

## EXPERIMENTAL BIOLOGY

### EFFECT OF AN EXCESS OF THYROID HORMONES IN RABBITS ON MITOTIC ACTIVITY OF THE REGENERATING LIVER CELLS

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Administration of thyroid extract to rabbits leads to an increase in the mitotic activity of the liver cells and accelerates regeneration after partial hepatectomy. In this case mitotic activity reaches a maximum 2 h sooner than in the control.

Certain doses of thyroid hormones have been shown [16, 1] to stimulate cell division in various tissues. This suggests that administration of thyroid hormones would stimulate repair processes and, in particular, regeneration of the liver after partial hepatectomy.

However, the results of investigations to study this problem, mainly studying the restoration of the mass of the liver, have been contradictory. Some workers [12-14] have observed acceleration of regeneration of the liver tissue under the influence of thyroid hormones while others found inhibition of repair processes [11]. Meanwhile, lowering the level of thyroid hormones by thyroidectomy had no effect on reparative regeneration [7, 10, 15].

The writers studied the effect of an excess of thyroid hormones on mitotic activity in the regenerating liver of rabbits receiving thyroid extract over a period of several days.

#### EXPERIMENTAL METHOD

Male rabbits weighing 2-2.5 kg were used. Thyroid extract was given to the experimental animals in increasing doses [6] for 7 days. On the 4th and 7th days of the experiment the rabbits were killed by air embolism, pieces of liver were removed and fixed in a mixture of ethanol and glacial acetic acid (3:1), and acetoorcein squash preparations were made. The mitotic index (MI) was calculated per thousand cells, 5000 cells being counted in each animal. In a special series of experiments two lobes of the liver (30% of the total weight of the organ) were resected under urethane anesthesia (0.3 g/kg) from rabbits receiving thyroid for 4 days. The animals were sacrificed between 64 and 76 h after the operation (two rabbits at each time). MI of the hepatocytes was calculated in the same way as in the experiments of series I. The concentration of thyroid hormones circulating in the experimental animals was estimated from the level of protein-bound iodine (PBI) in the blood serum [5, 8].

#### EXPERIMENTAL RESULTS

Administration of thyroid led to a progressive increase in the PBI concentration in the rabbits' blood. This index in the control animals was  $2.9 \pm 0.3 \mu\text{g}\%$  ( $n=12$ ). On the 3rd day after thyroid administration it was significantly ( $P < 0.001$ ) increased to  $10.0 \pm 1.1 \mu\text{g}\%$ , and on the 7th day to  $18.1 \pm 2.2 \mu\text{g}\%$  ( $n=5$ ). This last value differed significantly from the corresponding control level ( $P < 0.001$ ) and also from the results obtained on the 3rd day of the experiment ( $P < 0.01$ ).

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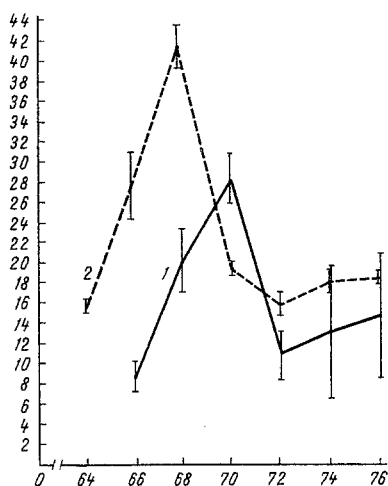


Fig. 1. Mitotic index of hepatocytes in control and hyperthyroid animals at various times after partial hepatectomy: 1) control; 2) experiment. Vertical lines represent confidence limits of variations ( $M \pm 2.5 m$ ). Abscissa, time after partial hepatectomy (in h); ordinate, mitotic index (in ‰).

hepatocytes at most by 4.6 times, and in the experimental animals by 4.2 times, i.e., by approximately the same number of times in the two cases.

It can accordingly be concluded that resection of the liver stimulates regenerative proliferation equally in the control animals and in the animals receiving thyroid hormone.

The absolute increase in mitotic activity in the liver of the hyperthyroid animals both under normal conditions and after partial hepatectomy was probably due to the effect of thyroid extract on synthetic processes taking place in interphase.

It was also interesting to note that the maximum of mitotic activity in the partially hepatectomized animals occurred 2 h sooner than in the controls. Allowing for the synchronization of cell division in the population characterizing the first maximum of mitotic activity, thyroid presumably led to shortening of the premitotic stages of the cell cycle. This conclusion is supported by results obtained by workers who postulate that thyroxine accelerates the passage of cells through the individual periods of interphase [3, 4, 9].

The results thus indicate that thyroid hormones have a marked influence both on mitotic activity of the cells of the intact liver and on regeneration of the liver after resection. The contradictory nature of data in the literature is presumably due to differences in the doses of thyroxine used by different workers, for it has been shown [2] that large and small doses of thyroid hormones led to different changes in nucleic acid and protein synthesis which lie at the basis of cell division. Another possibility is that the difference is due to inadequate assessment of the effect of thyroxine on the degree of increase in the number of mitoses in the liver during its regeneration.

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