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Influence of Metizol ("Polfa") on the Liver of Pregnant Rats

Wpływ Metizolu („Polfa”) na wątrobę ciężarnych szczurzy

Drugs are the largest group of substances inactivated by the liver. They may have a stimulatory or inhibitory effect on the system of hepatic enzymes.

Metizol is a thyreostatic belonging to the group of trimidazole derivatives. Its mechanism of action consists in inhibition of triiodothyronin and thyroxin secretion by the thyriod, owing to inactivation of the enzymes causing iodination of the thyrosine groups of thyreoglobulin (2). This relatively little toxic drug when used for a prolonged period may lead to hyperaemia of the thyroid, and in pregnant women (by passing through the placenta) its side effects may threaten the foetus (6). The future mother affected with hyperthyroidism should receive full Metizol doses to avoid the danger of a thyroid crisis. A radical improvement of her health should be reached before childbirth (4).

Since the liver plays an essential role in detoxication and the risk of injury to it is much greater than to other tissues, it was decided to histologically and histochemically examine the livers of pregnant rat females after application of increased doses of this preparation throughout the pregnancy period.

MATERIAL AND METHODS

The experiments were performed with female white Wistar rats divided into two groups, a control and an experimental one. The experimental animals received 2 mg of Metizol each in the form of suspension in distilled water for 21 days before the morning feeding. At the same time the control rats were given only distilled water. Three hours after the last dose of the drug or water the fasting animals were decapitated and segments of the liver were taken for histological (hematoxylin and eosin) and histochemical examination (tests for acid phosphatase by means of Gomori's method, for glucose-6-phosphatase — by means of Wachstein and Meisel's method; and glycogen — by PAS method after McManus).

RESULTS

Standard hematoxylin and eosin staining demonstrated that in the livers of the experimental animals the diameter of the capillaries increased and within their

lumen large numbers of erythrocytes could be seen. The cells lining of the capillaries also increased in size (Fig. 1).

The test for acid phosphatase indicated that the activity of this enzyme had greatly increased as compared with that in the control. The coloured grains in the hepatocytes occurred not only in the cytoplasm neighbouring the gallductules, but filled the whole cells. In the walls of the sinus vessels the cells were greatly enlarged and exhibited an intensive reaction (Fig. 2).

Glucose-6-phosphatase activity in the liver of the control animals was moderate, although their content of coloured grains was not equal (Fig. 3). In the experimental rats the reaction intensity was greatly enhanced, also in cells of the sinus vessels (Fig. 4).

Glycogen in the hepatocytes of the control group could be seen in the form of a diffusion reaction: the walls of the blood vessels stained deeply (Fig. 5). In the experimental animals groups of cells were found in the liver lobes filled with glycogen granules (Fig. 6), others were similar to the picture in the controls.

DISCUSSION

Hormone production by the thyroid depends on the demands of the tissues. It is regulated among other things by the physiological requirement of the organism, age, the circadian rhythm, season etc. (10). During pregnancy metabolic changes in "tuning" of many organs occur in pregnant females, leading as consequence to changes in the fate of drugs within the body and their effects. Examination of pregnant women demonstrated that the concentration of drugs in the blood is reduced, owing to their enhanced elimination with the urine and more intensive biotransformation (11). The liver in pregnancy is heavier loaded than normally and contributes to a greater toxicity of drugs (2, 4). Metizol is a drug which may be used in pregnancy, but for a period as short as possible. Because in the available literature data are lacking on the behaviour of the liver tissue of pregnant females treated with Metizol, it was decided to examine this gland both histologically and histochemically.

Hematoxylin and eosin staining demonstrated that no noticeable changes occurred in the hepatocytes, but the mesothelial cells and the Browicz-Kupffer ones in the walls of the sinus vessels became distended. The presence of erythrocytes in the lumen of the capillaries may be evidence of passive hyperaemia in the liver (9).

The activity of acid phosphatase increased after Metizol administration, especially in the cells lining the capillaries, thus indicating a strong participation of lysosomes in the lytic processes in the cells (3, 8).

The reaction for glucose-6-phosphatase in the hepatocytes is closely connected with the presence of glycogen, because the latter enzyme participates in

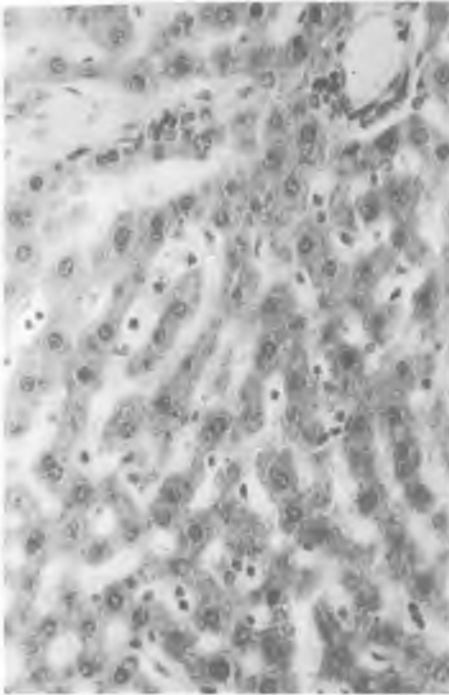


Fig. 1

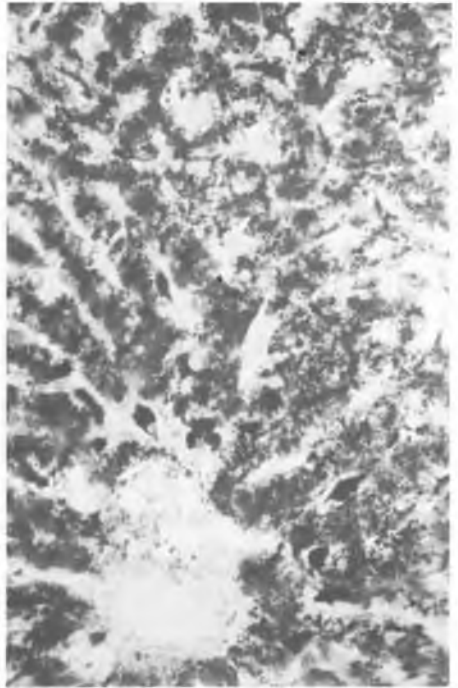


Fig. 2

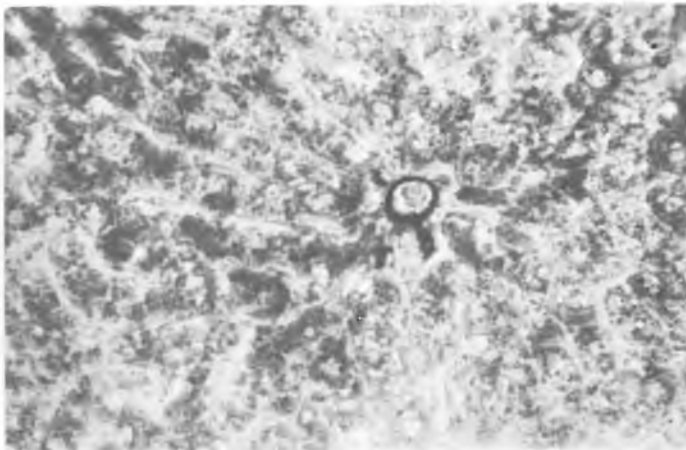


Fig. 3

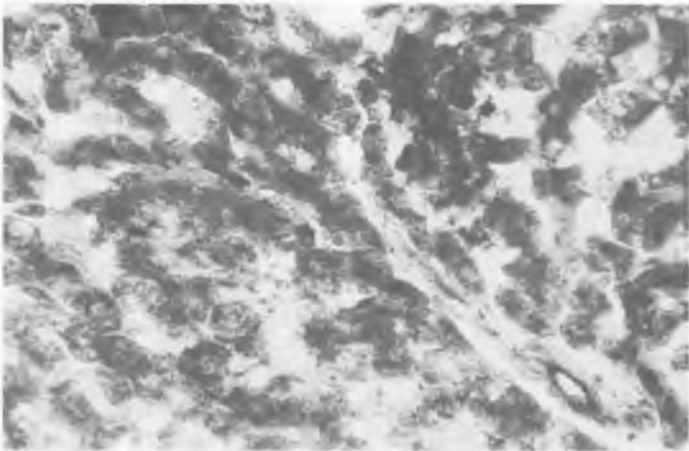


Fig. 4

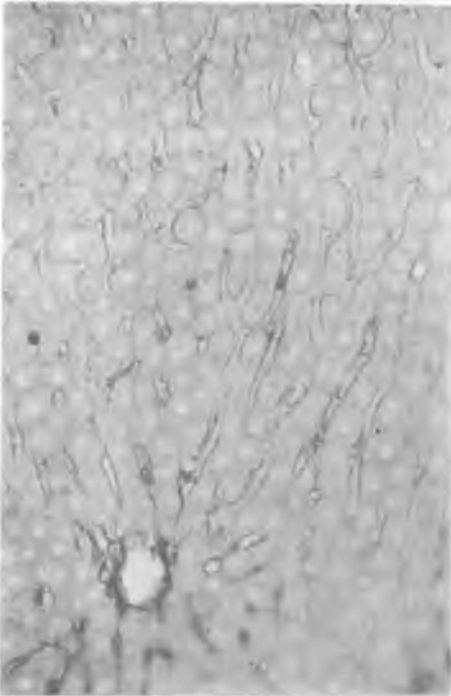


Fig. 5

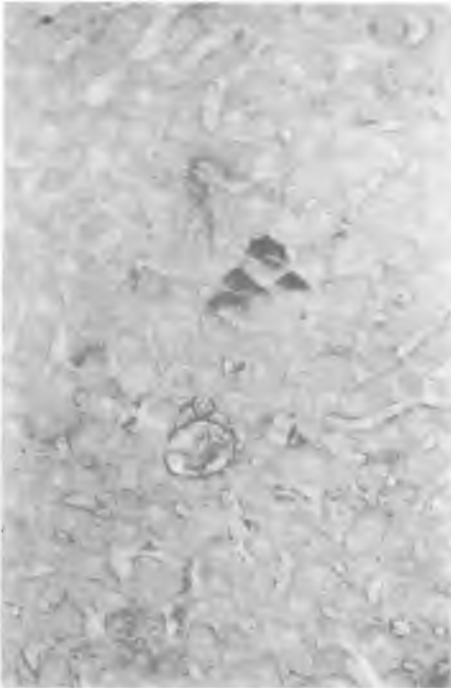


Fig. 6

glycogen synthesis and lysis. According to the literature (5), the amount of glycogen in the liver diminishes with increasing activity of the enzyme. The content of this polysaccharide depends on many factors both external (age, diet, time of the day, season, trauma or neoplasms), and internal ones affecting hydrocarbon metabolism: insulin, glycogen, adrenal cortex and thyroid hormones (10). The sex of the animal also makes a difference since it was ascertained that there is more glycogen in the liver of females. Under normal conditions there is a certain constant rhythm in the distribution and amount of glycogen, depending on the nutrition and nervous and hormonal regulation (1). Data have been reported on an exhaustion of glycogen stores in the liver as quickly as after several hours of starvation (7). It appeared in the present investigations that both in the control and the experimental livers the test for glycogen was almost negative. This probably was caused by the lack of food (24 hrs before decapitation) and the enhanced requirement of sugar in females before parturition.

The histochemical studies demonstrated that Metizol did not cause major changes in the microscopic pattern of the liver. It is, however, difficult to decide whether it would prove of equally low toxicity in the human liver. The influence of the drug on the progeny may be noxious (2), one should, therefore, use this drug with circumspection.

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EXPLANATION TO FIGURES

Fig. 1. The liver of the rat, experimental group. Hematoxylin and eosin. Magn. 200 × .

Fig. 2. The liver of the rat, experimental group. Acid phosphatase by Gomori method. Magn. 200 × .

Fig. 3. The liver of the rat, control group. Glucose-6-phosphatase by Wachstein and Meisel method. Magn. 200 × .

Fig. 4. The liver of the rat, experimental group. Glucose-6-phosphatase by Wachstein and Meisel method. Magn. 200 × .

Fig. 5. The liver of the rat, control group. PAS method by McManus. Magn. 200 × .

Fig. 6. The liver of the rat, experimental group. PAS method by McManus. Magn. 200 × .

STRESZCZENIE

Badano wątroby ciężarnych samic szczurów rasy Wistar, którym podawano przez 21 dni Metizol w dawce 6-krotnie większej niż stosowana u ludzi. Kontrolna grupa ciężarnych samic leku nie otrzymywała. Stosowano barwienie hematoksyliną i eozyną oraz wykrywano histochemicznie aktywność fosfatazy kwaśnej, glukozo-6-fosfatazy i glikogenu. W wątrobach zwierząt doświadczalnych uległy poszerzeniu zatokowe naczynia włosowate. Zwiększyła się aktywność fosfatazy kwaśnej oraz glukozo-6-fosfatazy w hepatocytach i komórkach wyścielających wyżej wspomniane naczynia. Reakcja na glikogen okazała się negatywna zarówno w wątrobach zwierząt kontrolnych, jak i doświadczalnych.