GENETIC AND METABOLIC STUDIES OF DIPHENYLHYDANTOIN-INDUCED TERATOGENESIS IN MICE

by

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a Thesis

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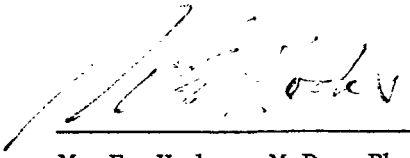

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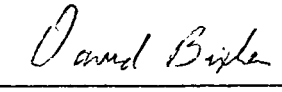

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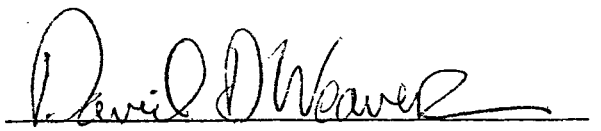

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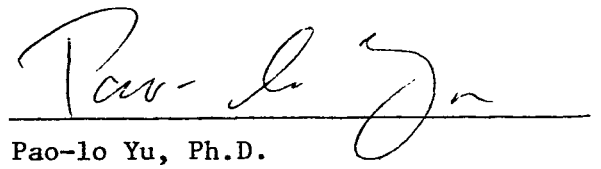

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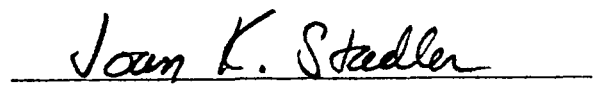

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TABLE OF CONTENTS

Genetic and Metabolic Studies of Diphenylhydantoin-induced Teratogenesis in Mice

by

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ABSTRACT

Diphenylhydantoin (DPH) is one of the most commonly prescribed anticonvulsant drugs on the market. Recent reports have implicated this drug in the production of various malformations present in the children born to epileptic women. Genetic factors have often been implicated in this process, but the role that they play has not been clarified. It is the purpose of this project to discern if predisposition to DPH-induced malformations may be genetic.

A mouse model system was used for the analysis. Several inbred strains of mice were utilized. DPH was injected into pregnant females of each strain during a critical period of fetal development. Females were sacrificed shortly before delivery, and the uterine contents were examined. Variables which were scored included the frequencies of resorptions, stillbirths, malformations, and orofacial anomalies as well as fetal weight, fetal length, and transumbilical distance. The data from treated animals were compared to data from control (vehicle-treated) animals within each strain.

Differences among the strains in their susceptibility to drug-induced malformations were obvious. A/J mice were particularly susceptible, and animals of the C57BL/6J strain were highly resistant. Susceptibility of hybrid animals was determined by the susceptibility of the maternal parent. F1 offspring of A/J mothers were as susceptible as inbred A/J mice, and the offspring of C57BL/6J mothers were as resistant as inbred C57BL/6J mice. F2 animals were as resistant as their C57BL/6J grandparents.

Differential maternal metabolism might account for this effect. Since the drug is predominantly metabolized by the cytochrome P-450 system of the liver in vivo, hepatic microsomes were prepared from males, females, and pregnant females of both the A/J and C57BL/6J strains. Quantitative differences in the levels of DPH metabolites produced were examined with a recently developed high performance liquid chromatographic assay. Several compounds known to induce various cytochrome P-450 enzyme activities were tested for their effect on DPH metabolism. There were no significant differences between the strains in the levels of metabolites produced, although there were differences which were dependent on the inducer employed.

These results suggest that differential maternal metabolism does not account for the maternal effect seen in F1 offspring. Other factors which might explain this effect are briefly discussed.