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EFFECT OF TOXIC LIVER DAMAGE ON THE GENERATIVE FUNCTION OF RATS

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There is convincing evidence in the literature that hepatitis and cirrhosis arising through the action of infectious or toxic agents are accompanied by marked disturbances of neuroendocrine regulation and metabolism, and by structural changes not only in the liver, but also in other organs and systems, including the reproductive sphere [1, 2, 4, 5, 7-9, 11, 12, 14, 15]. However, the effect of infectious and toxic liver damage on generative function has not yet been adequately studied. Naturally it is not always possible to study this problem fully under clinical conditions, and accordingly experimental investigations can be of definite assistance in this connection.

There are indications in the literature that liver damage caused by the alkaloid heliotrine, contained in the weed *Heliotropium lasiocarpium*, which occurs episodically at the present time, is characterized by a pathomorphological and, to a certain degree, a functional-metabolic picture which in many respects is similar to that of the changes in infectious hepatitis [1, 6, 10]. However, in the accessible literature no studies of the effect of this form of liver damage on reproductive function could be found.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats of both sexes weighing initially 120-140 g. Heliotrine poisoning was produced by subcutaneous injection of a solution of the alkaloid heliotrine in a dose of 25 mg/100 g body weight [1]. There were four series of experiments: I) control (12 females), II) injection of heliotrine into males which were mated with intact females (18 females) on the 25th day from the beginning of the experiment; III) injection of heliotrine into females which were mated on the 25th day with intact males (28 females). IV) Injection of heliotrine simultaneously into females and males, which were mated on the 25th day of poisoning (28 females).

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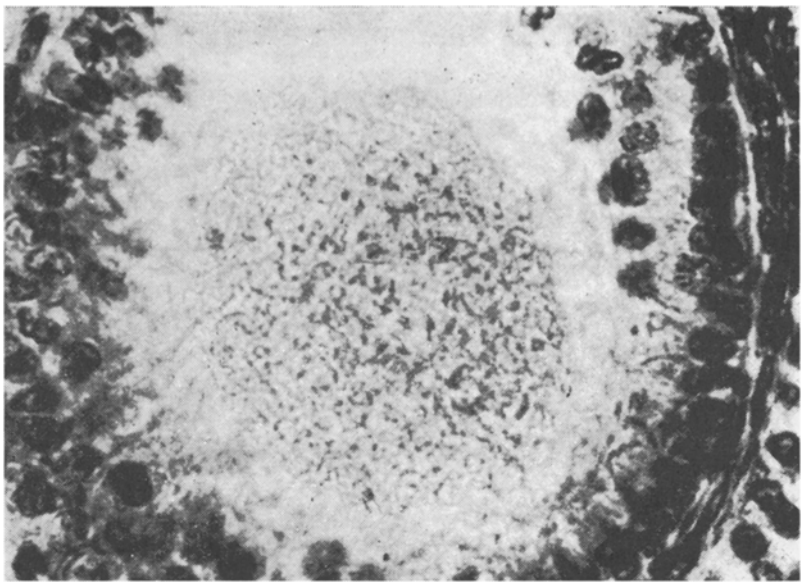

Fig. 1. Ovary of rat with heliotrine hepatitis. Degenerative changes in oocyte in growing follicle. Perinuclear edema in cells of follicular epithelium. Hematoxylin—eosin, 400 ×.

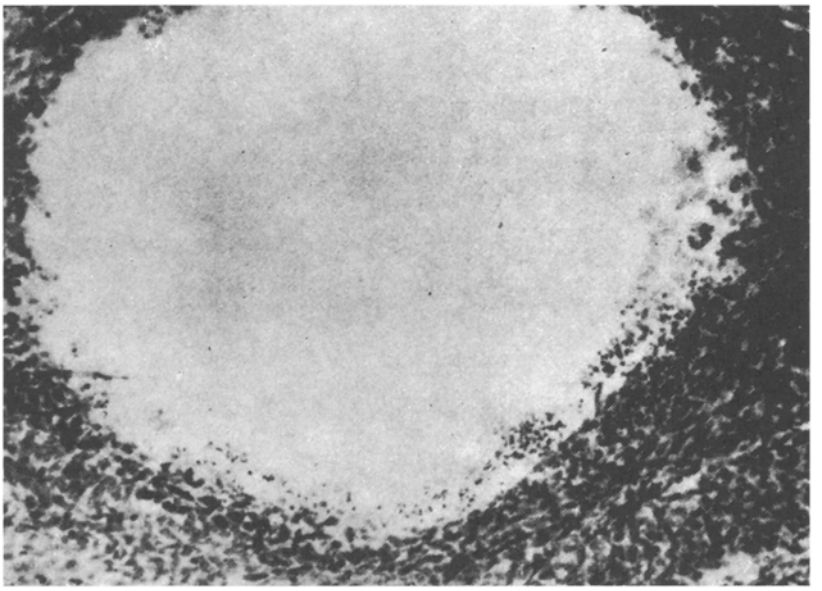

Fig. 2. Ovary of rat with heliotrine hepatitis. Formation of cyst-like cavity at site of former ripe Graafian follicle and fragmentation of zona granulosa. Hematoxylin—eosin, 400 ×.

We know from data in the literature that during heliotrine poisoning the most marked picture of acute toxic liver damage is observed on the 25th day after injection of heliotrine. Accordingly, and considering that pregnancy in rats lasts 19-21 days, when the experiments were planned these times were used for guidance and the animals were sacrificed on the 35th and 45th days from the beginning of the experiment, which corresponded to the first and second halves of pregnancy, respectively. The day after a female in the phase of estrus was mated with males was taken to be the first day of pregnancy. The presence of spermatozoa in the genital tract was determined by examination of vaginal smears [3].

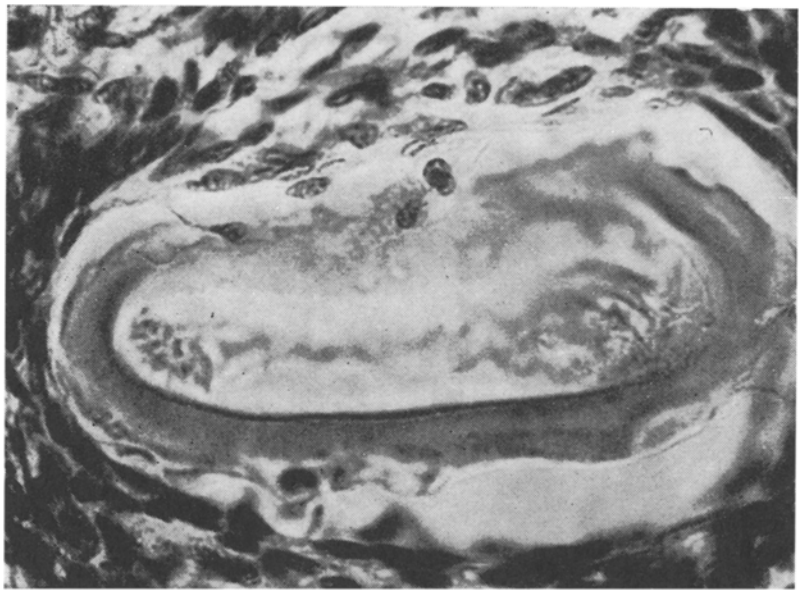

Fig. 3. Ovary of rat with heliotrine hepatitis. Considerable thickening of zona pellucida and death of oocyte. Hematoxylin—eosin, 400 ×.

EXPERIMENTAL RESULTS

Conception took place in 91.3% of animals of the control series, during the first 2-3 days after mating. Autopsy on the animals of this series showed that as a rule there were 8-10 or, occasionally, 12 fetuses, distributed almost uniformly in the uterine cornua. The results of the experiments of series II (only males were poisoned with heliotrine) showed that conception occured in six (33.3%) of the 18 animals, after a certain delay compared with the control series. At autopsy on the animals of series II no special differences were found compared with the experimental animals of the control series. Meanwhile a morphological investigation was made of the ovaries, both of the pregnant females and of those which had not conceived. No pathological changes were found in the ovaries likewise. The results of the experiments on animals of series III (the females were poisoned) showed that 12 (42.8%) of the 28 animals did not become pregnant. Conception in the remaining animals took place during the first 2 or 3 days after mating. However, as autopsy revealed, the number of fetuses in these animals was considerably reduced to 6-7, and their numbers were not uniformly distributed in the uterine cornua, and indeed, fetuses were sometimes absent in one cornu. Microscopic investigation of the ovaries of animals of this series which did not become pregnant showed marked circulatory disturbances on the 35th day of poisoning, with edema of the stroma of the ovaries, degenerative changes in the oocytes in the primordial and growing follicles (Fig. 1), and swelling of the follicular cells. Total destruction of oocytes and fragmentation of the zona granulosa were observed in some growing and ripe follicles (Fig. 2). An increase in the number of atretic follicles and proliferation of the theca-tissue were observed. In some cells of certain corpora lutea degenerative changes were found, but together with altered mature and growing follicles, ripe Graafian follicles without any special changes could also be seen. Changes of a similar type were found on the 45th and 65th days from the beginning of the experiment.

In the ovaries of the animals of series III, in which conception took place, microscopic investigation revealed a normal, undisturbed structure of the organ. Ripe corpora lutea could be seen, with individual growing follicles and interstitial tissue at the periphery.

In the experiments of series IV (both females and males were poisoned), 11 (61%) of the 18 animals did not become pregnant. In animals which did not conceive the number of fetuses was sharply reduced to 3-4 compared with 8-12 in the control series. In this series, just as in the previous one, the number of fetuses in one of the uterine cornua was reduced in animals sacrificed on the 35th and 45th days after poisoning.

Histological investigation of the ovaries revealed at all times changes identical with those in the experiments of series III both in the pregnant animals and in those which did not conceive (Fig. 3).

These changes can evidently be explained on the grounds that the liver is a target organ for several sex hormones, both male and female. Accordingly it must be assumed that the liver has a significant influence, both directly and through feedback, on functional and structural properties of the gonads and on their hormonal activity. When injured by a toxic agent, in this case by heliotrine, the liver parenchyma is less capable of maintaining the physiological level of metabolism and of inactivating hormones produced in the ovaries.

We know from data in the literature [13] that testicular function also is disturbed in liver pathology. This is also confirmed by the results of the present experiments, for the most marked changes in generative function were observed after poisoning of both males and females.

To sum up, it can be postulated that not only toxic (heliotrine, CCl_4, thioacetamide, etc.) but also, in all probability, infectious forms of hepatitis have a significant effect on the possibility of onset, development, continuation, and completion of pregnancy. This must be taken into account during the treatment of pregnant women suffering from virus or toxic hepatitis. The obligation to pay serious attention to functional-metabolic and structural changes in the liver, disorders of which may be one cause of disturbance of generative functions, during the treatment of women suffering from primary and secondary sterility, will be evident.

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