Thesis Title Induction of Hepatic Drug-Metabolizing Enzymes by Probenecid in Rats

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## ABSTRACT

The inductive effect of probenecid on hepatic drug-metabolizing enzymes in the rats has been studied both *in vivo* and *in vitro*. The model drugs used in this study are aminopyrine, aniline and p-nitroanisole. It was found that probenecid induced the activities of both aminopyrine N-demethylase and p-nitroanisole O-demethylase. Probenecid at 600 mg/kg, PO, twice daily for 5 days was found to produce maximum increase in the activities of both enzymes. The increased aminopyrine N-demethylase activity was prevented by prior administration (2 hr) of actinomycin D ( 0.1mg/kg, IP, at day 1 and 4 ) but not by cycloheximide ( 2 mg/kg, IP, at day 1 and 4 ). The inductive effect of aminopyrine N-demethylase reached its maximum in 4 days and declined to normal in about 5 days after cessation of the

drug. Kinetic studies provided support for the concept that the enzymes from both the normal and probenecid-treated livers were the same. However, this schedule of probenecid pretreatment had no effect on aniline hydroxylase activity. The nature of hepatic drug-metabolizing enzyme stimulation by probenecid appeared to resemble that of the phenobarbital-type inducers, especially because : (1) probenecid caused a noticeable proliferation of the smooth endoplasmic reticulum ; (2) the time required for maximal induction and duration of its effect were almost equal to that of phenobarbital ; and (3) the changes in apparent Vmax and Km values were in the same pattern.

The results from studies *in vivo* were also consistent with the *in vitro* findings. Probenecid ( 600 mg/kg, PO, twice daily for 5 days ) was found to shorten zoxazolamine paralysis time. This finding is also in accord with the results in human experiments of other investigators.