of the carbohydrates or in the presence of varying quantities of available oxygen.

These organisms could not be grown under anaerobic conditions. Cultures grown in limited oxygen supply grew until all the molecular oxygen was used and no further growth, carbohydrate utilization, or reaction changes of the media were demonstrable even after 2 months additional incubation. Carbohydrate utilization thus apparently takes place only in the presence of molecular oxygen.

The explanation suggested in the preliminary report,[1] namely that if the carbohydrate molecule is attacked at all it is oxidized completely to carbon dioxide and water, without any intermediate products appearing in the media, explains all phenomena observed relative to carbohydrate utilization by these organisms.

4660

Effects of Combined Administration of Extracts of Anterior Lobe of Pituitary and of Potassium Iodide on Thyroid Gland.

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In former investigations from this laboratory Loeb,[1] Gray[2] and Rabinovitch[3] have shown that potassium iodide may exert a stimulating effect on the thyroid gland of the guinea pig. It does not prevent compensatory hypertrophy, but may modify its character; in the normal gland it may increase the mitotic activity as much as 40-60 times, and quite commonly increases it 20 times. Furthermore, it produces a slight increase in the size of the acinus cells and a slight softening of the colloid and a very marked increase in the number of phagocytes in the colloid. Loeb[4] has shown that oral administration of anterior pituitary substance (Armour & Co.) prevents compensatory hypertrophy of the thyroid gland and McCordock[5] has shown that it prevents the hyperplasia caused by potassium iodide. However, if instead of oral administration of anterior

[1] Merrill, Malcolm H., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 574.

[1] Loeb, Leo, *The Am. J. Surg.*, New Series, 1929, vii, 12. Endocrinol., *Bull. of Assoc. for the Study of Internal Secretion*, 1929, xiii, 1.

[2] Gray, S. H., *Am. J. Pathol.*, 1929, v.

[3] Rabinovitch, Jacob, *Am. J. Pathol.*, 1928, iv.

[4] Loeb, Leo, *J. Med. Res.*, 1920, xli, 481; *Am. J. Pathol.*, 1929, v, 71.

[5] McCordock, H. A., *Am. J. Path.*, 1929, v.

pituitary we give daily subcutaneous injections of either acid or alkaline extracts of anterior pituitary, no inhibition of the thyroid gland results, but, on the contrary, a very pronounced stimulation (Loeb and Bassett[6]). Hyperplasia and hypertrophy of the acinar epithelium, liquefaction and absorption of the colloid proceed very rapidly. After 7 daily injections of such extracts extreme changes are found in the gland resembling in many respects those obtained in typical cases of Graves disease.

We have then in potassium iodide and in acid or alkaline extract of anterior pituitary gland 2 substances which stimulate the thyroid gland of the guinea pig and which produce a very pronounced cell proliferation in the epithelium of the acini. They differ, especially, in that the hypertrophy and softening of the colloid caused by KI is very slight as compared with the pronounced effects of anterior pituitary extracts and secondly, in that, under the influence of anterior pituitary extract, the colloid is rapidly absorbed from the acini, whereas under the influence of KI it is only slightly softened and largely retained in the acini. As the result of this retention ultimately pressure may be exerted on the acinar epithelium.

Under these conditions it was of interest to determine the effect of the combined administration of KI and of extracts of anterior pituitary. Three possibilities existed as to the effects of the combined action: (1) That these 2 substances might reenforce their stimulating action; thus a summation of effects would take place. (2) KI might prevent the hypertrophic and other changes produced by anterior pituitary; this would be in accordance with the view held by a number of investigators that KI tends to produce a resting condition in the thyroid gland, and (3) both substances might tend to produce their characteristic effects and thus a competition between the 2 types of changes would result from the simultaneous administration of these 2 substances.

Our experiments have shown so far that the third possibility is realized. Seven young male guinea pigs were fed daily for a period of 17 days with 0.05 gm. KI, and seven other guinea pigs with 0.1 gm. KI. From the 10th to the 17th day 5 animals in each group (10 altogether) were injected intraperitoneally daily with 1 cc. of acid extract of anterior pituitary substance. Four control guinea pigs received only KI for a period of 17 days and 5 other control guinea pigs received for a period of 7 days injections of acid extract of anterior pituitary.

[6] Loeb, Leo, and Bassett, R. B., PROC. SOC. EXP. BIOL. AND MED., 1929, xxvi, 860.

The microscopic examination of these thyroid glands confirmed the results of the previous investigators as to behavior of the control animals. We made some approximate determinations of the number of mitoses in the thyroids of all animals and found, as was to be expected, a great increase in mitotic activity, namely, an average of approximately 3000 in the KI controls, and of 8000 in the controls injected with the extract of anterior pituitary. The actual number of mitoses may have been somewhat greater, as our counting aimed only at an approximate determination; the other changes observed also correspond to those described previously. In the guinea pigs treated with a combination of these 2 substances we found effects characteristic of KI as well as of acid extract of anterior pituitary. In some places we found the picture characteristic of anterior pituitary extract, namely, very hypertrophic acinus cells, absorption of the greater part of the colloid, irregular form of the acini, the lumen of which often had the shape of slits. In other parts, changes were those seen after KI feeding: a considerable increase in mitoses, a slight increase in the size of the cells, and a slight softening of the colloid; while the colloid in a number of acini showed definite softening in these cases, other acini showed rather solid colloid without diminution in the quantity of this substance. There were many phagocytes present. In still other areas we found intermediate conditions between those characteristic of KI and of anterior pituitary extract. The acinus cells were higher than those seen in KI feeding, but not quite as high as in animals injected with anterior pituitary extract. The colloid was softened. In many acini the colloid took up much fluid. Thus the lumina of these acini increased considerably; they extended considerably and, secondarily, the pressure thus exerted upon the acinus cells led again to a flattening of the acinus cells and reduced probably the mitotic activity. This increase in fluid colloid in the acini and the pressure resulting therefrom caused in many cases a breaking through of the walls separating adjoining acini and thus there developed large irregular compound acini, into the lumen of which spurs, the remnants of broken through walls, protruded. There were considerable areas in which these enlarged acini were found. It is probable that the pressure thus secondarily exerted upon the acini by the swollen and liquefying colloid tended to diminish somewhat the number of mitoses; it was, on the average, 2500, therefore about 18 times more than is found in normal glands. In the thyroids of guinea pigs injected with anterior pituitary extract the number of phagocytes is increased, but not to the same extent as in KI guinea pigs. Similarly

in the animals treated with both substances the number of phagocytes is increased without being as frequent as in KI animals. Not only do we find different appearances in different parts of the same gland, but there are also differences in the glands of different animals as to the prevalence of one or the other type of reaction.

Characteristic of the guinea pigs subjected to the combined action of these 2 substances is, therefore, a combination of the effects of both potassium iodide and of anterior pituitary extract. This leads to a variegated appearance of these glands, areas with very dilated acini and very watery colorless colloid alternating with areas found in the KI gland and with other places in which the hypertrophy and the absorption of colloid are very pronounced. On the whole, the number of acini in which a dilatation has taken place is greater in these glands than in those of either the animals treated with potassium iodide or with anterior pituitary extract. This is probably due to a combination of the greater liquefaction which takes place under the influence of anterior pituitary extract and of the retention of the softened material in the acini for which the KI is responsible.

Conclusion: Potassium iodide and anterior pituitary extract each exerts thus its specific effects on the thyroid gland under the conditions of our experiments; no real summation, but a mosaic of areas in which one or the other effect predominates, is the result of these combinations. It is probable that the mechanism by which KI and anterior pituitary extract cause the great increase in growth processes in the epithelial tissues of the thyroid gland, is different in the case of both these substances; thus a simple summation does not take place. It appears, furthermore, that under the conditions of our experiment in which considerable quantities of KI were fed to the guinea pigs previous to the series of injections of anterior pituitary extract, and in which thus KI has an advantage over the latter substance, potassium iodide diminishes somewhat the reactivity of the thyroid gland to the effects of anterior pituitary extract. It is possible that the latter effect is mainly due to the greater retention of colloid in the acini of animals fed with KI.

In further investigations, which are being conducted at the present time, we intend to determine the effect of the combination of these two substances on the one hand, when they are administered simultaneously from the beginning and, on the other hand, when the first period in which KI alone is administered is still further increased.