CHANGES IN THE THYROID AND ADRENAL GLANDS DURING PROLONGED CCl_4 POISONING

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Following prolonged administration of CCl_4 to rabbits, leading to the development of cirrhosis of the liver with ascites and also 2-3 months after the end of injections of CCl_4, the morphological picture indicates a decrease in the level of thyroid activity and activation of the adrenal cortex. An increase in thyroid function is observed 4 months after partial hepatectomy following cessation of CCl_4 injections, and at this same time the functional stress on the adrenal cortex still remains high.

The object of this investigation was to study morphological changes in the thyroid and adrenal glands in animals with experimental cirrhosis of the liver produced by prolonged poisoning with CCl_4.

This investigation was based on results showing that the thyroid and adrenals play an important role in protective and adaptive responses of the body [2, 5, 13] and in processes of regeneration, growth, and differentiation of tissues [3, 4, 7, 10].

EXPERIMENTAL METHOD

Experiments were carried out on male rabbits [41] in which cirrhosis of the liver was produced in the usual manner by daily injections of 50% CCl_4 solution in peach oil for 3-4 months in a dose of 0.12 ml solution/kg body weight.

Paraffin and celloidin sections of organs were stained with hematoxylin-eosin by Van Gieson and Heidenhain's methods, and with silver nitrate by Karupu's method. Using an ocular micrometer, the diameter of the thyroid follicles (100 follicles in each section) and the height of the follicular epithelium (200 cells in each section) were measured.

EXPERIMENTAL RESULTS

From 3 to 4 months from the beginning of CCl_4 injections, the rabbits developed severe cirrhosis of the liver with ascites. In histological sections considerable thickening of the capsule and abundant proliferation of connective tissue inside the liver were observed, as a result of which the structure of the hapatic lobules was disturbed. Pseudolobules were formed, the sinusoids were arranged irregularly, and their lumen was reduced in size to between 2 and 8 μ because of swelling of the liver cells, whereas in the normal liver it is $12 \pm 2\mu$. The central and collecting veins were compressed by the excessive overgrowth of connective tissue and by nodules of regeneration. "Internal Eck's fistulas" were found.

Against the background of these changes in the liver, marked morphological changes also were observed in the thyroid (Fig. 1B). The relative weight of the thyroid gland was reduced from 0.06 ± 0.001 in normal animals to 0.02 ± 0.003% in animals with cirrhosis of the liver. The connective-tissue capsule of the organ was thickened. The follicles were circular or oval in shape, and the diameter of most of them varied from 30 to 60 μ. Very large solitary follicles, with a diameter of over 180 μ, were found. The folli-

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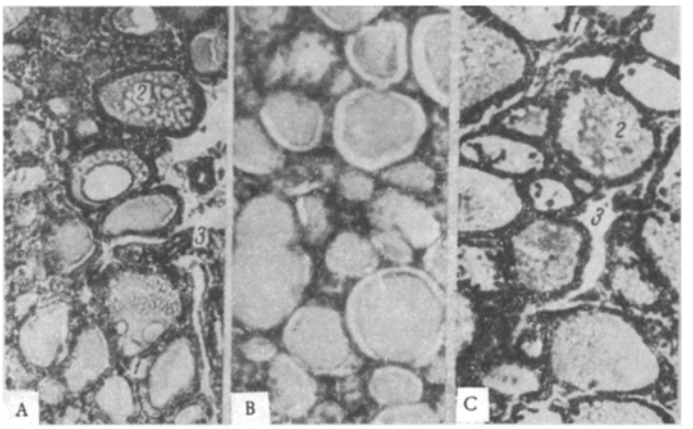

Fig. 1. Microscopic picture of the rabbit thyroid gland. A) Normal thyroid gland: follicles of varied shape, with high epithelium (1) and well vacuolated colloid (2), blood vessels of the gland well defined (3); B) thyroid gland of rabbit during chronic CCl_4 poisoning with marked experimental cirrhosis of the liver: follicular epithelium low, colloid almost free from vacuoles, blood vessels of gland cannot be detected; C) thyroid gland of rabbit 4 months after partial hepatectomy and stopping CCl_4 injections: follicular epithelium fairly high (1), colloid strongly vacuolated (2), blood vessels dilated (3). Hematoxylin-eosin, 1000×.

cular epithelium became low, cubical, and squamous, 2.8-4.2μ in height, whereas in intact animals the height of the follicular epithelium is 5.6-8.4μ.

The colloid of the follicles was dense and homogeneous in structure and almost free from vacuoles. In some follicles the colloid was so thick that it cracked during preparation of the histological sections. Compact collections of cells of follicular epithelium with single mitoses and amitoses were found in large numbers between the follicles. Round-cell infiltration was observed in the connective-tissue septa. These changes in the thyroid gland are evidence of depression of its functional activity [1, 4].

Morphological changes in the adrenals were as follows. Their relative weight was increased from 0.02 ± 0.001 to 0.04 ± 0.001 . The capsule of the adrenals was thickened. The zona glomerulosa was reduced in size, and its structure frequently was disturbed through penetration of connective-tissue bands from the capsule (Fig. 2B). The zona fasciculata was increased to almost twice its normal size. The boundaries between the zona glomerulosa, zona fasciculata, and zona reticularis were indistinct.

Increased proliferation of the zona fasciculata following prolonged administration of CCl_4 evidently indicates increased production of glucorticoids [4, 10].

Bearing in mind the conflicting data in the literature concerning the role of the thyroid and adrenal glands in regeneration of the liver [7, 11], and the results of investigations indicating stimulation of regeneration in the pathologically changed liver after partial hepatectomy [6, 8, 9, 12], the next stage was to study the morphology of the thyroid and adrenal glands in the animals at various times after stopping CCl_4 injections and after resection of the liver. Animals left as the "cirrhosis" control died with a picture of severe cirrhosis of the liver and ascites and general toxic manifestations 2-3 months after stopping the injections.

The absolute and relative weight of the thyroid in this group of animals was increased to almost twice its weight in normal animals. The capsule of the gland was thickened. Considerable proliferation of connective tissue in the parenchyma of the gland was observed. Most follicles varied in size from 15 to 45μ. Against this background there were some follicles whose diameter exceeded 150μ. The follicular epithelium was low-cubical and squamous in type, 1.4-4.2μ in height. The colloid of the follicles was dense, with

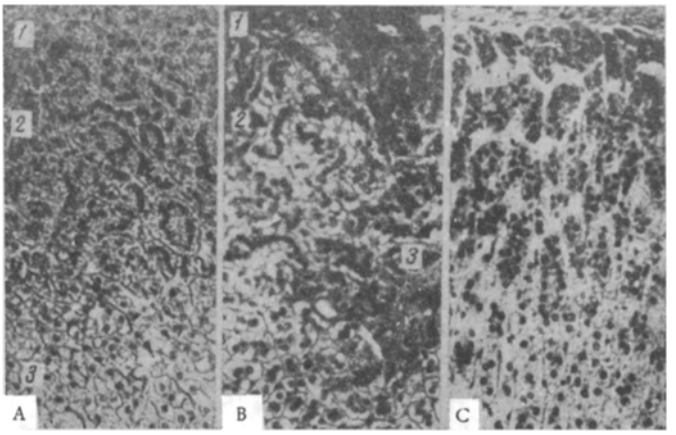

Fig. 2. Microscopic picture of the rabbit adrenal cortex. A) Adrenal cortex of normal rabbit: capsule of gland (1); zona glomerulosa (2) and boundary with zona fasciculata (3); B) adrenal cortex of rabbit with experimental cirrhosis of the liver: capsule of gland is thickened (1), zona glomerulosa is reduced in size and deformed (2) because of proliferation of connective tissue (3); C) adrenal cortex of rabbit 4 months after operation and stopping CCl_4 injections: capsule thickened, zona glomerulosa well defined. Hematoxylin-eosin, 1000×.

few vacuoles. Interfollicular islets were found between the follicles of the gland. These changes in the thyroid gland of the animals with experimental cirrhosis of the liver 2 months after cessation of CCl_4 injections are evidence of the persistence of its hypofunctional state resulting from prolonged poisoning.

The relative weight of the adrenals in the animals of this group was much greater than normal ($0.05 \pm 0.003\%$). The adrenals were hypertrophied. Histological investigation revealed thickening of the capsule, a decrease in size of the zona glomerulosa, and considerable proliferation of the zona fasciculata, evidence of functional stress on the adrenals.

In animals undergoing partial hepatectomy (one-third of the liver was removed), at various times after operation (2 weeks and 1 month), and with the injections of CCl_4 discontinued, the structure of the liver, thyroid, and adrenals remained considerably abnormal and differed only slightly from the morphological changes observed in the animals not undergoing hepatectomy.

Four months after partial hepatectomy, and after discontinuation of CCl_4 injections, different changes were observed in the part of the liver remaining after the operation. The quantity of connective tissue in the organ was reduced, and the connective-tissue bands were more compact. The argentophilic skeleton was considerably reduced in size. The hepatic lobules were larger. The sinusoids were more regularly arranged, converging radially around the central veins, and their lumen measured $9.0 \pm 1.0\mu$. The central, sublobular, and collecting veins were slightly dilated. No ascites was found, indicating an improvement in the blood flow in the liver.

In this same group of animals the follicles of the thyroid gland had become more uniform in size, their diameter varying from 20 to 140μ. The epithelium was cubical ($4.2-5.6\mu$) and prismatic in shape (11.2μ). The cytoplasm of the thyroid cells frequently appeared frothy. The colloid was highly vacuolated, and in some follicles it was absent (Fig. 1C). The blood vessels of the gland were dilated. These findings, regarding changes in the thyroid, are evidence of its increased functional activity [1, 4].

The relative weight of the adrenals remained just as high compared with normal as in the experiments of the previous series.

Histological investigation demonstrated an increase in size of the zona fasciculata. Compared with the "cirrhosis" control, the zona glomerulosa was larger (Fig. 2C), and the boundaries between the zona glomerulosa, zona fasciculata, and zona reticularis were clearly defined.

Prolonged poisoning with CCl_4, causing the development of experimental cirrhosis of the liver with ascites, is thus accompanied by considerable changes in the thyroid and adrenal glands, indicating depression of the functional activity of the thyroid and activation of the adrenal cortex.

In the late stages after partial resection of the cirrhotically changed liver and against the background of discontinuation of CCl_4 administration, a considerable improvement in the structure of the thyroid gland was observed, indicating an increase in its function, whereas the functional stress on the adrenals still remained high.

These results suggest that cirrhotic changes in the liver during chronic CCl_4 poisoning develop and follow their course against the background of a hormonal imbalance, affecting in particular the thyroid and adrenal hormones.

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