GENETIC ASPECTS
OF
LIVER DISEASE

ESSAY

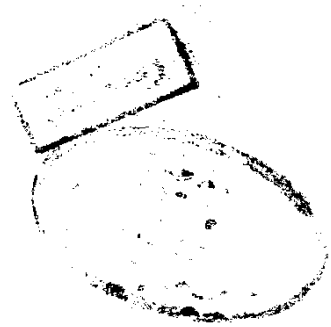
Submitted for Partial Fulfilment of

M.Sc. Degree in Pediatrics

By

MOHAMED ZAKI MOHAMED HUSSEIN

M.B.; B.Ch.



Supervised By

Prof. Dr. RABAH MOHAMED SHAWKI

Prof. of Pediatrics

Faculty of Medicine

Ain Shams University

Dr. NAGIA MOUSTAFA BAHGAT

Lecturer of Pediatrics

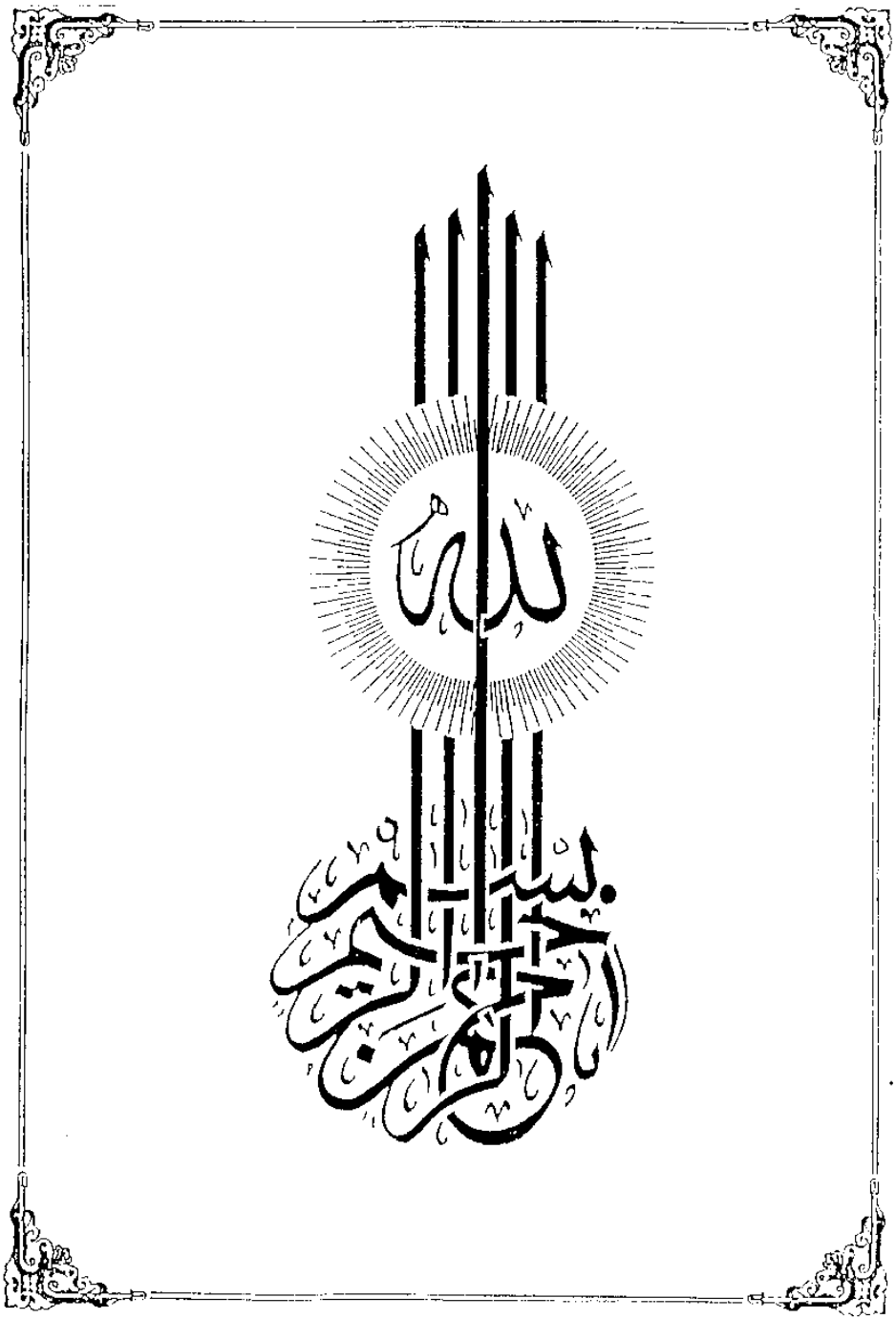
Faculty of Medicine

Ain Shams University

AIN SHAMS UNIVERSITY

1 9 8 6

بسم الله الرحمن الرحيم



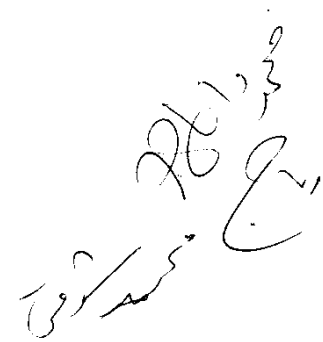
GENETIC ASPECTS
OF
LIVER DISEASE

ESSAY
Submitted for Partial Fulfilment of
M.Sc. Degree in Pediatrics

By

MOHAMED ZAKI MOHAMED HUSSEIN

M.B.; B.Ch.



Supervised By

Prof. Dr. RABAH MOHAMED SHAWKI
Prof. of Pediatrics
Faculty of Medicine
Ain Shams University

Dr. NAGIA MOUSTAFA BAHGAT
Lecturer of Pediatrics
Faculty of Medicine
Ain Shams University

AIN SHAMS UNIVERSITY
1 9 8 6

ACKNOWLEDGEMENT

It has been a great honour and extreme pleasure for me to proceed with this work under the supervision of **Prof. Dr. RABAH MOHAMED SHAWKI,** Professor of Pediatrics, Ain Shams University. Her kind supervision, valuable guidance, and generous advice have been a great help to me to harmonize the style throughout the entire essay.

I have no adequate words to express my gratitude and indebtedness for the close supervision, tremendous effort, active participation, and kind encouragement of **Dr. NAGIA MOUSTAFA BAHGAT,** Lecturer of Pediatrics, Ain Shams University.

The Candidate

CONTENTS

	Page
LIST OF ABBREVIATIONS	iii
LIST OF TABLES	v
INTRODUCTION AND AIM OF WORK	1
DEVELOPMENT OF LIVER STRUCTURE AND FUNCTION	2
DIAGNOSTIC ASSESSMENT OF LIVER DISEASE	12
REVEIW OF LITERATURE	
I. INBORN ERRORS OF METABOLISM THAT INVOLVE THE LIVER :	25
A. Inborn Errors of Carbohydrate Metabolism	25
B. Inborn Errors of Lipid Metabolism.	38
C. Inborn Errors of Lipoprotein Metabolism	48
D. Mucopolysaccharidoses.	52
E. Inborn Errors of Glycoprotein Metabolism	55
F. Inborn Errors of Protein Metabolism.	57
G. Inborn Errors of Porphyrin Metabolism	61
H. Inborn Errors of Bile Acid Metabolism.	64
I. Inborn Errors of Bilirubin Metabolism.	70
J. Inborn Errors of Metal Metabolism	75
II. IMMUNOLOGICALLY-MEDIATED LIVER DISORDERS :	78
A. Chronic Active Hepatitis.	80
B. Primary Biliary Cirrhosis.	83
C. Drug-Induced Liver Disease.	85
III. GENETIC ASPECTS OF HEPATOCELLULAR CARCINOMA.	89
IV. THE LIVER IN CHRONIC HEMOLYTIC ANEMIAS.	91
V. MISCELLANEOUS :	93
1. $Alpha_1$-Antitrypsin Deficiency.	93
2. Indian Childhood Cirrhosis.	94

Page

3. Cystic Fibrosis 95
4. Shwachman's Syndrome 96
5. Congenital Hepatic Fibrosis 97
6. Congenital Hepatic Fibrosis and Nephronophthisis 97
7. Infantile Polycystic Disease of the Liver and Kidneys 98
8. Chediak-Higashi Syndrome 99
9. Chronic Granulomatous Disease 99
10. Congenital Immunodeficiency States 100
11. Progressive Myoclonic Epilepsy (Lafora Body Disease) 100
12. Familial Hepatosteatosis 101
13. Leprechaunism 101
14. Idiopathic Neonatal Hepatitis 101
15. Hereditary Hemorrhagic Telangiectasia. 102

SUMMARY 103
REFERENCES 105
ARABIC SUMMARY .....

LIST OF ABBREVIATIONS

A.D.	Autosomal dominant
ALA	Aminolaevulinic acid
A.R.	Autosomal recessive
AST	Aspartate aminotransferase
BSP	Bromosulphalein
CAH	Chronic active hepatitis
C.F.	Cystic fibrosis
C.G.D.	Chronic granulomatous disease
CT	Computerized tomography
GGT	Gamma glutamyl transferase
GSD	Glycogen storage disease
HBV	Hepatitis virus
HCC	Hepatocellular carcinoma
HDL	High density lipoprotein
HFI	Hereditary fructose intolerance
HLA	Human lymphocyte antigen
H.S.	Heparan sulphate
ICC	Indian childhood cirrhosis
IPCD	Infantile polycystic disease
LDH	Lactic dehydrogenase
MHC	Major histocompatibility complex
NADH	Reduced nicotinamide adenine dinucleotide
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NANA	N-acetyl neuraminic acid
OCT	Ornithine carbamyl transferase

PAS	Periodic acid schiff
PBC	Primary biliary cirrhosis
PBG	Porphobilinogen
Pi	Protease inhibitor
SEA	Specific enzyme activity
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLE	Systemic lupus erythematosus
^{99m}Tc-PIPIDA	Technetium-99m-labelled paraisopropyliminodiacetic acid
Tm	Transport maximum
UDP	Uridine diphosphate
VLDL	Very low density lipoprotein.

LIST OF TABLES

Nº.	TITLE	PAGE
1	Composition of Human Hepatic Duct Bile	7
2	Specific Biochemical and Immunological Tests in the Diagnosis of Liver Disease	21-22
3	Enzymatic Defects in Type III GSD	30
4	Mucopolysaccharidoses	53-54
5	Urea Cycle Disorders	59
6	Clinical and Biochemical Features of Porphyrias	62-63
7	Drug-Induced Hepatic Toxicity	86
8	Clinical Features of IPCD	98

INTROUDCTION AND AIM OF WORK

INTRODUCTION AND AIM OF WORK

Genetic predisposition operates as an important contributing factor for some abnormalities of hepatic structure and function .

Despite the apparent rarity of these disorders, they are important for the following reasons :

- In several, the natural history of the disease can be altered favorably by means of therapeutic diet and other modalities of treatment.
- Identification of a genetic disease permits genetic counselling to the family as well as the possibility of earlier diagnosis and treatment for subsequent children.
- Individuals heterozygotic for a recessive defect, although appearing normal phenotypically, may be susceptible to acquired diseases.
- The study of these discrete defects provides a means for extending our knowledge of the normal pattern of biochemistry and physiology.

The aim of this work is to study liver diseases in which genetic factors operate such as those associated with metabolic errors referable in most instances to enzyme deficit preventing the assembly, excretion, and degradation of a particular metabolite. The study will also include the relative contribution of various genetic components in chronic liver diseases such as autoimmune type of chronic active hepatitis and the drug-induced liver diseases.

DEVELOPMENT OF LIVER STRUCTURE AND FUNCTION

DEVELOPMENT OF LIVER STRUCTURE AND FUNCTION

The liver, bile ducts, and gallbladder originate from a cluster of cells capping a ventral diverticulum in the primitive foregut. The diverticulum becomes segmented into two buds. The solid cranial bud (pars hepatica) evolves into the liver, while the hollow caudal one (pars cystica) develops into the gallbladder, cystic duct, and common bile duct. Epithelial cords and tubules extending from the cranial bud establish contact with the blood vessels in the adjoining mesenchymal septum transversum.

The basic architectural pattern of the adult liver lobule becomes established from the 5-6 week of gestation. The interlobular bile ducts differentiate from the intrahepatic ducts while the terminal ductules develop from vesicles that appear in hepatocytes around the smallest branches of the portal vein. Canaliculi, the specialised portion of the liver cell surface concerned with biliary secretion, appear as small vesicles between hepatocytes in 6 week embryo.

The portal vein, which is formed by the junction of superior mesenteric vein and the splenic vein, branches into a short right and a longer left trunk. The right branch gives rise to a lateral branch directed to the right upper lobe, an inferior branch supplying the area to the right of gallbladder, and a large central branch supplying the anterior superior portion of the liver. From the left trunk, superior, intermediate, and inferior branches supply the lateral aspects of the left lobe, the caudate and quadrate lobes. Anastomoses between the branches of the right and left portal vein branches are unusual. Each

terminal branch has a sharply defined territory, the smaller branches having the characteristics of end arteries.

The hepatic artery usually arises as a single trunk from the coeliac artery. Within the liver, the artery or its branches follow the appropriate branches of the portal vein. There are no intrahepatic communications between the right and left hepatic arteries.

The hepatic vein tributaries have sharply defined areas of drainage which do not relate directly to the portal vein end-branch or hepatic end-artery territory, yet they do interdigitate with these to give uniform drainage of the liver. They are characterized by being straight and follow a radial course to the inferior vena cava. The branches of the portal vein weave between these vessels.

The hepatic terminal of the biliary system consists of intercellular canaliculi empyting into the smallest ductules. These unite to form interlobular bile ducts which follow the terminal branches of the portal vein. Larger ducts arise from the converging interlobular ducts. The right and left lobar ducts continue outside the liver as the hepatic ducts which join to form the common hepatic duct. The common bile duct is formed from the union of the common hepatic duct and cystic duct.

The portal vein and hepatic artery branches, bile ducts, lymph vessels and nerves are surrounded by a coat of connective tissue continuous with the external capsule of the liver. This connective tissue, referred to as the limiting plate, bounds the portal space. From the