

Inability of 2-3 Dithiopropanol* (BAL) to Protect the Liver Against Toxic Action of Uranium Nitrate.

W. DEB. MACNIDER.

From the Laboratory of Pharmacology, The University of North Carolina.

In a recent issue of this journal¹ certain observations were presented concerning the hepatotoxic action in normal dogs of 2-3 dithiopropanol. This investigation was closed by the following conclusion: "The experiments indicate the ability of a dithiol when given to normal dogs in an appropriately large amount per kilo to induce an hepatic injury which is characterized by fatty degeneration of the hepatic epithelium and rarely by a necrosis of this tissue. Such observations do not necessarily imply that a similar order of cellular injury would be induced in the dog under the influence of an intoxication by salts of certain of the heavy metals. Such bodies offer a bond of union for the dithiols which in turn may prevent a toxic effect which they are capable of inducing in tissues of normal constitution."

In order to examine into the above assumption the following experimental procedures have been undertaken. Eight adult dogs have been given subcutaneously one injection of 4 mg of uranium nitrate per kg. As has been previously demonstrated² the hepatic injury from such a dosage of uranium nitrate usually reaches its height between the sixth and eighth day of the intoxication. All of the animals survived the period of experimentation. With this group of control animals biopsy material was obtained from the liver on the seventh day of the intoxication for purposes of histological study. Such tissue shows a diffuse type of degenerative process in the lobules without any tendency for the injury to be initially localized in the lobular

structure. The hepatic epithelium is increased in volume from an accumulation of granules of an assumed protein derivation and by granules and droplets of lipoid material which give the characteristic microchemical reaction with Scharlach R. Such droplets fuse to form larger areas of lipoid material with a displacement of the degenerating cell nuclei. Areas of extensive necrosis have not been observed.

A second group of 8 normal dogs have been intoxicated by the subcutaneous administration of 4 mg of uranium nitrate per kg. At the time of such an injection these animals were also given intramuscularly 15 mg of 2-3 dithiopropanol per kg. The dithiol injections were continued at 9 A.M. and 9 P.M. during the course of the uranium nitrate intoxication. Five of the animals of this group failed to survive the period of 8 days allowed for the experiments. The remaining 3 dogs were sacrificed on the eighth day. Liver tissue from these animals has shown an intensification of those changes which are induced in the liver when uranium nitrate constitutes the only toxic factor employed during the experiments. (Fig. 1.) The hepatic epithelium shows a diffuse necrosis. The liver cells are outlined by accumulations of lipoid material which in some instances has ruptured the cell membrane to fuse with such material in adjacent cells. The cell nuclei have disappeared as a part of the process of necrosis.

Conclusion. In the doses employed (15 mg per kg, twice daily for 8 days), 2-3 dithiopropanol was ineffective in protecting the liver of dogs against uranium nitrate in the amounts administered.

* 2-3 dithiopropanol (BAL), 10%, benzyl benzoate 20% in peanut oil.

¹ MacNider, W. deB., *PROC. SOC. EXP. BIOL. AND MED.*, 1947, **66**, 444.

² MacNider, W. deB., *J. Pharm. and Exp. Therap.*, 1936, **56**, 359.

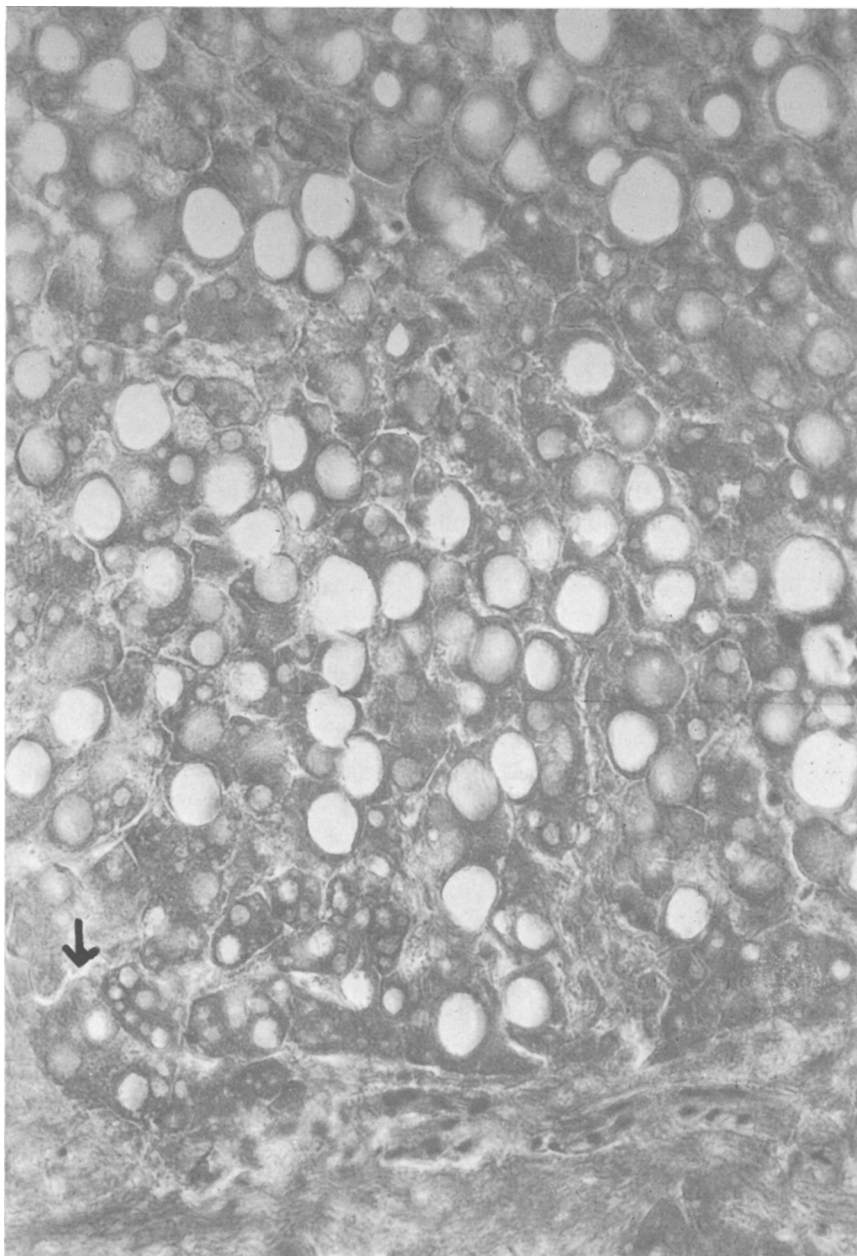


FIG. 1.

Microphotograph, Zeiss $\times 395$, hematoxylin and eosin. The figure is from the liver of animal 6, sacrificed on the eighth day of a uranium nitrate intoxication during which period the animal had received daily two intramuscular injections of 15 mg of 2-3 dithiopropanol. The figure indicates a diffuse order of hepatic necrosis with advanced fatty degeneration. The lower portion of the figure shows as outlined by fragments of nuclear material a collapsed interlobular vessel.