HISTOLOGICAL CHANGES IN THE ENDOCRINE GLANDS IN RABBITS WITH EXPERIMENTAL ATHEROSCLEROSIS

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Changes in a number of endocrine glands in atherosclerosis have been described in the literature [2-4], but there is no general agreement regarding the direction of these functional changes [4, 7, 16, 17]. Furthermore, usually only one gland has been studied, and not the endocrine system as a whole. In the present investigation a histological study was made of the neurosecretory supraoptic nuclei of the hypothalamus, the posterior and anterior lobes of the pituitary, the thyroid, and the adrenals in experimental atherosclerosis. In some of the rabbits the liver, spleen, and pancreas were among the organs investigated.

EXPERIMENTAL

Experimental atherosclerosis was produced in 11 rabbits by adding dry cholesterol (0.5 g per rabbit) to the daily diet for 100-120 days. Organs were taken from five intact rabbits for comparison.

The maximal blood cholesterol concentration reached 345-700 mg% (mean value 542 mg%). The degree of the atherosclerotic changes in the aorta varied from 0 to +++ (where ++++ represents the possible maximum).

The animals were sacrificed by air embolism. The material was fixed immediately after death in Bouin's fluid and Susa's mixture. Paraffin-wax sections were stained with hematoxylin-eosin, with erythrosin and Mallory's mixture, and in some cases azure II—eosin was used to investigate blood cells in tissue sections, and chromic hematoxylin or Gomori's aldehyde—fuchsin to detect the neurosecretory substance and secretory granules in the basophils of the anterior lobe of the pituitary and in the β-cells of the islets of Langerhans in the pancreas. In addition, one of the adrenals was fixed in 10% neutral formalin with the addition of 1% calcium chloride, and sections were cut on a freezing microtome. The sections were stained with a saturated solution of Sudan III and IV in Herxheimer's mixture or a solution of Sudan black B in 70% alcohol, or they were mounted unstained for examination in polarized light.

RESULTS

The administration of cholesterol had no appreciable effect on the state of the neurosecretory system. The amount of neurosecretory material in the supraoptic nucleus and in the posterior lobe of the pituitary remained moderate. In the anterior lobe of the pituitary cholesterol loading produced no significant visible changes in the basophils (apart from a higher incidence of vacuolation of these cells than is normal). The lateral portions of the anterior lobe consisted of acidophils and a small number of chromophobes. The acidophils responded more clearly than the basophils to cholesterol loading. Their size increased visibly. The cytoplasm of some acidophils was filled with numerous tightly packed and intensively stained secretory granules. Other acidophils were partly or almost completely devoid of granules (Fig. 1).

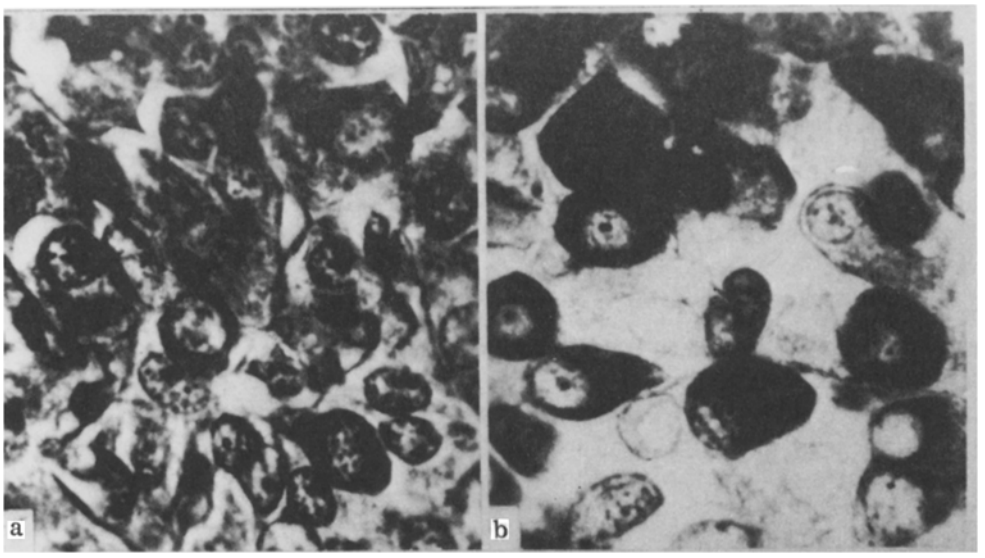

Fig. 1. Anterior lobe of the pituitary of a rabbit, site of α-cells. a) control, b) experimental hypercholesteremia. Stained with aldehyde–fuchsin and fuchsin–orange. Objective 90×, ocular 15×.

In some cases "acidophils" with an amphophilic cytoplasm and a normal or pycnotic nucleus were seen. Occasionally in normal conditions, and much more often in experimental hypercholesteremia, acidophils were seen with large, lightly stained, vesicular nuclei. Sometimes the nuclei of the acidophils were irregular in shape.

No information could be found in the literature on the question of the changes in the pituitary in experimental hypercholesteremia. The description given of the changes in the pituitary of human hypertensive patients with atherosclerosis [12, 18] differs from the findings obtained in the present investigation.

A suggested explanation of this dual reaction of the acidophils is that secretory cells of two types may be present in rabbits, just as has been demonstrated in other animals [21, 23, 24], reacting in opposite ways to cholesterol loading. The degranulation of the acidophils may also be associated with depression of the thyroid function [7, 14]. Admittedly, in the present experiments degranulation of the acidophils was found in all the experimental animals, whereas the thyroid activity, as will be shown below, was increased in some cases and decreased in others.

The diameter of the follicles most commonly found in the thyroid of the rabbit was 20-36μ. Normally the mean value of the incidence of follicles of this size is 65%, but in the experimental animals it fell to 46%. Meanwhile, in the experimental animals some of the follicles increased to $1\frac{1}{2}$ times their normal size. The height of the epithelium also changed in the animals with experimental atherosclerosis. Normally the commonest cells have a height of 7.5μ, but in the experimental animals the mean height fell by 30%. However, the scatter of the results was increased, and some cells were seen with a height of 11, or even 13μ.

Histological examination revealed a greater variety of pictures in the experimental animals than in the normal, both within the limits of one gland and when glands of different animals were compared. In 8 of 11 rabbits the resorption of colloid was rather slower, in 1 animal stasis of the colloid was present (Fig. 2b), in another–increased resorption (Fig. 2c), and in another–accumulation of colloid in some follicles and intensive resorption in others. The nonhomogeneity of the experimental pictures may be due to the fact that the thyroid was investigated in different phases of the change in its activity [2, 9-11, 15].

The islet-cell apparatus of the pancreas in normal conditions consists of well defined β-cells with a distinct Gomori-positive granulation, in most cases filling the whole body of the cell. A few acidophils are seen at the periphery of some islets. The lumens of capillaries can be seen clearly between the islet cells. In rabbits with experimental atherosclerosis the islets were very compact, the capillary walls were collapsed, and the cells were compressed. The number of Gomori-positive granules was appreciably reduced, especially in the perinuclear region (Fig. 3). No clear changes were observed in the acidophils. In two cases hypertrophied acidophils were more numerous than normally. Side by side with these glands, others were seen in which the number of acidophils was reduced.

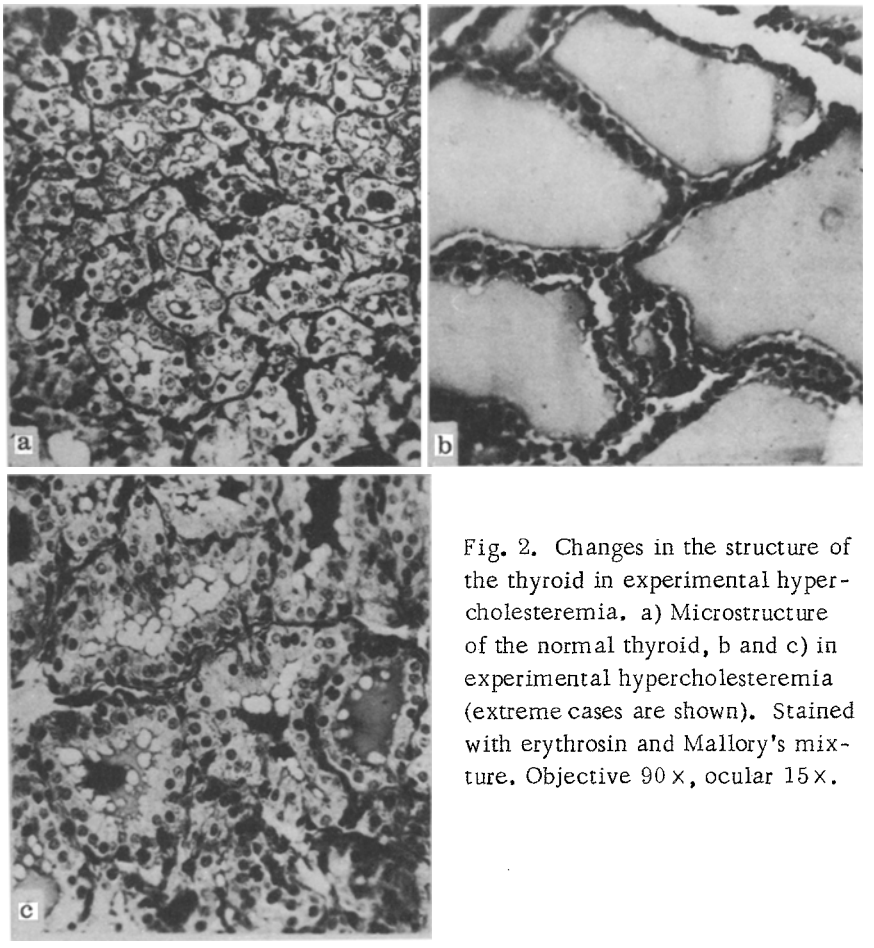

Fig. 2. Changes in the structure of the thyroid in experimental hypercholesteremia. a) Microstructure of the normal thyroid, b and c) in experimental hypercholesteremia (extreme cases are shown). Stained with erythrosin and Mallory's mixture. Objective 90×, ocular 15×.

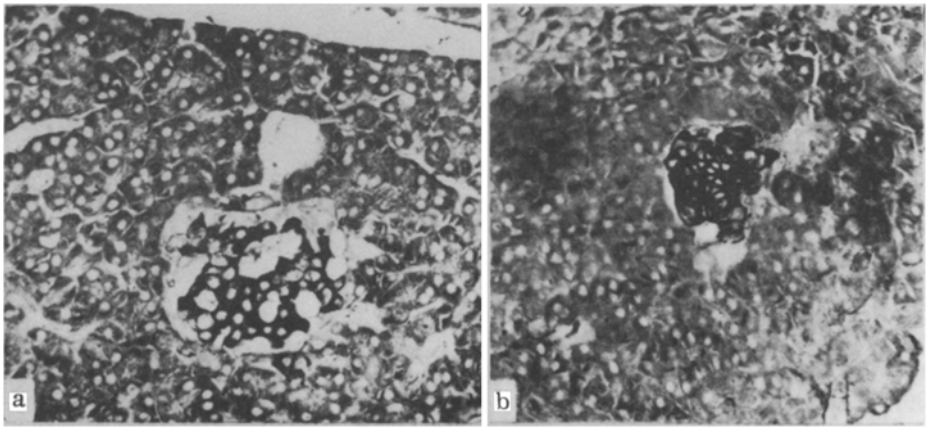

Fig. 3. Structure of the islet-cell apparatus of the pancreas in normal conditions (a) and in experimental hypercholesteremia (b). Stained with aldehyde-fuchsin and light green. Objective 90×, ocular 15×.

Hyperplasia of the adrenal cortex has often been described in both experimental atherosclerosis and in the disease in man [19, 22, 25]. It is caused by infiltration of the cells of the zona reticularis and, in particular, of the zona fasciculata, by lipids and cholesterol. Numerous degenerating cells are observed [8], forming extensive areas covering the zona fasciculata and zona reticularis. The border between the zones is obliterated. Among the degenerating cells, foci of extramedullary hemopoiesis which may be single or multiple are often encountered [19].

They contain many pseudoeosinophils, macrophages and, occasionally, basophils. The dimensions of the endothelial nuclei are greatly increased, and patterns of mitotic division are seen in these nuclei.

No direct relationship was observed between the intensity of the lesion in the adrenals, the level of the blood cholesterol, and the degree of atherosclerosis. However, there was a tendency for the severity of the adrenal lesion to increase with an increase in the blood cholesterol concentration: degenerating cells were seen more often and in larger numbers, the foci of extramedullary hemopoiesis became more extensive, and the number of cholesterol crystals increased. The absence of any sharp line of demarcation between the zones is evidence of the progressive transformation and activation of the adrenal cortex. The extensive degenerating areas in the same adrenals suggest that two opposite processes were proceeding simultaneously: on the one hand, death and destruction of areas of the cortex, and on the other – intensified growth and activation of areas not yet affected by the process of degeneration. Reports in the literature on the effect of ACTH or of the cortical hormones on the course of atherosclerosis are contradictory [4, 7]. The effect possibly depends on which process – degeneration or intensified growth and activation – is predominant in the adrenal cortex at the moment of administration of the ACTH or cortical hormones.

Among the endocrine glands the adrenal cortex is the most profoundly affected. The thyroid, pancreas, and the anterior lobe of the pituitary are affected to a lesser degree, but still considerably. No significant changes were discovered in the neurosecretory system.

From a comparison of the histological picture of the anterior lobe of the pituitary and the morphological data concerning the state of the neurosecretory system, no definite conclusions can be drawn about the effect of experimental hypercholesteremia on the system of the hypothalamus and pituitary in these experimental conditions. The absence of any such influence may rather be deduced. No parallel could be detected between the changes in the thyroid and the histological changes in the basophilic cells of the pars glandularis of the pituitary which might be attributable to technical faults or to the impossibility of indentifying thyrotropic cells in the anterior lobe of the rabbit's pituitary in these experimental conditions, which can be done in the rat's pituitary [5, 14, 20, 23]. However, it may be postulated that the central regulation by the "working organs" is effected in this case by an extrapituitary route [1]. Finally, it may be supposed that at this particular stage of the development of atherosclerosis, the "working organs" are more severely affected, and the higher regulatory centers can still compensate for the functional disturbances to such an extent that these disturbances are not yet manifested morphologically.

The data described are in agreement with the generally accepted idea that atherosclerosis is a disease of the whole organism. The endocrine system reacts to a definite degree to experimental hypercholesteremia. This remark applies above all to the adrenal cortex, the thyroid, the pancreas, and the anterior lobe of the pituitary. No obvious changes are found in the neurosecretory system of the hypothalamus and pituitary.

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