Posterior Pituitary.

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The effects of total ablation of the normal thyroid gland in man on the action of injected adrenalin and of insulin have been reported

previously.[1, 2] Studies of the effect of total thyroidectomy on the action of injected pressor principle of the posterior lobe of the pituitary are presented below. The antidiuretic effect, and blood pressure and heart rate following the subcutaneous injection of pitressin* have been studied. Several observations support the idea that the thyroid gland is a factor in maintaining water balance. Whether the antidiuretic action of pitressin is altered after thyroidectomy has not been established.

We have compared the effect of pitressin in postoperative hypothyroidism with its effect in subjects with normal thyroid function. Studies were made in 3 subjects with normal thyroid function, in 3 subjects with clinical and laboratory evidence of hypothyroidism which developed after total thyroidectomy, and in 1 additional subject both before operation and subsequently when hypothyroidism had developed. The elapsed time between operation and the pitressin studies varied from 1 to 9 months. Thyroidectomy in 2 of the 4 patients operated was performed for the relief of congestive heart failure, in the other 2 for angina pectoris, in accord with considerations outlined elsewhere by Blumgart and his associates.[3, 4] The basal metabolic rates of the 4 hypothyroid patients studied ranged between —19 and —36% and averaged —27%, clinical signs varying from those of mild hypothyroidism to rather marked myxedema were present. The antidiuretic effect of pitressin in each instance was evaluated by studying the urine output after a liter of water, both on a control day and on a day when pitressin was administered.[5]

The following regimen of study was utilized: at 7:00 A. M., the patient received a standard light breakfast with no coffee or added salt. At 9:00 A. M., with the patient in the recumbent position, blood pressure and heart rate measurements were made at 5-minute intervals until constant readings were obtained. The patient then emptied his bladder, and either 0.10 or 0.15 cc. of pitressin was administered subcutaneously, the site of injection being massaged. (On the control day pitressin was omitted.) The patient then in-

[1] Abrams, M. I., and Gilligan, D. Rourke, *Am. J. Med. Sci.*, 1934, **188**, 796.

[2] Riseman, J. E. F., Gilligan, D. Rourke, and Blumgart, H. L., *Arch. Int. Med.*, in press.

* Pitressin (Parke, Davis Co.) contains 20 pressor units per cc.

[3] Blumgart, H. L., Levine, S. A., and Berlin, D. D., *Arch. Int. Med.*, 1933, **51**, 866.

[4] Blumgart, H. L., Berlin, D. D., Davis, D., Riseman, J. E. F., and Weinstein, A. A., *J. Am. Med. Assn.*, 1935, **104**, 17.

[5] Gargle, S. L., Gilligan, D. Rourke, and Blumgart, H. L., *N. Eng. J. Med.*, 1928, **198**, 169.

gested 1000 cc. of water. The urine voided between 9 A. M. and 2:00 P. M. was collected at hourly intervals: the volume, specific gravity, and chloride content of the 5 specimens were measured. The chloride contents of the urine were measured by the method of Folin.[6] Blood pressure and heart rate measurements were made every 15 minutes for the first hour following pitressin injection, and at 1½ and 2 hours after injection. The results were compared with those obtained on a control day. Basal metabolic rate measurements were made with a Benedict-Roth apparatus, the results being calculated with reference to the Aub-DuBois normal standards.[7]

The diuresis following a liter of water on control days was similar in the patients with normal thyroid function and those with hypothyroidism.

The subcutaneous injection of 0.15 cc. of pitressin caused a marked delay in the excretion of the ingested water in 3 subjects with normal thyroid activity. When no pitressin was given the total 5-hour urine volume was approximately 1000 cc., whereas after pitressin, the volume averaged 350 cc. The most marked antidiuretic effect was evident during the first 2 hours after pitressin when

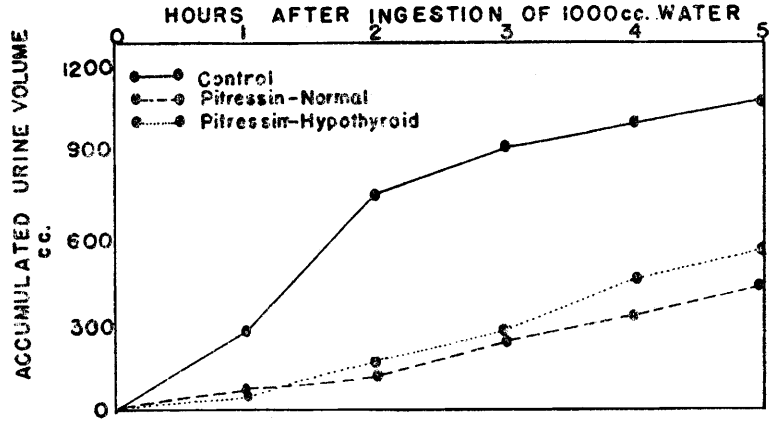

FIG. 1.

Average Antidiuretic Effect of Pitressin in Hypothyroid and Normal Subjects. The urine volumes at a given hour represent the total amounts excreted up to that hour. The "Control" curve represents average of 8 experiments without pitressin. "Pitressin-Hypothyroid" and "Pitressin-Normal" represent average of 4 studies each after pitressin in hypothyroid and normal individuals. Results obtained after 0.10 and 0.15 cc. pitressin have been averaged together since the difference in effect was small.

[6] Folin, O., Laboratory Manual of Biological Chemistry, 1926, Ed. 4, 167. D. Appleton and Co., New York.

[7] Aub, J. C., and DuBois, E. F., *Arch. Int. Med.*, 1917, **19**, 823.

the urine volume averaged approximately 100 cc., as compared with 750 cc. on control days. The antidiuretic effect of 0.10 cc. of pitressin in one additional subject with normal thyroid activity was slightly less prolonged than in the subjects who received 0.15 cc. of this drug. The administration of pitressin always caused an increased specific gravity of the urine and usually caused a decreased chloride output.[5]

In 4 patients with hypothyroidism 0.10 to 0.15 cc. of pitressin likewise caused a decreased urinary volume, an increased specific gravity, and a decreased chloride output; the degree of antidiuretic effect in these patients was not significantly different from that obtained in the subjects with normal thyroid activity (Fig. 1). Comparison of the results obtained in one patient before and after total thyroidectomy revealed no change in sensitivity to pitressin.

The heart rate and blood pressure were not significantly affected in any of the subjects by injections of 0.10 or 0.15 cc. of pitressin. After the intramuscular injection of larger doses of pitressin (0.4 cc.) in normal individuals Grollman and Geiling[8] observed consistently a slight blood pressure rise.

In one subject 0.10 cc. of pitressin, and in another 0.15 cc. caused mild abdominal cramps, nausea, and pallor persisting for about one hour after injection. In a third patient, receiving 0.15 cc. pitressin, the study was terminated because of marked discomfort from these symptoms. One of these subjects who had subjective effects after pitressin was normal; the other 2 were hypothyroid.

We have found no previous reports of the effect of thyroidectomy on the action of posterior pituitary extracts. Clark[9] and Appel,[10] have reported that dogs fed with large doses of whole thyroid died of cardiac depression within a few minutes after 0.2 cc. of pitressin intravenously.

Conclusions. The antidiuretic effect of the pressor principle of posterior lobe pituitary (pitressin) injected subcutaneously is the same in patients with hypothyroidism as in subjects with normal thyroid function. The blood pressure and heart rate are not appreciably affected, either in normal subjects or in patients with hypothyroidism, by the subcutaneous injections of 0.10 and 0.15 of pitressin.

[8] Grollman, A., and Geiling, E. M. K., *J. Pharm. and Exp. Therap.*, 1932, **46**, 447.

[9] Clark, A. G., *J. Physiol.*, 1929, **68**, 166.

[10] Appel, S., *Arch. f. Exp. Path. u. Pharm.*, 1932, **168**, 726.