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Further Investigations Concerning the Stimulating Effect of Anterior Pituitary Gland Preparation on the Thyroid Gland.

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We have shown that while feeding of Armour's tablets of anterior pituitary has an inhibiting effect on the activity of the thyroid gland as indicated by the structural changes it induces,¹ injections of acid or alkaline extracts of anterior pituitary prepared in our own laboratory from cattle gland have a very markedly stimulating effect, comparable to that characteristic of the thyroid in typical Graves' disease.² We furthermore compared with the effects of the extracts, the effects of inoculation of anterior pituitary gland substance as such, obtained from guinea pig, rabbit, or cattle. These investigations suggested the conclusion that there are apparently several active substances in the anterior pituitary and that the substance responsible for the growth of the ovarian follicle and ovulation is not identical with the substance responsible for the hypertrophy of the thyroid gland, but that the latter seems to be identical with the substance which causes the production of interstitial gland and of pseudolutein bodies in the ovary of the guinea pig.³ Silberberg⁴ has

¹ Loeb, Leo, *Am. J. Path.*, 1926, **2**; 1920, **42**, 77. Loeb, Leo, and Kaplan, E. E., *J. Med. Res.*, 1924, **44**, 557.

² Loeb, Leo, and Bassett, R. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1929, **26**, 860.

³ Loeb, Leo, and Bassett, R. B., *PROC. SOC. EXP. BIOL. AND MED.*, 1930, **27**, 490.

⁴ Silberberg, Martin, *PROC. SOC. EXP. BIOL. AND MED.*, 1929, **27**, 166. *Krankheitsforsch.*, 1930, **8**, 171.

shown that if acid extract of anterior pituitary and KI, both of which given singly stimulate the thyroid gland, are administered simultaneously, not only is there a lack of summation of the stimulating effects exerted by these substances, but a diminution of the hypertrophy which otherwise would have been caused by acid extract of anterior pituitary alone. We now report on the continuation of our investigations into the relation between the anterior pituitary and thyroid glands.

I. *Effect of administration of thyroid substance on the hypertrophy caused by acid extract of anterior pituitary.* Loeb⁵ found that daily administration of 0.1 grain tablets of thyroid substance (Armour's) to guinea pigs in which the greater part of the thyroid had been removed, prevented the occurrence of hypertrophy, whereas administration of KI did not have this effect. Similarly simultaneous administration of thyroid substance was able to prevent almost entirely the increase in activity in the thyroid gland caused by feeding of potassium iodide (Gray and Rabinovitch).⁶

In the case of the hypertrophy produced by injections of acid extract of anterior pituitary, Silberberg, as stated above, found that feeding with KI causes a diminution in the hypertrophy. In the following experiments begun in December, 1929, we studied the effect of feeding of thyroid substance on the hypertrophy ordinarily caused by acid extract.

We used, in a large majority of cases, guinea pigs weighing between 170 and 200 gm. Altogether 36 experiments were carried out. In 19 experiments we gave the combined treatment, in 17 control guinea pigs, either anterior pituitary extract—1 cc. of the extract, prepared as stated previously,² was injected daily—or thyroid tablets each containing 0.1 grain thyroid substance were administered singly. In some of the 19 experiments, both substances were administered concomitantly daily over a period of 15 days. In other experiments, in a preparatory period lasting 3 to 5 days, the thyroid tablets alone were given each day, while in a succeeding period, varying in length between 3 and 8 days, both thyroid tablets and pituitary extracts were given combined; the preparatory period was inserted in order to increase the chance for the thyroid substance to produce its effect. For the same purpose, in a number of experiments we increased the quantity of thyroid substance from one tablet to 2 tablets daily. In the former experiments to which we referred only one tablet had been given. Notwithstanding these measures

⁵ Loeb, Leo, *J. Med. Res.*, 1920, **41**, 481.

⁶ Gray, S. H., and Rabinovitch, J., *Am. J. Path.*, 1929, **5**, 485.

tending to intensify the thyroid effect, we found that thyroid substance could only to a certain extent diminish, but was not able to prevent the hypertrophy caused by extracts of anterior pituitary substance. As a result of the concomitant action of thyroid substance, the colloid was usually present in a larger quantity, remained somewhat harder and did not undergo solution processes and absorption with the same intensity as in experiments in which acid anterior pituitary extract alone was given; also with the combined treatment the mitoses were less numerous and the acinus cells a little lower. On the other hand, in some cases there was hardly any effect of the administration of thyroid substance. There was, therefore, some variation present in the intensity of the action of thyroid substance, but in general the latter caused merely a certain diminution in the intensity of the hypertrophy without preventing it. Thus, the administration of thyroid substance was much less potent in mitigating the effects of anterior pituitary extract than in diminishing compensatory hypertrophy or the stimulating effects of KI. It was possible to prevent the latter 2 processes almost entirely through feeding of thyroid tablets, while as stated, the effects of extracts of anterior pituitary could at best be made less intense. We have in all these cases to deal with quantitatively balancing conditions. These observations prove that the injection of extracts of anterior pituitary is much more potent in producing hypertrophy of the thyroid gland than removal of a great part of the gland or administration of stimulating doses of KI.

This result is of interest also in another respect. The fact that the administration of thyroid substance prevents compensatory hypertrophy might be interpreted as indicating that lack of thyroid hormone directly or indirectly acts as a stimulant on the thyroid gland, and that if we supply the necessary amount of hormone by feeding thyroid, this stimulus is lacking and therefore compensatory hypertrophy does not take place. However, the fact that thyroid substance also inhibits to some extent the effect of substances directly stimulating the thyroid epithelium, indicates that the presence of thyroid hormone or of a substance associated with it exerts a continuous depressing effect on the activity of the thyroid gland and in addition renders it less responsive to various kinds of stimulation. Furthermore, it suggests the possibility that the greater the amount of thyroid hormone which is available in the organism, the lower is the level of thyroid activity and responsiveness. We intend to test this suggestion in further experiments.

II. It was of interest to determine the time necessary for the

return of the thyroid gland to its normal condition after hypertrophy had previously been produced through administration of acid extract of anterior pituitary gland, and also to compare the rate of retrogression subsequent to the cessation of the injections of the extract with the rate of retrogression observed by Rabinovitch⁷ after cessation of the administration of potassium iodide. One cc. of acid extract of anterior pituitary was injected daily for 5 consecutive days. The injections were then discontinued and the gland allowed to recover.

Briefly the results were as follows: One day after completion of the series of injections, we found a very marked hypertrophy. Numerous mitoses were present and a great part of the colloid had been absorbed. The shape of the acini was usually irregular and in many acini the lumina had been reduced to slits. After 3 days there was still a marked hypertrophy, but it was not quite so great as before; in some places the epithelium was less high. New solid colloid began to be produced at this period and at the same time the number of mitoses was much reduced. Further retrogression was noted after 6 days, when the harder colloid was still more increased in quantity. Again we found the number of mitoses very much reduced. Yet, while these changes had taken place, on the whole, there was much hypertrophy noticeable. After 9 days moderate hypertrophy was observed in some acini, but in other areas the hypertrophy was very much diminished. The acini generally contained solid colloid, although in a number of acini peripheral vacuoles were present in the colloid. After 11 days there was still slight hypertrophy in some places. After 22 days the thyroid had almost become normal; yet the epithelium was slightly higher than in a normal gland. In addition some irregular acini were found. After 31 days the hypertrophy had disappeared and the gland had regained its usual appearance.

Comparing with the results obtained by Rabinovitch in the case of hyperactivity of the thyroid gland caused by KI it will be noted that in the latter case the return to a normal state was in certain respects similar to that observed after anterior pituitary extract administration. In both cases the mitoses fell very suddenly within a few days after cessation of stimulation; likewise in both series of experiments hard colloid was soon secreted and it took the place of the softened colloid. However, while after cessation of KI feeding the hypertrophy disappeared within 2 weeks, a certain degree of hypertrophy following injection of pituitary extracts remained visi-

⁷ Rabinovitch, Jacob, *Am. J. Path.*, 1930, **6**, 71.

ble up to at least 3 weeks. This delay in retrogression corresponds to the greater intensity of the changes produced by acid extract of anterior pituitary as compared with the changes produced by potassium iodide administration.

III. While all the doses of acid extract of anterior pituitary used by us produced marked hypertrophy, and while in some cases smaller doses could produce about as marked hypertrophy as the larger ones, in general, it was found that the hypertrophic changes caused by daily injection of 3 cc. of the extract were greater than those caused by daily injections of 1 cc. and $\frac{1}{2}$ cc. of the extract. Thus, after a daily injection of $\frac{1}{2}$ cc. of acid extract during a period of 6 days, marked hypertrophy of the thyroid was obtained. Instead of typical round or oval acini we found some slits in the center of the glands; in other acini peripheral vacuolization in the colloid was noticeable. Mitoses could be seen in increased number and the epithelium was high. Yet there was more colloid retained in the acini than after daily injection of 3 cc. extract over the same period of time, and some of the colloid was relatively hard and slightly retracted. However, even after daily administration of 3 cc. acid extract, the peripheral acini are still relatively wider and contain a larger amount of colloid than the central ones; but in these glands the colloid which is still present in the peripheral acini, is usually very soft, or it may disintegrate to small granules. While there is thus no direct correspondence between the amount of acid extract injected and the intensity of hypertrophy attained, on the average, larger doses of acid extract of anterior pituitary are more effective than smaller ones.

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Cranial and Cranio-Tympanic Bone Transmission.

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The perceptive mechanism of the internal ear may be said to occupy a position of reasonable physiological quiet so far as air sounds are concerned because the end organ is immersed in liquid and because of the depth to which the apparatus is buried away from the surface. The writer has shown elsewhere¹ that this acoustic insula-

¹ Pohlman, A. G., *Anat. Rec.*, 1930, **45**, 236.