A STUDY OF THE NEUTROPHIL FUNCTION

IN THE ASPLENIC PERSON

Thesis submitted for partial fulfilment
of the M.D. degree in General Surgery

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Acknowledgement

I am much indebted to **Prof. Dr. J. Seifert** for allowing me the chance of doing this research in his department and for his close supervision, his invaluable advises, his indispensable help and his kind hospitality.

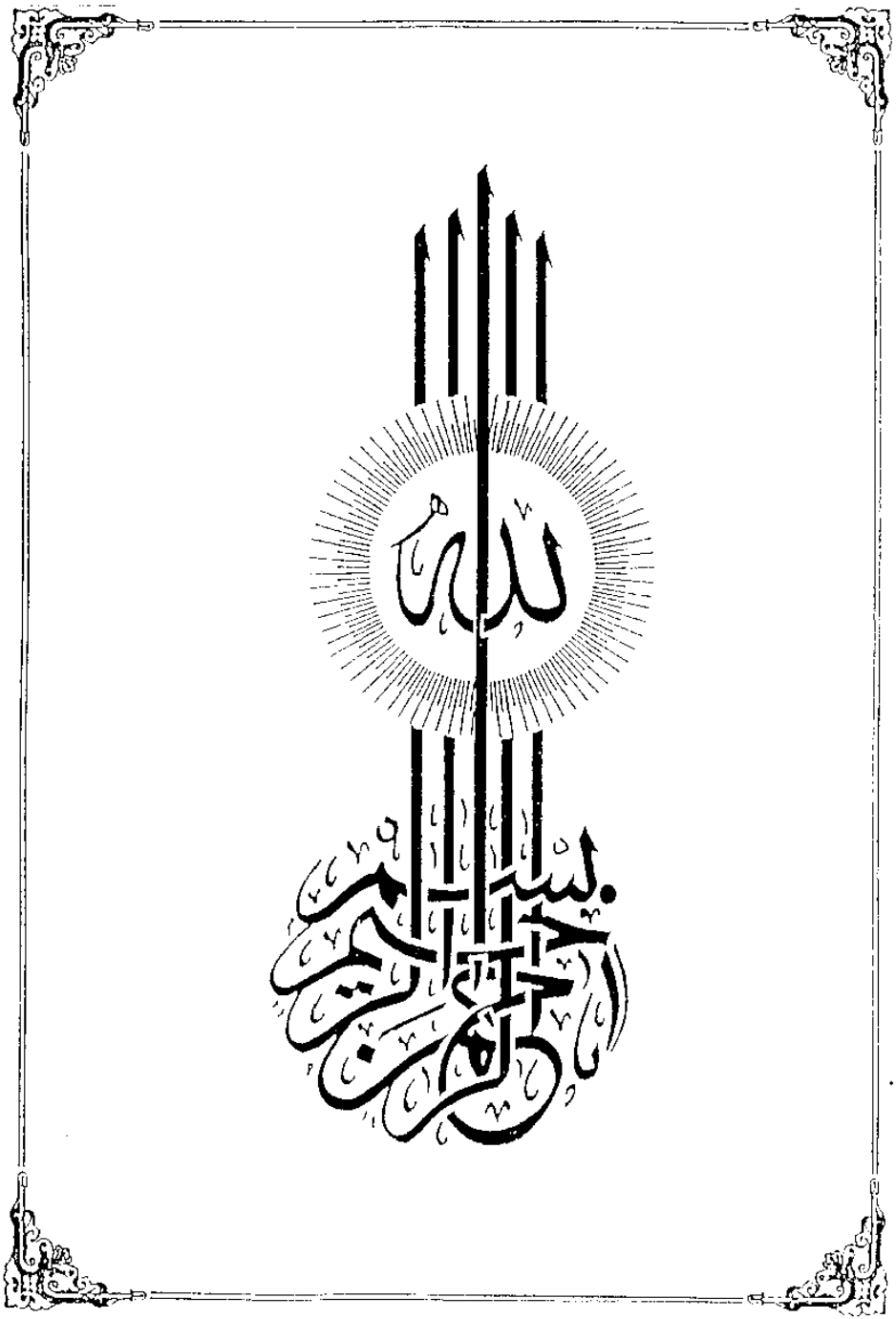
I declare my great appreciation and my sincere thanks to **Prof. Dr. T. Sallam** for offering me the idea of this work, for deciding upon the laboratory methods with the eye of the expert immunologist and for his endless patience in explaining even the basic laboratory work which I knew nothing about.

I would like to express my deep gratitude to **Prof. Dr. S. Draz** for the time and effort he spent in, and the concern and interest he gave to the supervision of this thesis and for the guidance through out the conductance of this research.

I am very much thankful to **Prof. Dr. A. Sedky** for his ever encouragement, the sincere advises, the worthful criticism and the valuable remarks and supervision of this work since the very early time of deciding upon this subject.

I extend my thanks and acknowledgement to **Prof. Dr. D. Havemann** for allowing me the patients of his causuality department for this research, to **Priv. Doz. Dr. W. Sass** for his readily available help whenever needed, to **Misses S. Lohmann** for her great efforts in organizing the visits of the patients and her excellent computer typing of this text in its present form, and to **Misses Kalmutzke** and her co-workers in the blood bank Seroplasm for the help with the control group.

I am thankful to my parents, and my professors and colleagues for the encouragement and support.



INDEX

List of Abbreviations:

* Symbols used for the chemical elements are those of the standard international system and are not enlisted in this list of abbreviations (eg. O for oxygen, R- for alkyl radicle, H for hydrogen, etc.)

* Symbols used for amino acids are the 3 letter abbreviations of the standard nomenclature in protein chemistry and are not enlisted in this list of abbreviations (eg. Thr for threonine, Lys for lysin, Pro for proline, etc.)

* Symbols used for caliberation units are those of the standard international (SI) units and are not enlisted in this list of abbreviations (eg. nM for nanomole, μm for micrometer, ml for milliliter, etc.)

* Symbols used in statistical formulas are discribed in the text and are not enlisted in this list of abbreviations

* The full names of the following abbreviations are not shown in the text:

abs.:	absolute
B-cells/lymphocytes:	the bursa fabricic type of lymphocytes
DNA:	deoxyribonucliac acid
MCH:	mean corpuscular haemoglobin
MCHC:	mean corpuscular haemoglobin concentration
MCV:	mean corpuscular volume
pH:	the negative log of the hydrogen ion concentration
R.B.C.:	red blood cells
T-cells/lymphocytes:	the thymic type of lymphocytes

U.S.A.	United States of America
v:	volume
Vmax:	maximal velocity of a reaction
W.B.C.:	white blood cells

* The full names of the following abbreviations are shown with their corresponding abbreviations (in brackets) at least at the first time they appear in the text:

ABC:	argon beam coagulator
ADCC:	antibody-dependent cellular cytotoxicity
AIDS:	acquired immune deficiency syndrome
AMP:	adenosine monophosphate
$C_{(1,...9)}$:	the first to the ninth complement components
C_{3a}:	fragment a of C_3
C_{3b}:	fragment b of C_3
C_{5a}:	fragment a of C_5
C_{5b}:	fragment b of C_5
CGD:	chronic granulomatous disease
CR_1:	complement receptor number one
CSF:	colony stimulating factor
CT:	computed tomography
DIDS:	4,4'-diisothiocyanostilbene-2,2'-disulfonic acid
DPL:	diagnostic peritoneal lavage
E. coli:	Escherichia coli
EAS:	endotoxin activated serum
EDTA:	ethylenediaminetetraacetic acid

Fab:	antigen binding fraction of the immunoglobulin
Factor B:	the mediating serum enzyme of the alternative pathway for complement system activation
Factor D:	the protein complement activating factor "D" of the alternative pathway
Factor XII (a):	Hageman factor of the coagulation system. "a" is the activated product of the factor
Factor XII f:	prekallikrein activator factor
Fc:	constant fraction of the immunoglobulin
FG:	fibrin glue
FMLP:	N-formyl-methionyl-leucyl-phenylalanine
FMF:	flow microfluoremetry
GCP:	granulocyte chemotactic protein
GFA_2:	granulocyte functional antigen 2
GM-CSF:	granulocyte-monocyte colony stimulating factor
GMF:	guanosine monophosphate
GSH:	reduced glutathione
GSSG:	oxidized glutathione
HETE:	hydroeicosatetraenoic acid
HPETE:	hydroperoxyeicosatetraenoic acid
I.C.U.:	intensive care unit
Ig:	immunoglobulin
IL:	interleukin
Km:	Michaelis constant
LIF:	leukocyte inhibitory factor
LPS:	lipopolysaccharide
LT (A_4, B_4...etc.):	leukotrein (A_4, B_4...etc.)
m.w.:	molecular weight
MAb:	monoclonal antibody

MDNCF:	monocyte-derived neutrophil chemotactic peptide
MDP:	muramyl dipeptide
MHBSS:	modified Hank's balanced salt solution
MONAP:	monocyte-derived neutrophil activating peptide
MPS:	mononuclear phagocytic system
$NADP^+$:	nicotinamide adinine dinucleotide phosphate (oxidized)
NADPH:	nicotinamide adinine dinucleotide phosphate (reduced)
NAF:	neutrophil activating factor
NBT:	nitroblue tetrazolium
NIF:	neutrophil immobilization factor
NK:	natural killer
OPSI:	overwhelming postsplenectomy infection
PAF:	platelet-activating factor
PG (E_2, H_2...etc.):	prostaglandin (E_2, H_2...etc.)
PMA:	phorbol myristate acetate
PMN:	polymorphonuclear neutrophils
S-thal:	sickle cell ß-thalassaemia
S. pneumoniae:	Streptococcus pneumoniae
SCA:	sickle cell anaemia
SITS:	4-acetamido-4'-isothiocyanostilbene-2,2'disulfonic acid
SRBC:	sheep red blood cells
SRS-A:	slow reacting substance of anaphylaxis
TNF:	tumor necrosis factor
Tx A_2:	thromboxane A_2
U:	unit

INTRODUCTION

INTRODUCTION

Although its physiology is incompletely understood, the human spleen has storage, reticuloendothelial and immunologic functions. The production of blood elements by the spleen is limited to the fetal life and is present in adults only in certain diseases such as myeloid metaplasia in which hematopoeitic cells develop in the spleen.

The role of the spleen as a reservoir for blood is more prominent in some animals than in humans. The human spleen has a relatively thinner capsule which is made mostly of fibroelastic fibres and only few smooth muscle fibres.

The clearing of aged, faulty or damaged blood elements is a function of the reticuloendothelial activity of the spleen. This function is shared with other reticuloendothelial organs but a major part belongs to the spleen where normally 30 % of platelets and most of the senescent red cells are sequestered. Blood traverses the spleen via several routes, with normal cells passing rapidly and abnormal and aged cells being retarded and entrapped. It is estimated that each normal red cell makes an average of 1000 passes through the spleen each day. It seems that this function could not be completely compensated for by other reticuloendothelial organs and in patients undergoing splenectomy thrombocytosis is a transient feature in some but is also long standing in others. Abnormal red cells and Howel-Jolly bodies are detected in blood of those patients. The contribution of these defects to the development of disease such as portal or deep venous thrombosis has been proposed since a long time and was sometimes considered to be the main subsequent threat of splenic function loss.

At present, much focus is made on the immunologic aspect of splenic functions. In the last few decades several reports were made on clinical infections and impairment of different immune parameters following splenectomy. Some of these infections had certain characteristic features so that a definite syndrome of overwhelming postsplenectomy infection (OPSI) was recognized. Initially, postsplenectomy infections were considered true and definite only in pediatric patients and with much suspicion in the adults. Today there are strong evidence that they occur in adults as well and little controversy remains regarding their true existence but much controversy is still present concerning the magnitude of the risk.

There are several defined immune functions of the spleen. Following splenectomy, specific alterations in immune defences have been reported including diminished circulating immunoglobulin M, reduced levels of tuftsin, decreased levels of complement component properidin, a loss of T-cell amplification following exposure to a mitogenic stimulus and reduced polymorphonuclear leukocyte (PMN) function. The specific defect responsible for the occurrence of clinical infections is not defined but it is likely to be multifactorial. The PMN is the cell at the first line of immune defences against bacterial infections which are commonly encountered in spleenless patients. The breakdown of this front due to PMN dysfunction might offer an important defect for the offending organisms to rapidly break through, settle down and establish infection in the host before other immune defences, which might also be impaired, could come in action. Repeated infections are known to occur in diseases where neutropenia or PMN dysfunctions are present. These infections were better contained when PMN functions were more adequate.

Abnormal PMN function has been demonstrated in patients with increased incidence of infections following splenectomy. However, these reports are very

controversial and some claim a normal PMN function in spleenless patients so that the occurrence of infections in those patients could not be attributed even in part to this immune parameter. If PMN dysfunction following splenectomy is true, this would be clearly meaningfull as a major immunologic defect with a definite risk of possible serious infections.

AIM OF WORK

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The aim of the study is to detect the long term effects of the asplenic state on specific functions of the circulating polymorphonuclear neutrophils and on the occurrence of clinical complications related to that condition. The study may extend to include other blood parameters which relate to the spleen like platelet counts and general evaluation of the trends and adequacies of management of traumatic splenic injuries.

REVIEW OF LITERATURE