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Mitoses in the Livers of Rats Treated with Thiourea.

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The purpose of the present communication is to report the remarkable effect of large doses of thiourea on the liver of rats. This effect is manifested by the appearance of numerous mitoses in the liver cells.

Material and Methods. Thirty-six young male albino rats, weighing between 70 and 100 g were used in these experiments. Four-tenths of a gram of thiourea in a 10% aqueous solution was injected by the intraperitoneal route at daily intervals. Six rats died a few hours after the first injection, 3 succumbed after the second and 8 after the third. Fifteen rats survived 3 injections and were sacrificed 2 to 12 hours after the last injection. Of the remaining 4 rats 3 were sacrificed after 4, and 1 after 7 injections.

The livers were fixed in Carnoy's fluid or in Zenker's solution. Paraffin-celloidin sections 5 μ in thickness were stained with hematoxylin-eosin or with Heidenhain's hematoxylin.

Results. In the 23 rats which succumbed or which were sacrificed after 3 daily injections of thiourea, the gross appearance of the livers was normal. Microscopically, there was central congestion of the sinusoids and slight to moderate vacuolization of the liver cells in the central parts of the lobule, as well as slight alterations in the lining of the central vein. The outstanding feature was the presence of all stages of mitotic figures in the liver cells (Fig. 1). Mitoses were found in all animals receiving this treatment, but there were variations in the number of mitoses from rat to rat. In 22% of the treated rats the number of mitoses was extremely high (12 to 18 mitoses in each microscopic field);* in 26% they were numerous (6 to 12 mitoses

in each microscopic field); a moderate number of mitoses was present in 35% of the animals (1 to 6 mitoses in each microscopic field) and in 17% of the treated rats the number of mitoses was small (one mitosis being found in 1 to 3 microscopic fields).

The configuration of the mitoses was in most cases completely normal and the different phases of the mitotic processes were encountered in the usual proportions. In a number of livers abnormal mitotic figures were found in moderate or appreciable numbers. The pathological mitoses were characterized by clumping or scattering of the chromosomes. In some experiments mitosis with widely scattered chromosomes was the only type encountered. At the result of chromosomal scattering, liver cells with bizarre nuclear structures appeared at times: some loaded with minute nuclei and others with single or multiple large, lobated nuclei. The multinuclear liver cells were often exceptionally large.

In rats which died or were sacrificed within 24 to 31 hours after the first injection no mitoses were found in the liver cells. After 4 injections, *i.e.*, 72 to 96 hours after the start of the experiment, the number of mitoses was considerably lower than after 3 injections. In one rat examined after 7 injections no mitoses were found. It is thus evident that the mitotic effect is not immediate, but appears only after a certain latent period. The extensive mitotic activity of the liver seems to be limited to a time period of 48 to 72 hours after the first injection.

Comment. The occurrence of mitoses in the liver or in other visceral organs, excepting for the thyroid gland, following treatment with thiourea has not as yet been noted. In the thyroid glands of rats, receiving thiourea,

* The mitotic counts were made in microscopic fields of 0.4 mm diameter.

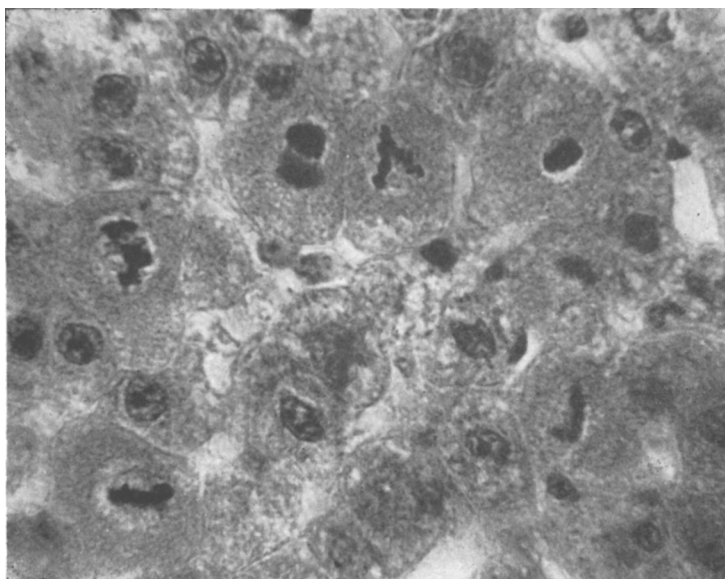


FIG. 1.
Liver of rat treated with 3 doses of 0.4 g thiourea. Mitoses in liver cells. Hematoxylin-eosin. $\times 850$.

mitoses were described by Paschkis and associates.¹

Mitoses in the normal liver of the adult rat are extremely rare.² It is well known, however, that loss of liver tissue by removal of a part of the organ or by necrosis is followed by a compensatory multiplication of liver cells. It was occasionally noted that mitoses in the liver may also occur in the absence of visible changes in the hepatic parenchyma after the administration of staphylococcus toxin,³ ma-

cerated livers, trypaflavine⁴ or trypan blue.^{5,6} No satisfactory explanation has been advanced for a mitotic reaction of this kind.

The nature of the mitotic response of liver cells to thiourea is likewise not clear. The possibility may be considered that thiourea has a direct stimulating effect on the mitotic activity of the liver cells. On the other hand, occurrence of mitoses may be regarded as a secondary phenomenon, namely as a reparatory reaction following discrete liver damage. The arguments in favor or against each of these possibilities will be dealt with in the complete communication.

Summary. The occurrence of mitosis in the liver cells of rats receiving daily intraperitoneal injections of thiourea is reported. Both mitosis of normal configuration and pathological mitosis were encountered. Thiourea induced mitotic activity of the liver seemed to be at its height during the period of 48 to 72 hours after the first injection.

¹ Paschkis, K. E., Cantarow, A., Rakoff, A. E., and Rothenberg, M. S., *Endocrinology*, 1945, **37**, 133.

² Dawson, A. B., *Growth Suppl.*, 1940, **2**, 91.

³ de Walsehe, L., *Arch. de biol.*, Paris, 1931, **42**, 185.

⁴ Mayer, Ch., *Arch. internat. de méd. exp.*, 1935, **9**, 427.

⁵ Pfuhl, W., *Z. f. Anat. u. Entwicklungsgesch.*, 1938/9, **109**, 99.

⁶ Deane, H. W., *Anat. Rec.*, 1944, **88**, 245.