Teratogenic Effects of the Antiepileptics and Antipsychotics

Thesis

Submitted for Partial Fulfillment of
M. D. Degree
In
Anatomy

By
Hemmat Abdel Kader Abdel Hamid
M.B., B.Ch. - M.Sc. (Ain Shams)

Under the supervision of

Prof. Dr. Sawsan A. Abdel Rahman
Professor of Anatomy
Faculty of Medicine
Ain Shams University

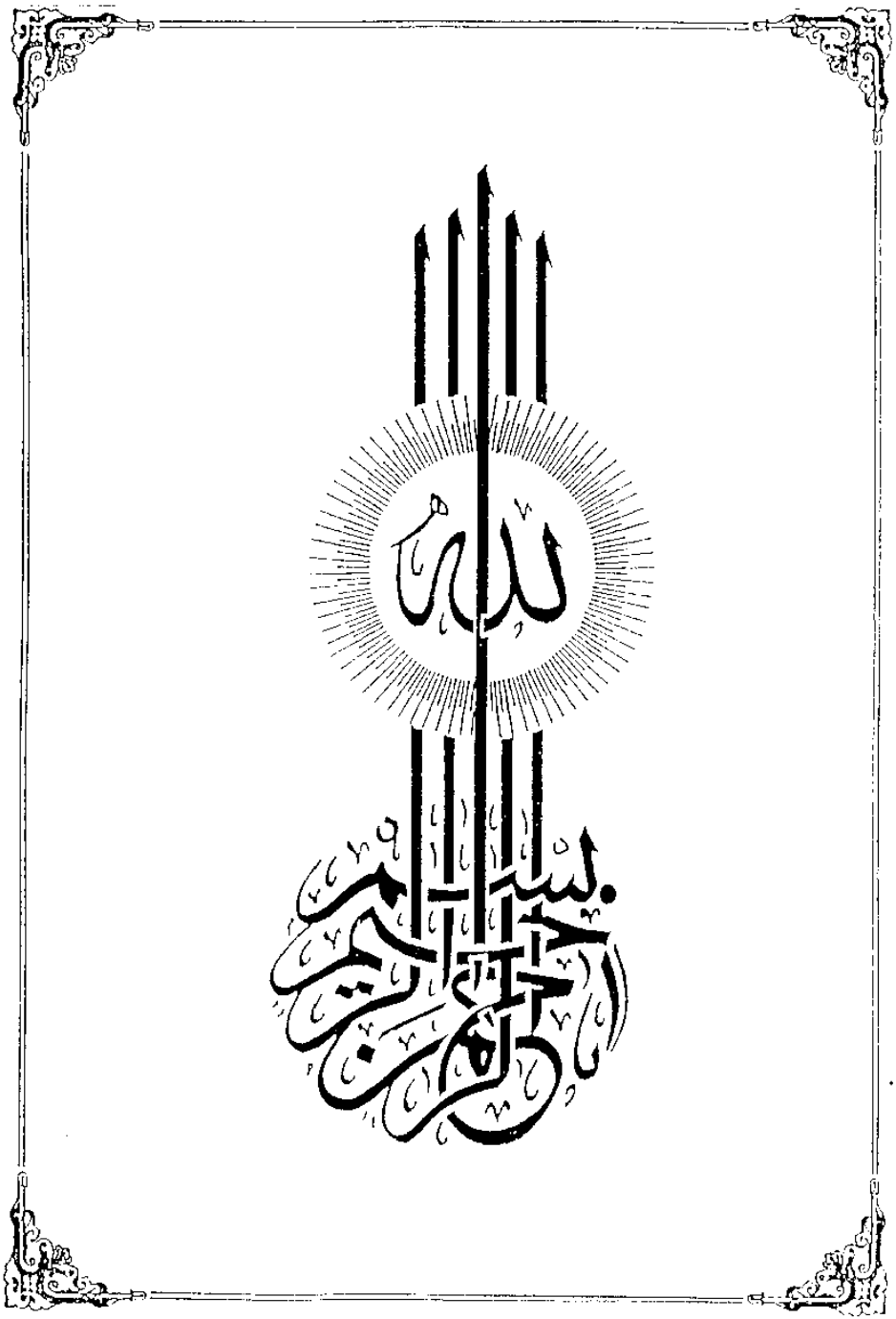
Prof. Dr. Mohamed S. Abdel Rahman
Professor of Pharmacology
Director of Toxicology
Unitversity of Medicine and
Dentistry of New Jersey
U.S.A.

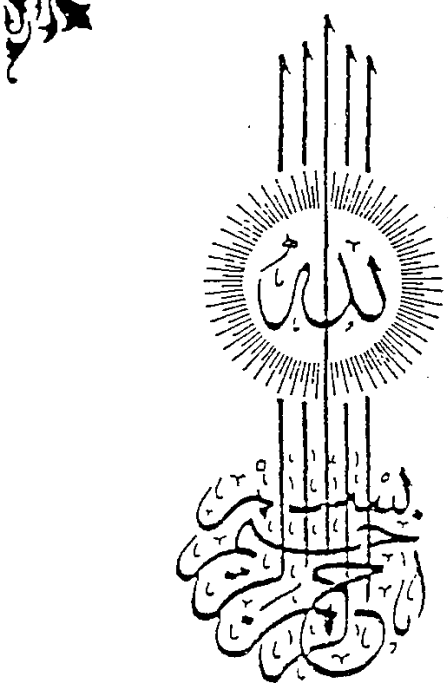
Prof. Dr. Wagdy Mahmoud Ghally
Professor of Anatomy
Faculty of Medicine
Ain Shams University

Dr. Hany El-Hessy
Ass. Prof. of Anatomy
Faculty of Medicine
Ain Shams University

Dr. Salwa Saad Lashin
Ass. Prof. of Anatomy
Faculty of Medicine
Ain Shams University

Faculty of Medicine - Ain Shams University
1996





﴿ وعلمك ما لم تكن تعلم
وكان فضل الله عليك عظيما ﴾

صدق الله العظيم [النساء ١١٣]

ACKNOWLEDGEMENT

I wish to express my thanks to my supervisor ***Prof. Dr. Sawsan A. Abdel Rahman,*** Professor of Anatomy, Faculty of Medicine, Ain-Shams University, for her valuable supervision, criticism and discussion.

I wish to express my gratitude to ***Prof. Dr. Mohamed Shawky Abdel Rahman,*** Professor of Pharmacology and Director of Toxcicology, New Jersey, Medical School, for his continuous support and guidance.

I feel grateful to ***Prof. Dr. Wagdy Mahmoud Ghally,*** Professor of Anatomy, Faculty of Medicine, Ain-Shams University, for his help to accomplish this work.

I would like to thank ***Ass. Prof. Dr. Hany El-Hessy,*** Assistant Professor of Anatomy, Faculty of Medicine, Ain-Shams University, and ***Ass. Prof. Dr. Salwa Saad Lashin,*** Assistant Professor of Anatomy, Faculty of Medicine, Ain Shams University, for their continuous support and guidance.

I am deeply indepted to all the ***Members of the Department of Pharmacology and the Department of Anatomy, New Jersey Medical School,*** for their great care and valuable support.

I should also acknowledge the ***Depatment of Missions of the Ministry of Education and the Egyptian Cultural and Educational Bureau of the Egyptian Embassy in Washington, D.C., USA,*** for sponsoring this experimental work.

CONTENTS

Introduction & Aim of The Work

INTRODUCTION
&
AIM OF THE WORK

Teratology is the branch of science concerned with all aspects of abnormal prenatal development including the study of all causes and pathogenesis of congenital defects.

Drugs vary considerably in their teratogenicity. Some of them cause severe disruptions of development if administered during the organogenetic period. Others produce mental growth retardation and other anomalies if used excessively throughout development. Several studies have indicated that some pregnant women take an average of four drugs, excluding nutritional supplements, and about half of these women take them during the first trimester of pregnancy *(Schardein, 1993)*. It is estimated that between seven and ten percent of human birth defects result from disruptive actions of drugs, viruses and other environmental factors *(Brent and Beckman, 1990)*.

The incidence of epilepsy is between 1 - 2% in the general population. In most cases, epilepsy begins before 20 years of age, and must be treated with antiepileptics (anticonvulsants) throughout life, including the reproductive years in the females *(Schardein, 1993)*. Diphenylhydantoin (phenytoin) is a major anticonvulsant that has been in use since 1938, and is generally considered to be the single most effective drug in treating most forms of epilepsy *(De Lorenzo, 1989)*.

Fluphenazine is an antipsychotic drug that is used effectively to treat psychotic symptoms in pregnant women. It has a long duration of action and a strong anti-emetic but weak sedative effect. Fluphenazine when used in the therapy of psychosis, anxiety, nausea and vomiting, readily provokes extrapyramidal disturbances, hypotension and jaundice *(Grella and Onnis, 1963).*

Since the literature available on the teratogenic effect of fluphenazine and the combined action between phenytoin and fluphenazine is scarce, this study has been conducted to evaluate the teratogenic potential of phenytoin and fluphenazine each separately and the effect of their combined use on mice offspring when the drugs are given during the period of organogenesis to pregnant dams.

In this teratogenic study all treated dams of the different groups will be observed daily for their gross appearance and behavior to ensure that the maternal dose has been far below the toxic level. Half the litter of each dam will be processed for external and visceral examination while the other half will be cleared and stained for skeletal examination after using their livers for light and electron microscopic studies.

Phenytoin is considered by many investigators to be hepatotoxic *(Gabler and Falace, 1970).* However, the hepatotoxic potential of phenytoin has not been evaluated at the fetal level if the mother has been exposed to phenytoin during pregnancy. In an attempt to find any relationship between phenotypic anomalies and alterations in the

liver cells, fetal livers from the litters of each treatment regimens will be fixed and processed for light and electron microscopic study.

In relation to these fetal hepatic ultrastructural studies, it has been suggested to investigate the activity of an enzyme related to the liver function such as alkaline phosphatase, and the protective role of reduced glutathione against hepatic damage in the mother's blood under different treatment regimens.

Phenytoin and fluphenazine are two drugs that act on the central nervous system development *(Swaiman, 1980)*. The effect of these drugs on the mouse foetal cerebellar cortex was studied before *(Blank, Nishimura and Seil, 1982)*. There is no available literature on the effect of these two drugs on the developing cerebral cortex. Therefore, it has been planned to find out any alteration in the histological and ultrastructural picture of the cerebral cortex of the fetuses. Fetal brains from the litters of each treatment regimens will be fixed and processed for both light and electron microscopic studies.