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CERTIFICATE OF COMPLETION

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This is to certify that the above mentioned completed all the requirements at Graduate School of Medical Sciences, Toyama Medical and Pharmaceutical University and graduated with the Degree of Doctor of Medical Science on March 20, 1991.

March 20, 1991

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SUMMARY

In the present study, isolated periportal (PP) and perivenous (PV) hepatocytes from normal and drug-treated rat livers by a collagenase gradient perfusion technique were used to examine the following; the intralobular localization of cytochrome P450 IA, P450 IIB, P450 IIE and P450 IIIA dependent monooxygenase activities and the effects of phenobarbital (PB), beta-naphthoflavone (BNF) and pregnenolone-16 alpha-carbonitrile (PCN) on the zonal induction of these monooxygenases.

Among the four monooxygenase activities only ethylmorphine N-demethylase (EMND) activity, which is revealed by P450 IIIA, was significantly dominant in the PV zone. Therefore the PV dominance of cytochrome P450 IIIA dependent monooxygenase activity is suggested to play a pathogenic role for the centrilobular necrosis due to bromobenzene. Again, among the drug induced P450 dependent monooxygenase activities only EMND activity following PB-treatment showed the PV dominance. Therefore this condition is suggested as one of the factors responsible for the aggravation of bromobenzene induced centrilobular liver necrosis following PB-treatment.