Effects of carbon disulphide on the liver of rats

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Bond, E. J., Butler, W. H., de Matteis, F., and Barnes, J. M. (1968). *Brit. J. industr. Med.*, 26, 335-337. Effects of carbon disulphide on the liver of rats. Normal rats surviving a single oral dose of carbon disulphide (CS₂) show liver enlargement and depression of drug-metabolizing enzymes but no liver necrosis. If the drug-metabolizing enzymes are stimulated by phenobarbitone before exposure to CS₂, the LD₅₀ does not change but liver necrosis is produced.

The toxic effects of carbon disulphide (CS₂) are well known and affect mainly the central and peripheral nervous systems, in some cases after damage to blood vessels. There is very little published work on the effects of CS₂ on experimental animals, and no generally accepted idea on its precise mode of action (Brieger and Teisinger, 1967). It is known that CS₂ is partly metabolized to dithiocarbamates, and conversely dithiocarbamates such as disulfiram (Antabuse) may be partly metabolized to release CS₂. What role the metabolites play in initiating the pathological lesions is unknown.

This paper records the observations that pretreatment with a drug (phenobarbitone), which stimulates liver microsome enzyme activity, significantly alters the degree of liver cell damage produced by CS₂. While the significance of this finding cannot yet be properly assessed, it is recorded and discussed briefly since it suggests that exposure of people to drugs or other chemicals might alter their response to CS₂. The biochemical changes induced in the liver by single doses of CS₂ are described in detail elsewhere (Bond and de Matteis, 1969).

Materials and methods

Male albino rats (150-180 g.) of the Porton strain, fed M.R.C. Diet 41B (Bruce and Parkes, 1956), were fasted

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overnight before being given by mouth CS₂ 1:1 in arachis oil. Control rats received arachis oil only.

Pretreatment by phenobarbitone involved two doses, six hours apart, of 50 mg./kg. two days before and a single dose of 80 mg./kg. one day before the CS₂. The drug, 2-diethylaminoethyl 2,2-diphenylbutyrate (SKF 525A), was used to depress the drug-metabolizing enzymes stimulated by phenobarbitone, and for this purpose 40 mg./kg. was given intraperitoneally 45 minutes before the carbon disulphide.

At autopsy tissues from the major organ were fixed in 10% formol saline. Paraffin sections were prepared in the usual fashion and stained with Harris's haematoxylin and eosin. Frozen sections were stained with oil red O for fat.

Results

Rats killed 24 hours after a dose of 1 ml./kg. CS₂ often had stomachs somewhat dilated with clear fluid, and might show moderate congestion with some haemorrhages into the lungs. The other organs appeared normal, and histologically no changes were found in the kidneys, spleen, pancreas, heart or adrenals. The liver weight of these animals was greater than that of fasted controls, but histologically little change was seen except for an increase in fat in the periportal zone. In the centrilobular zone of one animal a few cells with pyknotic nuclei and dense eosinophilic cytoplasm were present, but at no time was a zonal necrosis seen. In the remaining animals this change was not seen (Fig. 1). At a dose of 0.5 ml./kg. no histological change was seen in the liver.

Rats pretreated with phenobarbitone showed no

FIG. 1. Liver of rat killed 24 hours after treatment with carbon disulphide, 1 ml./kg., showing normal lobular pattern and no evidence of zonal necrosis. H. and E. $\times 160$.

FIG. 2. Liver of rat pretreated with phenobarbitone for two days and killed 24 hours after treatment with carbon disulphide, 1 ml./kg., showing extensive centrilobular necrosis and hydropic cell change. H. and E. $\times 160$.

difference in their general behaviour after a single dose of 1 ml./kg. CS₂, nor was the single dose LD₅₀ of CS₂ significantly changed. The most striking difference was the extent of cellular damage in the livers of these animals. At 24 hours there was an extensive centrilobular zone necrosis with a very marked hydropic change (Fig. 2). In the surrounding viable liver there was some increase in fat. An animal killed at 48 hours showed a well-developed centrilobular coagulative necrosis, but the hydropic cells were less evident. In the surrounding intact parenchymal cells, multiple mitotic figures were present. The lesion described here is very similar to that induced by carbon tetrachloride. That the production of liver damage was linked with an increased activity of the liver microsome enzymes is suggested by the experiments with the drug SKF 525A. This compound is said to depress the activity of the drug-metabolizing enzymes in the liver, and when it was given to rats that had been pretreated with phenobarbitone, CS₂ no longer produced severe liver cell necrosis.

Discussion

It is impossible to interpret these experimental observations at the present time, and there is no evidence from very extensive human experience that liver damage forms part of the picture in acute or chronic poisoning by CS₂. However, these observations do suggest that CS₂, despite its chemical reactivity, only damages some cells after it has been enzymatically converted into a toxic metabolite. Any attempt to learn more about the mode of action of CS₂ must take such a possibility into account.

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