DRUG INDUCED HEPATOPATHY

THESIS

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BY

ASMAA AHMED FAWZY ASSAF

[M.B., B. Ch.]

DEMONSTRATOR IN FORENSIC MEDICINE & CLINICAL TOXICOLOGY

DEPARTMENT

SUPERVISED BY

PROF. DR. NAILA A. EL NAYAL

PROF. OF FORENSIC MEDICINE & CLINICAL TOXICOLOGY

PROF. DR. MAGDI M. EL MELIGUI

PROF. OF FORENSIC MEDICINE & CLINICAL TOXICOLOGY

DR. SAWSAN ABDEL FATTAH SHALABY

ASSIST. PROF. OF FORENSIC MEDICINE & CLINICAL TOXICOLOGY

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

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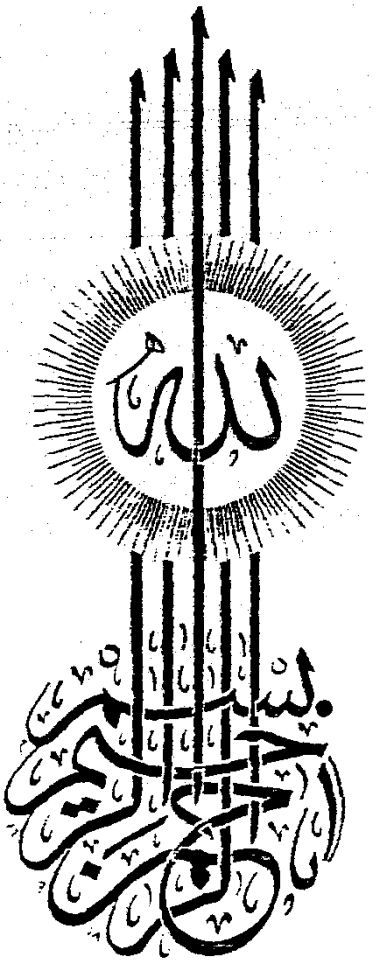

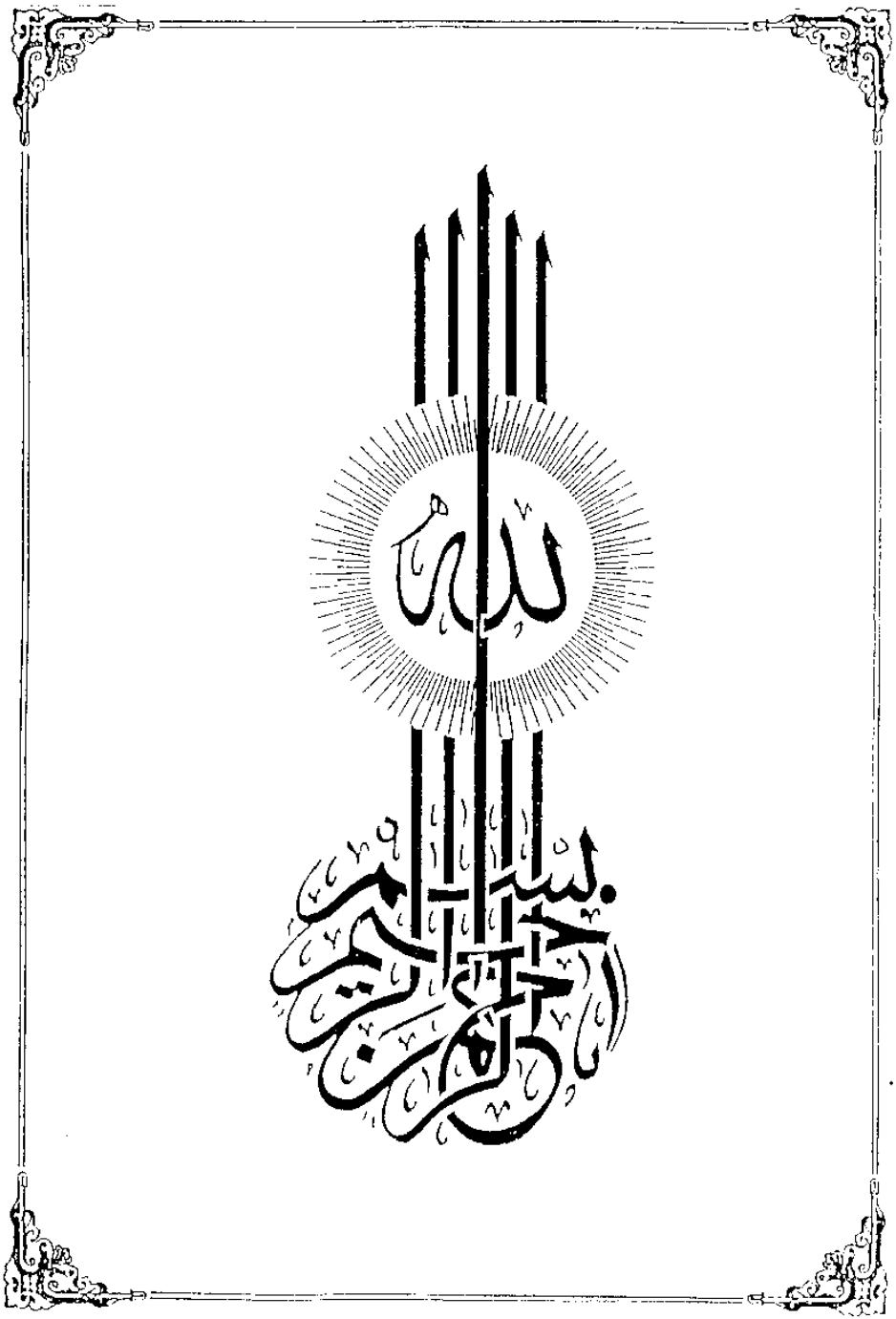

TO MY PARENTS

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CONTENTS

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INTRODUCTION

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The liver is the main site for metabolic transformation of drugs. Through a number of enzymatic steps it renders lipophilic pharmacological agents sufficiently water soluble for final elimination by the kidneys or biliary system (Bircher, 1983).

Liver injury induced by chemicals has been recognized as a toxicologic problem for close to 100 years [Zimmerman, 1978]. This problem of drug induced liver disease becomes a formidable one, despite an increased awareness of the hepatotoxic potential of certain drugs [Greenberger and Winship, 1979].

Many factors underlie the liver's susceptibility to injury by drugs. The role of liver in converting lipid-soluble drugs to water-soluble products results in high drug concentration in the liver. Moreover the liver is exposed to high levels of orally ingested compounds. Finally, the liver's conversion of drugs to reactive metabolites and excretion of these agents in bile make it liable for injury [Feinberg, 1981].

Zimmerman [1978] pointed out that adverse reactions to drugs account for only a small fraction of overt liver disease. However, in various surveys, Zimmerman pointed out

that among the causes of massive hepatic necrosis, drug-induced injury accounts for between 20-30 percent of cases. D'Arcy and Griffin [1981] denoted that the severity of drug-induced hepatocellular injury converts a low absolute incidence to a major cause of serious hepatic necrosis.

The incidence and severity of hepatotoxic reactions can be minimized by the thoughtful use of drugs and by an informed clinical approach to patients with possible drug induced liver disease [Feinberg, 1981].

REVIEW OF LITERATURE

ANATOMY AND HISTOLOGY OF THE LIVER

The liver is a large solid organ which normally weighs about 1,500 g. It is roughly wedge-shaped and mostly lies in the upper right portion of the abdominal cavity with its wedge end extends across to left [Hall and Craggs , 1985].

The greater part of the liver lies under cover of the ribs and costal cartilages in contact with the diaphragm which separates it from the pericardium, the right pleural cavity and lung [Romanes, 1981].

Histologically, the liver is divided into hepatic lobules. It appears hexagonal in cross section with a central vein at its centre and portal canals containing the hepatic artery, portal vein and bile duct peripherally at the corners [Lesson et al., 1985]. The cells of the lobule closest to the artery are termed the periportal hepatocytes "Zone 1". The cells closest to the central vein are termed centrilobular hepatocytes "Zone 3". The cells between both areas are termed midzonal hepatocytes "Zone 2" [James, 1985]. The microsomal enzymes is found to be largely concentrated in centrilobular area " Zone 3" [Rappaport, 1976]. On the other hand the periportal area "Zone 1"

contains higher concentrations of glutathione transaminase enzymes [James, 1985].

The smooth endoplasmic reticulum [SER] which is prominent in the cytoplasm contains the microsomes. It is the site of bilirubin conjugation and detoxification of many drugs [Sherlock, 1986].

PHYSIOLOGY OF THE LIVER

The liver has many functions among which are: storage, synthesis , formation and secretion of bile and drug metabolism [Keele et al., 1984].

Storage:

The liver stores glycogen, fat, protein, vitamins and other substances concerned in blood formation and destruction.

Synthesis:

The liver synthesizes the plasma proteins, fibrinogen prothrombin and heparin.

Bile formation and secretion:

All hepatic cells continually form bile, which is secreted into the bile canaliculi [Guyton, 1986].

Drug metabolism:

The primary objectives of drug metabolism [Biotransformation] : are to alter a chemical substance so as to change its biologic effects, and to transform the chemical to a more polar and therefore more water soluble species [James, 1985].

In the initial phase of drug metabolism [phase I], the compound is rendered slightly water soluble by a variety of processes of which hydroxylation is the most important. The hydroxylating enzyme system is cytochrome P-450. It belongs to the group of mixed-function oxidases [Bouchier, 1982]. Other enzymatic systems involved in this phase are : amine oxidase, epoxide hydratase, esterase, amidases and alcohol dehydrogenase [Plaa, 1986].

Compounds may undergo a second phase of synthetic reactions that conjugate the altered drug with glucuronides, sulfates, and amino acids to further enhance water solubility [Anderson and Schrier, 1981]. There are several enzyme systems that catalyse phase II reactions, namely, Glucuronyl transferase, Glutathione S-transferase, N-acetyl transferase, and sulfotransferase [James, 1985].

FACTORS AFFECTING HEPATIC DRUG REACTIONS

Several factors may influence the sensitivity of the liver to the toxicity of chemicals, for example, age, sex, diet, genetic, metabolic factors and liver disease [Reeves, 1981].

Hydroxylation, demethylation and acetylation rates are lowered by age. This results in a prolongation of plasmahalf life of some drugs [Hellemans and vantrappen, 1984]. Sherlock [1986], recorded that hepatic drug reactions are more frequent in the female sex. Low protein diet decreases enhances or inhibits xenobictic metabolism, also calcium and copper defeciencies reduce metabolism as do defeciencies of zinc or iron [James, 1985]. Certain individuals having a genetic inability to perform a particular transformation. A good example is the fast and slow acetylation of isoniazid [Morgan et al., 1984].

One of the factors that can potentiate hepatotoxicity is the effect of a second drug, this second drug may act as an inducing agent, or inhibiting agent [Plaa, 1986]. Inducing agents increase drug metabolism by inducing the synthesis of more cytochrome P-450, while inhibiting agents inhibit drug metabolism by inhibiting cytochrome P-450 [James, 1985].