EXHAUSTION PHENOMENON IN THYROID PRODUCED BY PITUITARY TREATMENT: HISTOLOGICAL STUDY OF RABBIT'S THYROID UNDER VARYING DEGREES OF ANTERIOR PITUITARY THERAPY

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INTRODUCTION

In the course of a series of experiments on the relationship of the anterior pituitary body to the thyroid gland, we observed that the degree of hyperplasia obtained by prolonged treatment of rabbits with crude extracts of anterior lobe tissue did not parallel the dosage or the duration of treatment. We were struck by the appearance of the thyroid glands of animals which had received rather large doses of pituitary materials over a period of more than seven days. They showed involutional and atrophic changes which were totally unexpected since it was assumed on a priori grounds that they would show increments of hyperplasia with the increased dosages and duration of the injection periods.

PLAN OF EXPERIMENTS

Fifty rabbits of the blue bevern and Flemish giant strains were used. They ranged from 14 to 20 weeks of age. It was early evident that strain, alone, had no great influence upon the normal histology of the rabbit's thyroid. The first experiments in the series were made using saline emulsions of freshly obtained anterior pituitary glands of beef. In later experiments saline, acetic acid, and weak alkaline (NaOH) extracts were used. The latter were rendered sterile by passage through Seitz filters. Control injections were made into animals kept under the same environmental conditions as those of the experimental series. Control injections were made of heated pituitary extract, pregnancy urine extract and suspensions of fresh brain tissue of cows.

The dosages of the actively thyreotropic materials ranged from 0.1 gram of tissue in suspension to 1.0 gram; in the case of the various extracts the amounts of extract derived from these quantities of fresh tissue were used. The injections were carried out daily for periods of 2 to 28 days and were given intramuscularly. Pregnancy urine extracts were given intravenously. Paraffin sections were made and stained with haematoxylon-phloxin and eosin methylene blue.

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RESULTS

The histological appearances of the thyroid glands fell into three groups. Each stage is illustrated by a camera lucida drawing of a representative section.

Histology of Normal and Control Thyroids

Figure 1 illustrates the findings as seen in normal and control animals. The animal from which this thyroid was taken was an untreated reference control and received no injections. The acini were closely packed, of fairly uniform size and separated by very thin connective tissue stroma which was poor in blood vessels and not very cellular. The epithelium was low cuboidal. The colloid was plentiful in amount, stained deeply, and but

Figure 1. Camera lucida drawing of thyroid gland of rabbit No. 622, which was an untreated reference control (Normal) (x 430).

slightly vacuolated. Occasionally small areas suggesting mild degrees of hyperplasia were seen in focal areas of some of the control glands, but in none were there found the generalized changes which will be described below.

Histology of Thyroids of Animals Treated with Actively Thyreotropic Pituitary Materials

Figure 2 illustrates the type of change encountered in the thyroid glands of animals which received from 0.1 to 1.0 gram of pituitary tissue or equivalent of an active extract for from 2 to 7 days. The striking increase in cellularity, the heightened epithelium and the increased vacuolization of the colloid with its diminution in amount and depth of staining were quite characteristic of this group. In addition, the stroma showed an

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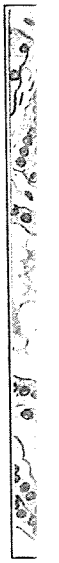

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increase in extent with numerous small blood vessels, increased number of nuclei and considerable mononuclear cell infiltration. Occasionally phagocytic cells were found in the colloid of hyperplastic glands.

Figure 3 illustrates the end stage of a series of involutional changes observed in animals treated for 12 to 28 days. Intermediate stages were seen between the appearances represented in Figures 2 and 3. We saw the gradual reaccumulation of colloid, the regression of the epithelium and diminution of vascularity of the glands as the treatment of the animals became more chronic until the stage seen in Figure 3 was reached. Here the strikingly distended acini, filled with a non-vacuolated colloid and composed of extremely low epithelium ("resembling endothelial lining of blood vessels") indicated a high degree of regression or involutional atrophy. Indeed, this latter picture is reminiscent of the findings in typical colloid

Figure 2. Camera lucida drawing of thyroid gland of rabbit No. 636, which received treatment with active thyreotropic extract for three days (Hyperplastic) (x 430).

goiter of man rather than those of the hyperfunctioning thyroid of Graves' disease.

DISCUSSION

Anderson and Collip (1) made allusion to the phenomenon herein reported as it occurred in three rats treated daily for 13 days with 4 cc. of their thyreotropic extract. They called attention to the rise in oxygen consumption which was regularly produced by the early injections; but failed to remark concerning the equally interesting, though unexpected, decrease in oxygen utilization which their animals showed on continuation of the treatment. The histological appearance of one of the rat thyroids illustrated in their paper corresponds to our stages of hyperplasia with involution.

Silberberg (2) reported his experiences in the guinea pig with anterior pituitary treatment following partial thyroidectomy. In Figure 6 of his report he illustrated a section of guinea pig thyroid taken from an animal which had received 18 days' treatment with 1½ cc. of anterior pituitary extract in daily dosage following removal of one lobe of the thyroid. The appearance illustrated was entirely comparable to that seen by Collip and Anderson. It showed evidence of hyperplasia plus a moderate degree of involution despite continuous and prolonged treatment.

A similar appearance was incidentally noted by Schockaert (3) in the duck treated by fresh suspensions of anterior pituitary of beef. In subjects treated 19 to 24 days a pathological picture similar to that of the "thyroid of man in the chronic stages of Basedow's disease" was recog-

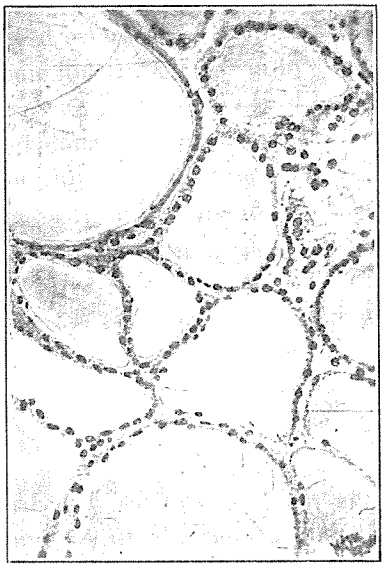

Figure 3. Camera lucida drawing of thyroid gland of rabbit No. 701, which received treatment with a proved thyreotropic extract for twenty-eight days (Involutional and atrophic) (x 430).

nized. His illustrations indicate stages of partial involution and regressive hyperplasia in these animals. No definite evidence of atrophy was seen and no metabolic data at this level of "thyroid stimulation" were recorded.

However, the extensive metabolic data collected by Szarka (4) and reported by Evans in his recent monograph indicated a primary rise in oxygen consumption in rats subjected to treatment with anterior pituitary alkaline extract. The rise was not found if the injections were preceded by total thyroidectomy. It was not eliminated by castration. The rôle of the thyroid in the metabolic rise, as independent from the gonadotropic effect of extracts, was therefore quite clear. These authors could offer no explanation for the gradual decrease of the oxygen consumption on prolongation

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of the treatment. After prolonged treatment they frequently determined consumption below the initial normal levels. The degree of decrease in oxygen consumption following such treatment was comparable to that obtained following total thyroid ablation in the normal animal. Whether this decreased metabolism was maintained after cessation of the injections was not stated, but mention was made of a metabolic decrease subsequent to cessation of treatment in some of the animals which did not show a maximal metabolic decrease during the period of injections. We interpret these findings in the light of our histological data at the various stages of pituitary treatment as evidence of an exhaustion phenomenon in the thyroid as a result of the prolonged thyreotropic activity.

Friedgood (5) drew the conclusions for the guinea pig which Schockaert brought forward for the duck. He contended that anterior pituitary treatment reproduced the clinical course of the disease of exophthalmic goiter quite faithfully, indeed even to the detail of occurrence of spontaneous remissions. The anatomic illustrations given by him indicate a sequence quite similar to that seen in our own series. In discussion Friedgood suggested as an alternative explanation for the occurrence of remission the "possible exhaustion of the thyroid epithelium."

The studies of Marine (6) demonstrated the cycle of change from normal to hyperplastic to "exhaustion atrophy after spontaneous prolonged hyperplasia" and related these phenomena to the iodine content of the gland. The re-introduction by Plummer of iodine therapy in exophthalmic goiter stimulated the study by biopsy of the thyroid before and after iodine treatment. The concept of involutional thyroid change is very well summarized by Cattell (7) and Rienhoff (8) as applied to human material.

The phenomena described by the above authors are remarkably similar to those which we have observed in the rabbits under pituitary treatment and incidentally seen by other observers in similar studies. This point of view is brought forward to suggest the logical possibility of the clinical application of the thyroid exhaustion phenomenon for the induction of involution of the thyroid and of remission in human disease. The production of atrophic changes and the lowering of metabolism (Szarka) by non-surgical means seems to us to be of importance to the clinic as well.

Thyreotropic hormone is slowly becoming available in relatively pure form (Collip and others). Practical matters of therapeutic application for the above purposes will have to await carefully controlled human experiments.

Our experience in animals with respect to the gonadotropic materials of pituitary origin would indicate that none of these can be considered suitable for these purposes since even in massive dosage they are lacking in any important effect upon the thyroid.

SUMMARY

In a series of experiments on 50 rabbits varying in age from 14 to 20 weeks, groups were treated with saline emulsions and sterile (Seitz) acid and alkaline extracts of anterior pituitary glands of beef and with control injections of heated pituitary suspensions, fresh brain emulsions and pregnancy urine extracts.

Animals treated for periods of 2 to 7 days (daily intramuscular injections of 0.1 to 1.0 gram or equivalents of extracts used) showed thyroid hyperplasia. Animals treated for longer periods, i.e., 7 to 12 days, showed early regressive and involutional changes with remnants of hyperplasia in their thyroids. The thyroids of animals treated for from 12 to 28 days showed increasing degrees of involution and finally atrophy of the epithelium and marked colloid storage. Control extracts are without effect.

The above sequence is interpreted as indicative of an exhaustion phenomenon in the thyroid as a result of prolonged thyreotropic action. Metabolic evidence in support of this hypothesis and its possible clinical application are briefly discussed.

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