FUNCTIONAL AND MORPHOLOGICAL STUDIES OF THE GASTRIC MUCOSA IN DOGS WITH EXPERIMENTAL THYROTOXICOSIS

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Following administration of triiodothyronine in a dose of 10 μg/kg body weight daily for 30 days or 20 μg/kg body weight daily for 17 days to dogs with a Basow gastric fistula, besides a decrease in the acidity and proteolytic activity of the gastric juice, changes were observed in the gastric mucosa: an increase in its thickness, proliferation of connection tissue and sclerosis of the blood vessels in it, and increase in the content of PAS-positive substances in the evacuatory portion of the stomach and, in some places, evidence of enteralization.

Conflicting results have been obtained concerning the secretory function of the stomach in dogs with experimental thyrotoxicosis produced by feeding the animals on dried thyroid or thyroid extract [2, 4, 7, 9]; the more potent substances α-thyroxine and triiodothyronine, induce definite inhibition of gastric secretion [3, 11]. Nor is it clear what is the role of morphological changes in the gastric mucosa in the genesis of these disturbances of function.

A parallel study has been made of the function and morphology of the gastric mucosa in dogs with experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Experiments were carried out on six mongrel dogs weighing 13-24 kg. In three dogs with a Basow gastric fistula, the initial state of the gastric secretory function was determined four times before the beginning of the experiment by the following method: the basal gastric juice was collected for 1 h, after which the dog received a subcutaneous injection of 1 ml 0.1% histamine solution, and the gastric juice was again collected for 1 h. The volume of the hourly secretion, the total acidity and free HCl (in titration units), the hourly production of free HCl. the pepsinogen concentration (by Tugolukov's method), and the gastromucoprotein (by the method of Glass and Boyd) were investigated in both samples of gastric juice and, in addition, the blood plasma pepsinogen was determined on the fasting animals (by Tugolukov's method). After the basal gastric secretion had been established, the dogs were given briiodothyronine (the Hungarian preparation "Lyothyronine") in a dose of 10 μg/kg daily for 30 days by mouth, and every 3-4 days in this period the gastric secretion of the animals was investigated by the method described above. A similar investigation of the gastric secretory function was carried out on one dog with a Basow gastric fistula over the same period of time, but this animal did not receive triiodothyronine (control). Two dogs received triiodothyronine in a daily dose of 20 μg/kg for 17 days (their gastric secretion was not studied). Administration of this substance caused thyrotoxicosis in all the dogs, manifested clinically by increased pulse and respiration rates, thirst, and loss of weight of between 0.5 and 2.4 kg.

After the end of the experiment, the dogs were electrocuted in the early morning before feeding and autopsied. Pieces were taken from different parts of the gastric mucosa, fixed in 10% formalin or Carnoy's

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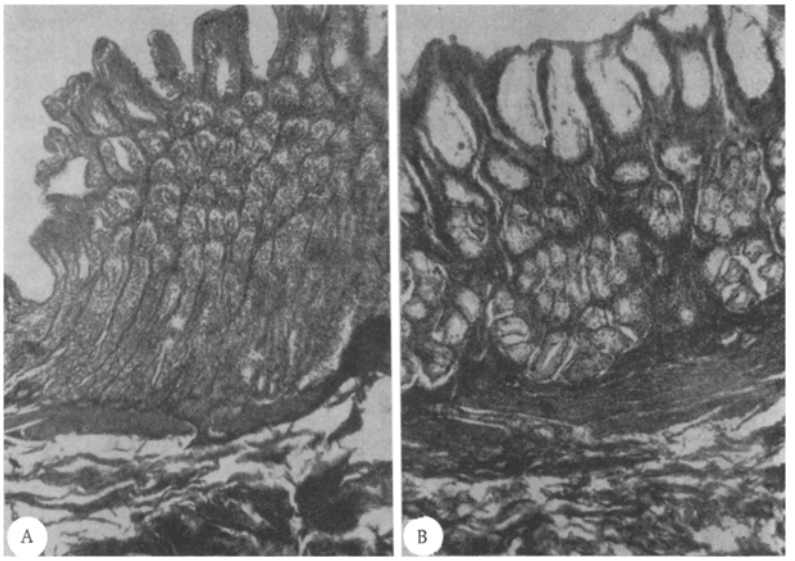

Fig. 1. Section through gastric mucosa of a dog (56×): A) hematoxylin-eosin; B) Van Gieson.

fluid, dehydrated, and embedded in paraffin wax. Sections were stained with hematoxylin-eosin, by Van Gieson's method, and with toluidine blue (to detect metachromatic staining), and Brachet's (for RNA) and the PAS (for polysaccharides) reactions were carried out. Sections from the gastric mucosa of a dog in which the histamine gastric secretion had periodically been studied, and also sections from the stomachs of another two healthy intact dogs, kept on the same diet as the experimental animals, were used as controls.

EXPERIMENTAL RESULTS

In one of the three dogs receiving the smaller dose of hormone, signs of thyrotoxicosis were slight, and the gastric secretory function tests revealed changes only in the secretion of gastromucoprotein. The morphological structure of the gastric mucosa of this dog differed from that of the controls only in its slightly greater thickness and the greater content of mucus in the gastric pits.

In the other two dogs receiving triiodothyronine in the smaller dose the volumes of gastric secretion in response to insulin was increased, but the total acidity of this portion of the juice and its content of free HCl were reduced. The hourly production of free HCl also was reduced in both dogs, in one of them after a slight initial increase in this index of the acid-producing function of the stomach. Changes in the pepsinogen concentration in the basal gastric secretion were biphasic: after an increase which was observed in the first 10 days of the experiment, a decrease in this index below its initial level followed. Changes were particularly marked in the secretion of gastromucoprotein. Whereas this was either not found at all or was detected only as traces in the basal secretion of all dogs, after administration of triiodothyronine its concentration rose in all dogs on the average to 70-80 mg%; a less clear increase in the gastromucoprotein concentration was also found in the gastric juice secreted in response to histamine. As regards the other indices of gastric secretion and the plasma pepsinogen concentration, no definite changes could be seen. The gastric secretion of the control dogs also was unchanged.

The gastric mucosa of dogs receiving triiodothyronine in a dose of 10 μg/kg was considerably thickened. The degree of hyperplasia varied even in neighboring portions, thus causing variation in its height, especially in the region of the fundus (Fig. 1A). Thickening of the mucosa took place because of widening and deepening of the pits and also lengthening of the glands. In some places the glands were thin, in others thick, but in both cases they were long and tortuous; the parietal and chief cells were clearly distinguishable, and the latter were pale (empty). The nuclei of the chief cells were pale and vesicular. Proliferation of connective tissue was found in the walls of the gastric pits, with an increase in their thickness. The epithelium of the gastric pits of one of the dogs was desquamated, and in places marked enteralization of the mucous membrane was observed (Fig. 1B). The blood vessels of the gastric mucosa were sclerotic. Frequently zones of lymphoid infiltration were observed in the thickness of the mucosa.

Brachet's reaction showed a uniformly clear pyroninophilia of the cell nuclei of the gastric mucosa. The content of PAS-positive substances in the gastric pits was slightly less than in the control, while in the apical portions of the tubules of the glands and in the deeper layers their content was normal. In the evacuatory portion of the stomach, an excess of mucopolysaccharides was present. Metachromatic staining of the gastric mucosa was found in one of the dogs.

The gastric mucosa of the two dogs receiving triiodothyronine in the larger dose (20 μg/kg) also show marked hyperplasia. Hyperemia of the mucosa, edema of the submucosa, and collections of lymphoid cells at its border, and a decrease in the number of chief cells were observed. There was a well marked fibroblastic reaction; thin bands of connective tissue became thicker nearer to the lumen of the stomach; proliferation of the perithelium and swelling of the endothelium were present in the capillaries and arterioles. The vessels were sclerotic, and the intima and media were greatly thickened (myoelastofibrosis), and white mural thrombi were seen.

Uniform pyroninophilia was present in the cell nuclei of the gastric mucosa and was particularly clear in nuclei of the epithelium of the gastric pits. The content of PAS-positive substances in the epithelium of the gastric pits was normal; along their whole length the glands were more deeply stained than in the control. Metachromasia was absent.

In the gastric mucosa of dogs with experimental thyrotoxicosis, two processes are apparently observed simultaneously: hyperplasia and atrophy of the glands. The final stages of these changes are atrophy, enteralization, and fibrosis of the mucosa.

According to the most widely held opinion [1], histamine is a direct humoral stimulus of the parietal cells of the gastric mucosa. Atrophy and enteralization of the mucous membrane, with a decrease in the number of oxyphilic cells, thus explain the decrease in production of acid by the stomach in experimental thyrotoxicosis.

Indirect evidence of the role of the intramural nervous system of the stomach in HCl formation by the gastric mucosa in response to injection of histamine was obtained previously [5, 10], but more recently the hypothesis regarding the predominantly indirect action of histamine on the parietal cells via the nervous system has obtained more solid support [8, 12]. For this reason, and because of the occurrence of destructive processes in Meissner's and Auerbach's plexuses of the stomach in thyrotoxicosis [6], the inhibitory effect of triiodothyronine on histamine gastric secretion associated with changes in the nervous apparatus of the stomach must be considered.

The severity of the thyrotoxicosis, rather than its duration, evidently plays an important role in the development of metaplasia of the gastric mucosa, for evidence of enteralization was found in the dogs receiving a smaller dose of triiodothyronine but for a longer time, and it was absent in animals receiving twice the dose of the hormone but for approximately only half the period.

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