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د راسة هستوباثولوجيه ومورفومترية للتغيرات التي تحدث في كبد الفئران نتيجة انخفاض نشاط الغده الدرقية

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أجرى هذا البحث لد راسة تأثير انخفاض معدل نشاط الغده الدرقية على الكبد ، ولقد استخدمت مادة الميثيل ثيويوراسيل بحقنها تحت الجلد في حيوانات التجارب ، واستخدم في هذا البحث عدد ٥٠ (خمسون) فأراً أبيض قسموا الى أربع مجموعات كل مجموعة من ١٠ (عشرة) فئران بالاضافة الى مجموعة خامسة لم تحقن واستخدمت للمقارنة .

ولقد تم د راسة التغيرات الهستوباثولوجيه وكانت عبارة عن استحاللات بروتينية واحتقان في الكبد .

كذلك تم د راسة التغيرات المورفومترية التي حدثت في الكبد واستخدم لذلك قياس حجم الأنوية الخاصة بخلايا الكبد ، ولقد وجد أن حجم الأنويه قد زاد زيادة ملحوظة في المجموعتين الأولى والثانية التى حقنت بتركيز عال من الميثيل ثيويوراسيل .

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EXPERIMENTAL STUDY OF HYPOTHYROIDISM IN RATS
2- HISTOPATHOLOGICAL AND MORPHOMETRICAL CHANGES IN THE LIVER
(With 1 Table, 1 Histogram & 1 Figure)

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SUMMARY

The present study was designed to investigate the effect of experimental hypothyroidism induced by subcutaneous injection of methylthiouracil (MTU) on the morphological and morphometrical changes in the liver of the rat. Fifty rats were used in this experiment. They were divided into four groups A,B,C and D and injected by subcutaneous route with methylthiouracil at a dose level of 10, 0.5, 0.2 and 0.1 mg. per kg. body weight respectively. In addition, a fifth group (E) of 10 rats was used as a control. The histopathological examination revealed pronounced congestion together with focal degenerative changes. The morphometrical changes were characterized by an increase in the nuclear diameter of hepatic cells in the first two groups.

INTRODUCTION

Severe thyrotoxicosis requires a prolonged therapeutic course of antithyroid drug which may result in severe complications. The later include, beside many other abnormalities, a hepatotoxic effect (SCHARF, 1963). Moreover, the liver plays an important role in thyroxine metabolism. It is the site of synthesis of thyroxine binding globulin and of the formation of glucuronide and sulphate conjugates of the thyroid hormones. In addition, the liver is also the site of active thyroxine deiodination and of degradation of the alanine side chain of thyroxine. It is also a major target site of thyroxine conversion to triiodothyroxine and for the metabolic actions of thyroxine and triiodothyroxine (DEGROOT and STANBURY, 1975).

The aim of the present work was to study the side effects of administration of methylthiouracil as an antithyroid drug both histopathologically and by use of karyometry as a sensitive indicator of the functional and metabolic cell-activity.

MATERIAL and METHODS

The materials* employed in the present work included 50 male wistar rats (200 - 250 gm. body weight). The experimental animals were manipulated under the environmental condition of 22°C room temperature and were rationed ad libitum and adequately supplied with tap water. The animals were regularly exposed to light for 12 hours per day. The rats were divided into 4 groups A,B,C,D of 10 animals each. The animals were individually treated daily with subcuta-

* This experiment was done in the institute of pathology, school of veterinary medicine, Hannover.

neous injections of 6-hydroxy-2-mercapto-4-methyl-pyrimidin, methylthiouracil (MTU) for one week at adose level of 10, 0.5, 0.2 and 0.1 mg. per kg. body weight for groups A,B,C,D respectively. In addition, a fifth group (E) of 10 animals was used as a control.

The liver was collected from the rats after they were sacrificed (by decapitation) and was fixed in 10% neutral buffer formalin. Paraffin sections were cut 4-5 microns thickness and were stained with haematoxylin and eosin stain.

The histological slide was projected on a screen using a "Karl Zeiss" microscope with a halogen lamp to obtain a magnification of 800 folds. Each liver was represented in 5 serial sections. From each animal the diameter of 50 hepatic cell nuclei which are located around the central vein were measured. Statistical methods were carried out to postulate the changes given in each test. The mean values of each measurement for different groups were statistically analysed using computer.

RESULTS

I- Histopathological change:

The main histopathological changes in the liver in case of methylthiouracil administration were focal degenerative changes together with pronounced congestion. These changes had a centrilobular distribution and varied from granular proteinous dystrophy to perinuclear light swelling and reached its summit as cell hydrops in individual hepatocytes (Fig. 1).

Group A, in which the animals received 10 mg. methylthiouracil per kg. body weight, was more severely affected and the degenerative changes involved wide areas of the hepatic lobules than in the other groups which received the smallest dose. Moreover, congestion was much more prominent in this group.

II- Morphometrical changes:

Data from the morphometrical parameter of the diameter of nuclei of the hepatic cells are shown in (Table 1). Statistical analysis of this data revealed a significant difference ($P/0.001$) of the average value of diameter of hepatic cell nuclei in groups A and B given the highest doses of methylthiouracil as compared with control animals (Histogram 1). No changes were recognized in the diameter of hepatic cell nuclei in the other two groups.

DISCUSSION

Thiouracil group, specially methylthiouracil, is a thyrostatic drugs preventing the synthesis of thyroxine by inhibition of iodination MARTINI, 1950, FORSTER *et al.* 1955 and LUDEWIG, 1960). Accordingly, a decreased level of thyroxine production, or its depletion, threw a decreased burden on the liver in the process of degradation of thyroxine or triiodothyroxine.

In the present work, statistical analysis revealed that the diameter of the nuclei of hepatic cells was significantly increased in animals of the first two groups administered methylthiouracil at a dose level of 10 and 0.5 mg. per kg. body weight. These results are in contrast with that recorded by SCHARF *et al.* (1969) who showed that administration of 25 mg. per kg. body weight of methylthiouracil alone or in combination with other substances (hydroxypropionphenon, diiodotyrosine, alloxan) to rats were associated with a decrease in the volume of hepatic cell nuclei. These authors concluded that the decrease in the volume of hepatic cell nuclei is a manifestation of a relative inactivation of the liver as the antithyroid drugs depressed the total basal metabolism and oxygen turnover. Increased nuclear volume of the hepatic cells

EXPERIMENTAL HYPOTHYROIDISM IN RATS

in the first two groups in the present experiment, therefore, can not be an expression of increased functional activity. In our opinion, the process may be probably of a regenerative character specially that the dystrophic changes of the hepatic cells were mild ones. This was indicated by SCHARF *et al.* (1967) who found that after the administration of methylthiouracil to rats (25 mg. per kg. body weight for 47-58 days), the liver damage was manifested in delayed regenerative capacity and glycogenic infiltration. However, the above mentioned authors (SCHARF *et al.* 1967 and 1969) used a larger dose of methylthiouracil for a longer experimental period than in our experiment.

As the metabolism of methylthiouracil occurs in the liver, the increased mean diameter of the hepatic cell nuclei in the present study may be also due to a direct action of the antithyroid drug on it. This may be correlated with the results of SCHLICHT *et al.* (1968) who found an increase in the diameter of hepatic cell nuclei of rats after administration of barbiturates.

From our results, it was found that changes of the mean diameter of the hepatic cell nuclei at a dose level of 0.2 mg. methylthiouracil per kg. body weight were insignificant. This finding is of a pharmacological importance as at a dose level of 0.2 mg. methylthiouracil, hypothyroidism can happen with no effects on the liver. At the same time, this can be regarded as an ideal model of inducing hypothyroidism in rats without any pathological alterations in the liver.

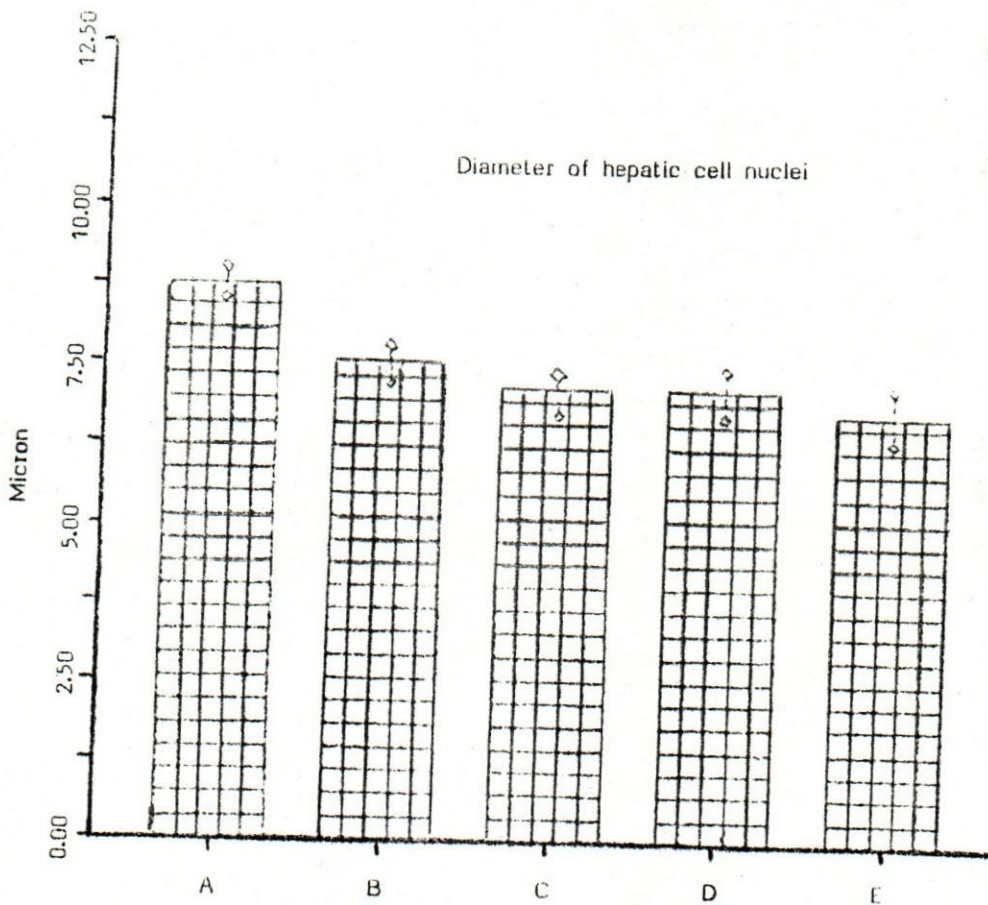
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Table (1)
Diameter of hepatic cell nuclei

Group	Mean	Standard deviation
A	8.75 ***	+ 0.23
B	7.56 ***	+ 0.11
C	7.16	+ 0.22
D	7.16	+ 0.28
E	6.78	+ 0.42

* = $P/0.5$
 ** = $P/0.01$
 *** = $P/0.001$



Histogram (1): showing the average diameter and standard deviation of the hepatic cell nuclei under different dose level of MTU.

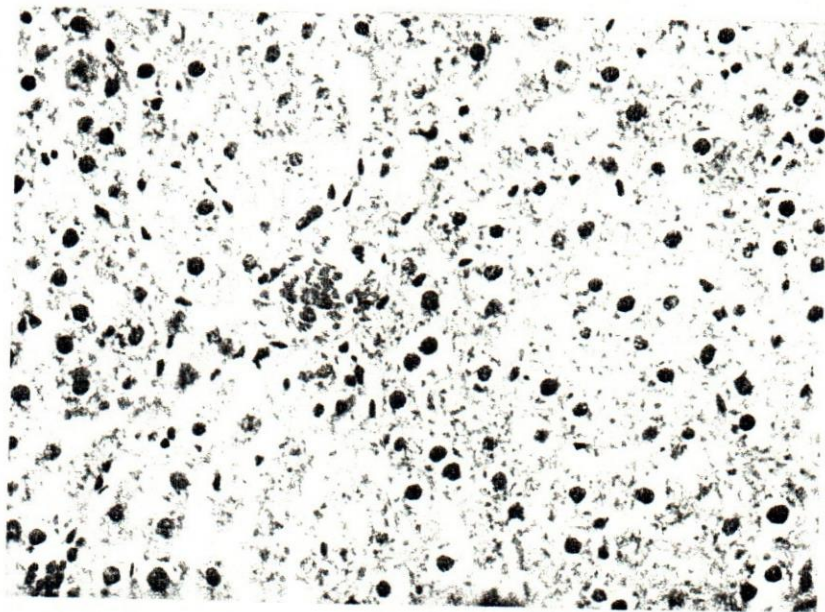


Fig. (1): Liver showing centrilobular granular proteinous dystrophy, perinuclear light swelling and hydropic degeneration. H. & E. stain. X 250.