A STUDY OF SOME HISTOPATHOLOGICAL, BIOCHEMICAL AND IMMUNOLOGICAL ASPECTS IN CHILDREN WITH NEPHROTIC SYNDROME

THESIS

SUBMITTED IN PARTIAL FULFILLMENT FOR

DEGREE OF M.D. IN PEDIATRICS

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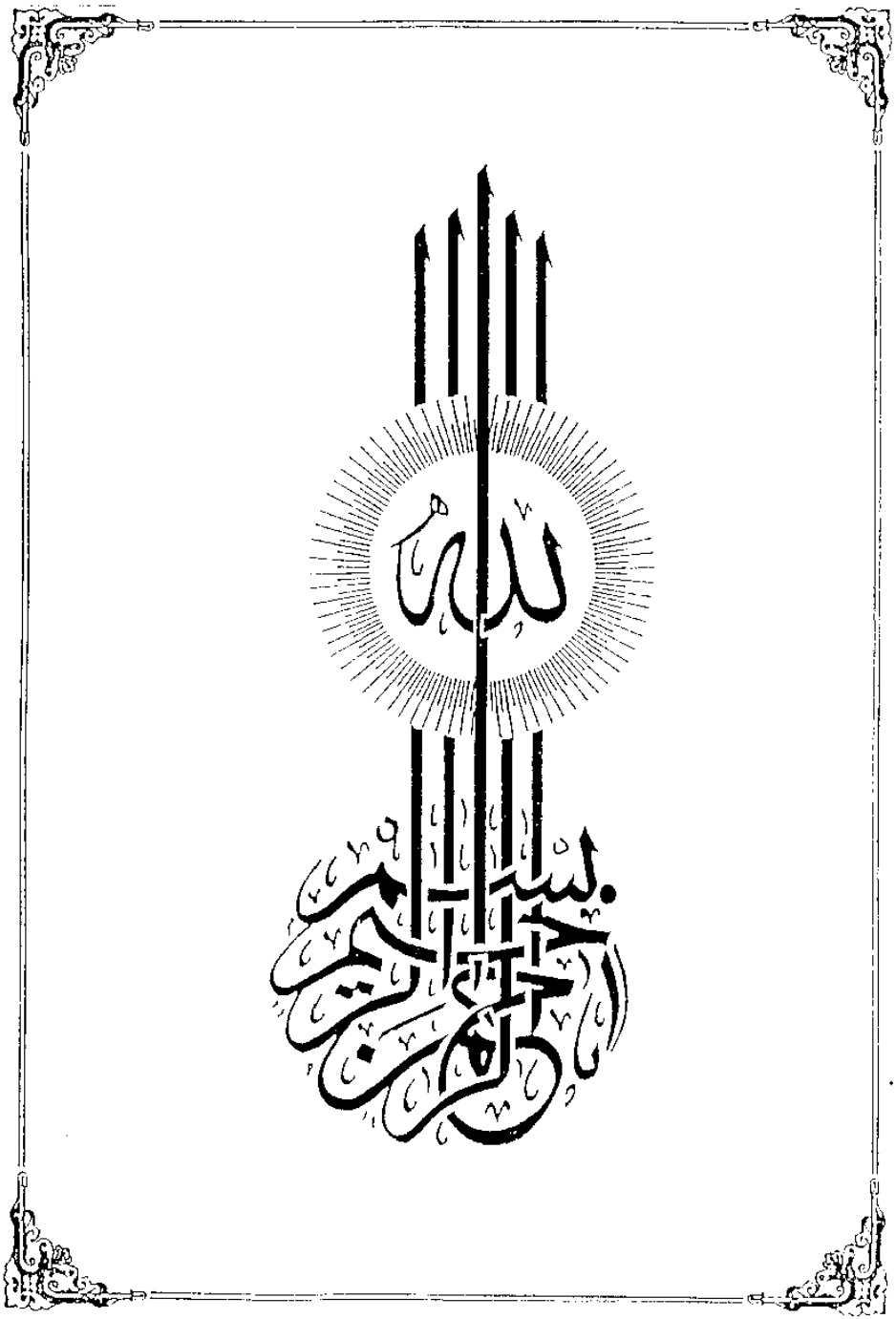
1997

ACKNOWLEDGMENT



ACKNOWLEDGEMENT

Thanks to our merciful **GOD** who enabled me to prepare this thesis and who always helps us in every affair throughout life.

It is a pleasure to express my immense gratitude and appreciation toward ***Dr. Ahmad Gad El-Rab Askar,*** Assistant Professor of Pediatrics, Faculty of Medicine, Assiut University for his guidance, kind supervision and sincere help all through the course of this study. He kindly offered his experience.

I express my great thanks to ***Dr. Ekram Aly Hashem,*** Assistant Professor of Pediatrics, Faculty of Medicine, Assiut University for suggesting the subject of the study, for her guidance in proposing it, and for her keen supervision, fruitfull suggestions, encouragement and kind help during the conduction of this thesis.

I'm greatly and deeply indebted to ***Dr. Monazzama Abd-El-Al*** Assistant Professor Of Clinical Pathology, Faculty of Medicine, Assiut University, for her kind supervision, patience and paramount help in most of the laboratory aspects of this study.

I owe a particular debt to ***Dr. Sanaa Sotohi,*** Assistant Professor of Pathology, Faculty of Medicine, Assiut University, for her patience, skillful experience and persistent willingness to achieve accuracy of the pathological study in this thesis.

I record my deep thanks and appreciation to ***Dr. Elham Abd-El Samie,*** Lecturer of Clinical pathology, Faculty of Medicine, Assiut

University, for her skillful help and expert assistance of the laboratory work of this study.

I gladly acknowledge ***Dr. Tarek Shata,*** Assistant Professor of Microbiology and Immunology, Faculty of Medicine, Assiut University, for his active participation in the laboratory work of this thesis.

Last but not least I wish to extend my great thanks and feelings to all members of the Pediatric Department and to everyone who helped me to produce this work.

Mohammad Mahrous Sayed.

1997

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ABBREVIATIONS

LIST OF ABBREVIATIONS

ACE	:	Angiotensin Converting Enzyme.
APC	:	Antigen Presenting Cells.
BAFPN	:	British Association for Pediatric Nephrology.
C3	:	Complement 3
C4	:	Complement 4
CD	:	Cluster of Differentiation
C1q	:	Complement 1q.
ELISA	:	Enzyme Linked Immuno Sorbent Assay.
Eq/L	:	Equivalent / Liter.
FGS	:	Focal Glomerulosclerosis.
FSGS	:	Focal Segmental Glomerulosclerosis.
GBM	:	Glomerular Basement Membrane.
GFR	:	Glomerular Filtration Rate
H	:	Heavy
HBSS	:	Hanks Buffered Salt Solution.
HDL	:	High Density Lipoprotein.
HLA	:	Human Leucocyte Antigen.
IDL	:	Intermediate Density Lipoprotein.
IgA	:	Immunoglobulin A
IgE	:	Immunoglobulin E
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IL-2	:	Interleukin-2
IL-2 R	:	Interleukin-2 Receptor.
INS	:	Idiopathic Nephrotic Syndrome.
ISKDC	:	International Study of Kidney Disease in Children.
L	:	Light

LAK	:	Lymphokine-activated killer.
LCAT	:	Lecithin Cholesterol Acyl Transferase.
LDL	:	Low Density Lipoproteins.
LPL	:	Lipoprotein Lipase
MAC	:	Membrane Attack Complex.
MC	:	Minimal Change
MCGN	:	Mesangiocapillary glomerulonephritis.
MCNS	:	Minimal Change Nephrotic Syndrome.
MGN	:	Membranous Glomerulonephritis.
MHC	:	Major Histocompatibility.
MPGN	:	Mesangial Proliferative Glomerulonephritis.
MW	:	Molecular Weight.
NK	:	Natural Killer.
NS	:	Nephrotic Syndrome
NSAIDs	:	Non-Steroidal Anti-Inflammatory Drugs.
PBMN	:	Peripheral Blood Mononuclear Cells.
PHA	:	Phytohaemagglutinin.
PMN	:	Polymorphonuclear Cells.
RBP	:	Retinol Binding Protein.
SD	:	Standard Deviation
SDNS	:	Steroid Dependent Nephrotic Syndrome.
SIL-2 R	:	Soluble Interleukin-2 Receptor.
SIRSL	:	Soluble Immune Response Suppressor Lymphokine
SLE	:	Systemic Lupus Erythematosus.
SRNS	:	Steroid Resistant Nephrotic Syndrome.
SSNS	:	Steroid Sensitive Nephrotic Syndrome
TCR	:	T-Cell Antigen Receptor.
TDT	:	Terminal Deoxynucleotidyl Transferase.
VLDL	:	Very Low Density Lipoprotein.

INTRODUCTION AND AIM OF THE WORK

The pathogenesis of minimal change nephrotic syndrome (MCNS) remains unknown. Shalhoub (1974) postulated that this disease might be the result of a disorder of T-cell function and several subsequent studies revealed T-cell dysfunction (Fodor et al., 1982; Beale et al., 1983; Gupta and Yuceoglu 1985; Yokoyama et al., 1987; Schnaper and Aune 1987; Mandreoli et al., 1992; and Kobayashi et al., 1994). Other reports have associated the suppressed immune responsiveness in this disease with alterations in T lymphocyte numbers and function, thereby indicating a role for T lymphocytes in the pathogenesis of the nephrotic syndrome (N.S.) (Taube et al., 1984; Schnaper, 1990; and Hulton et al., 1994). However, there is no satisfactory proof that such abnormalities of T-cell function contribute to the pathogenesis of MCNS. Some investigators have demonstrated that the abnormalities in T-cell numbers and function in MCNS are also present in nephrotic syndrome caused by other types of glomerular disease (non-minimal-change nephrotic syndrome: non-MCNS) (Martini et al., 1981; Sasdelli et al., 1981; Heslan et al., 1982; and Taube et al., 1981, 1984) and considered that the abnormalities were a consequence of the nephrotic syndrome.

Steroid therapy induces remission in most children with idiopathic nephrotic syndrome (INS) (Kleinknecht et al., 1981), but it is often complicated by drug toxicity. The most troublesome group are those with high-dose steroid dependency, in whom standard alkylating therapy (e.g. cyclophosphamide) commonly fails to maintain a remission (ISKDC, 1974). The long-term immunosuppression in these patients and the cumulative risk of further alkylating therapy are worrying in a condition

that ultimately has an excellent prognosis (BAFPN, 1991). An alternative therapy with an immunostimulant would be an attractive option, especially in conditions characterised by altered cellular immunity (Schnaper, 1989).

Levamisole is one such immunostimulant drug. In therapeutic concentrations levamisole restores to normal, both in vivo and in vitro, many of the effector functions of T-cells and phagocytes, and induces the maturation of immature T-cells. However, these effects are reproducible only when the immune system is depressed (Amery, 1978 & Amery and Gough, 1981). The drug has no demonstrable anti-inflammatory properties or effects on B cells and, despite extensive research, there is no acceptable explanation of its mechanism of action (BAFPN, 1991).

There are several reports of successful treatment of INS with levamisole, with and without concomitant corticosteroid therapy (Niaudet et al., 1984; BAFPN, 1991 and Xu et al., 1991)

This study was undertaken to evaluate the immunological state of children with nephrotic syndrome, to detect the relation between different immunological parameters and severity of the disease, and to assess the role of levamisole in the management of this disease.

REVIEW OF LITERATURE

NEPHROTIC SYNDROME

Nephrotic syndrome is a clinical entity characterized by proteinuria, hypoproteinemia, oedema and hyperlipidemia (Bergstein, 1996). Although hypertension and renal insufficiency are not generally observed, a minority of patients may have these unusual features (Kher et al., 1988).

The incidence of nephrotic syndrome was found to be ranging from 2 to 2.3 new cases per 100,000 children per year (Glassock et al., 1986).

CLASSIFICATIONS:

The multiplicity of aetiologic factors, associated conditions, underlying pathology and pathogenesis makes it difficult to review nephrotic syndrome without encompassing all of the diseases that constitute the general group of glomerular diseases (Cameron and Glassock, 1988). Indeed except for those processes that rapidly destroy the entire nephron population, virtually any glomerular lesion may be associated, at least temporarily, with proteinuria of sufficient magnitude to result in hypoalbuminemia and thus set into motion the pathophysiologic processes responsible for the constellation of findings we call the nephrotic syndrome (Glassock et al., 1991). Table (1) shows the aetiologic classification of nephrotic syndrome (Kher et al., 1988).