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## PREVENTION OF ACETAMINOPHEN HEPATOTOXICITY BY DISULFIRAM

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Acetaminophen, in Europe called paracetamol, is a widely used antipyretic and analgesic. It is well established that acute liver damage occurs after overdose. The toxic mechanism has been associated with hepatic metabolism of the drug.

The major part of a dose is metabolized in the liver by conjugation and sulfation, and a small part is metabolized by cytochrome P-450 mixed-function oxidases. The metabolite is thought to be a reactive metabolite with arylating properties that is detoxified immediately by hepatic glutathione and excreted as acetaminophen mercapturate and cysteine. Following a large overdose, hepatic glutathione is depleted and the reactive metabolite is assumed to bind covalently to hepatic macromolecules thereby initiating the processes leading to hepatic necroses (1). According to this mechanism, inhibition of the toxic pathway should reduce the covalent binding of acetaminophen to hepatic macromolecules, provided that the major pathways are unchanged.

In the present study, we used disulfiram to inhibit the toxic pathway. We used female Wistar rats pretreated with disulfiram for 18 hr or twice a week for 3 weeks prior to acetaminophen (4.25 g/kg BW) given by gastric tube.

Histological examination 24 hr after acetaminophen showed hepatic necroses in untreated animals. Necroses were abolished in animals pretreated with disulfiram.

Hepatic function, estimated as the prothrombin index, was reduced following acetaminophen overdose. In animals pretreated with disulfiram the depression of hepatic function was less severe after acetaminophen overdose, in accordance with the lesser histological changes in that situation.

The depletion of hepatic glutathione after acetaminophen overdose was also counteracted by disulfiram pretreatment.

The mechanism by which disulfiram prevents acetaminophen hepatotoxicity was examined by estimating the excretion of acetaminophen-mercapturate and -cysteine into urine, and by estimating the covalent binding of tritiated acetaminophen to hepatic proteins. Disulfiram pretreatment reduced the excretion of glutathione adducts into urine. However, covalent binding of acetaminophen was practically identical in untreated and disulfiram-pretreated animals. These findings are in accordance with our earlier data (2,3).

In conclusion, this study demonstrates that disulfiram pretreatment prevents the hepatotoxicity of an acetaminophen overdose. The mechanism by which this prevention is accomplished is not quite clear. Although the supposed toxic pathway appears inhibited, and glutathione depletion is abolished, the prevention is not due to a reduction in the covalent binding of acetaminophen.

### REFERENCES

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