CYTOKINES AND THEIR ROLE AS IMMUNOMODULATORS

ESSAY
Submitted for the partial fulfillment of
Master Degree in **Clinical Pathology**

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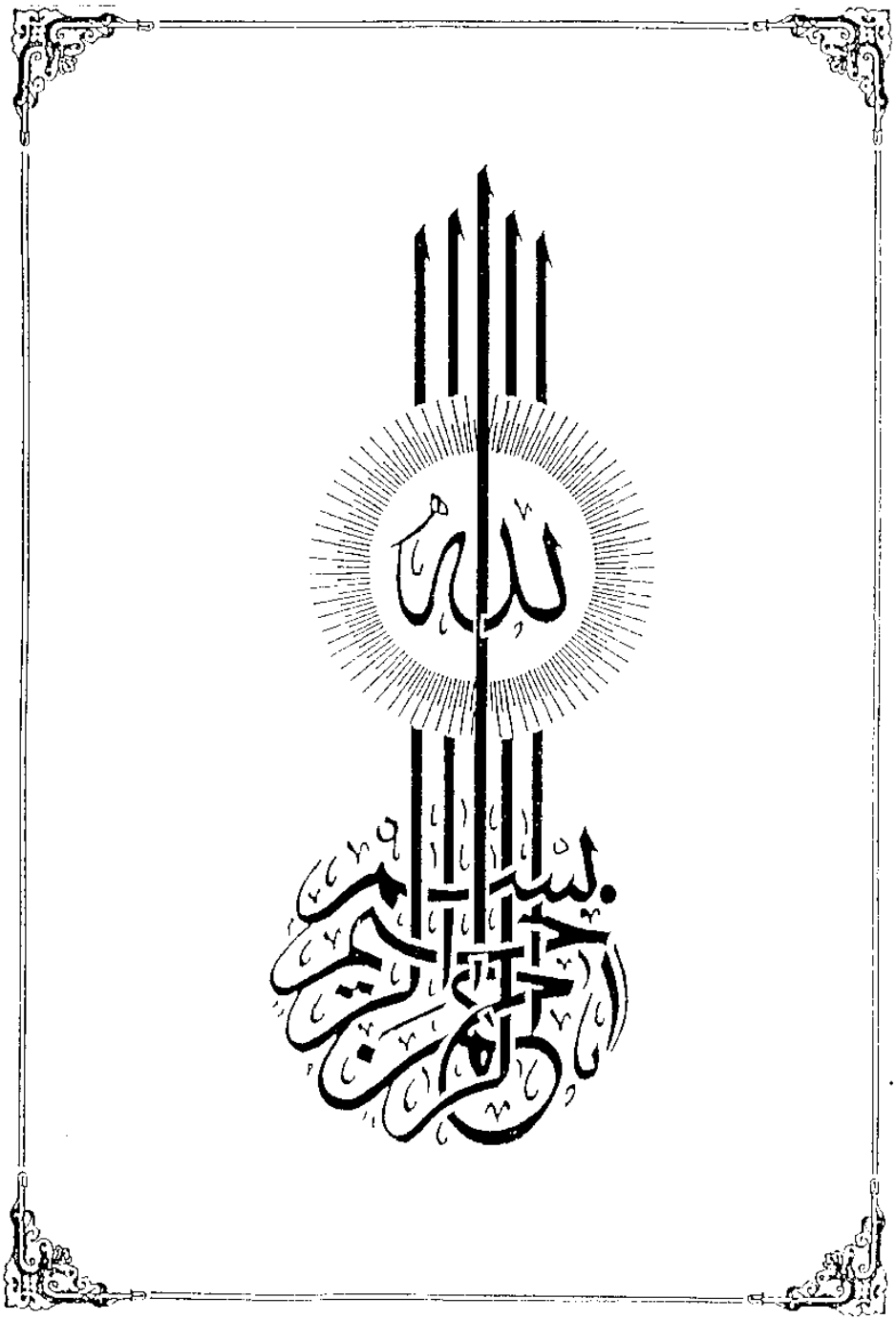
1993

بسم الله الرحمن الرحيم

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا

إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

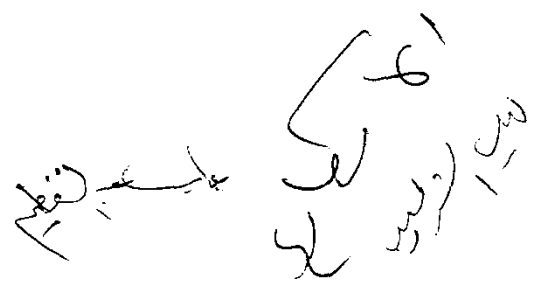
سورة البقرة - آية ٣٢



DEDICATED TO

MY

LOVELY PARENTS



ACKNOWLEDGEMENT

First of all thanks to GOD to whom I relate any success in achieving any work in my life.

I wish to express my sincere gratitude to Prof. Dr. Laila Abd El-Aala El-Shawarby, Professor of Clinical Pathology, Ain Shams University, for his great help and supervision.

Also, my great appreciation to Dr. Mona Mohamed Rafik, Assistant Professor of Clinical Pathology, for his keen supervision and continuous guidance.

Also, I wish to thank Dr. Hala Ahmed Talkhan, Lecturer of Clinical Pathology, Ain Shams University, for his great help and cooperation throughout this work.

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LIST OF ABBREVIATIONS

ABMT	*After bone marrow transplantation*
ACTH	*Adrenocortico tropic hormone*
ADCC	*Antibody dependent cell mediated cytotoxicity*
AGE	*Advanced glycosylation end product*
ANA	*Antinuclear antibody*
ANC	*Absolute neutrophilic count*
ANLL	*Acute non lymphocytic leukemia*
APC	*Antigen presenting cell*
ARC	*AIDS-related complex*
AZT	*Azidothymidine*
BCDF	*B cell differentiation factor*
BCG	*Bacillus calmette guerin*
BCGF	*B cell growth factor*
BCRF	*B cell replacing factor*
BFU-E	*Burst forming unit-erythroid*
BSF	*B cell stimulating factor*
C	*Complement*
CAH	*Chronic active hepatitis*
CD	*Cluster of differentiation*
CFU-G	*Colony forning unit, granulocyte*
CHC	*Chronic hepatitis C*
CML	*Chronic myelogenous leukemia*
Con-A	*Concanavalin-A*
CPH	*Chronic persistant hepatitis*
CR	*Complete response*
CSF	*Colony stimulating factor*
CTCL	*Cutaneous T cell lymphoma*
CTL	*Cytotoxic T lymphocyte*
CTL	*Cytotoxic T lymphocyte*
DIC	*Dissiminated intravascular coagulopathy*
EBV	*Epstein-Barr virus*
EDF	*Eosinophil differentiation factor*
EGF	*Epidermal growth factor*
ELISA	*Enzyme linked immunosorbent essay*
Fc	*Fragment crystallizable*
FMLP	*Formyl methionyl leucyl phenyl alanine*
G-CSF	*Granulocyte colony stimulating factor*
GEMM	*Granulocyte, erythroid, macrophage and megakaryocyte*

GM-CSF	*Granulocyte macrophage colony stimulating factor*
GVHD	*Graft versus host disease*
HBV	*Hepatitis B virus*
HCL	*Hairy cell leukemia*
HCV	*Hepatitis C virus*
HDV	*Hepatitis D virus*
HIV	*Human-immunodeficiency virus*
IDDM	*Insulin dependent diabetes mellitus*
IFN	*Interferon*
IFNα	*Interferon alpha*
IFNβ	*Interferon beta*
IFNγ	*Interferon gamma*
KHF	*Killer helper factor*
L IFN	*Lymphocyte interferon*
LAK	*Lymphocyte activated killer*
LPS	*Lipopolysaccaride*
LT	*Lymphotoxin*
M-CSF	*Macrophage colony stimulating factor*
M:E	*Myeloid : Erythroid*
MDS	*Myelodysplastic syndrome*
MHC	*Major histocompatibility complex*
MM	*Multiple myeloma*
Mo-Ab	*Monoclonal antibody*
NCI	*National cancer institute*
NK	*Natural killer*
P.B	*Peripheral blood*
PHA	*Phytohemagglutinin*
PR	*Partial response*
PWM	*Pokeweed mitogen*
rh-GCSF	*Recombinant human granulocyte colony stimulating factor*
rIFN	*Recombinant interferon*
SAC	*Staphylococcus aureus cowan l*
SLE	*Systemic lupus erythematosus*
TCGF	*T cell growth factor*
TCR	*T cell receptor*
TCRF	*T cell replacement factor*
TGF	*Transforming growth factor*
T_h	*T helper*
TNF	*Tumor necrosis factor*

INTRODUCTION AND AIM OF THE WORK

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Immunomodulators are substances that directly modify a specific immune function or have a net positive or negative effect on the activity of the immune system *(Oppenheim et al., 1992)*. The potential uses of immunomodulators in clinical medicine include the reconstitution of immune deficiency (e.g. the treatment of acquired immunodeficiency syndrome [AIDS]) and the suppression of normal or excessive immune function (e.g. the treatment of graft rejection or autoimmune disease) *(Schandenel, et al., 1993)*. Recent advances in molecular biology have identified a growing number of substances capable of modulating immune function. These include interferons, interleukins, colony-stimulating factors, tumor necrosis factors, and monoclonal antibodies. These immunomodulators have more specific effects than do products from microorganisms such as bacillus Calmette - Guerin (BCG) and Corynebacterium Parvum *(Alvares et al., 1992)*.

Before the availability of highly purified compounds produced by recombinant DNA technology, a variety of non specific immunomodulators were used to augment host immune

response in certain clinical settings. They may be divided into 3 classes products of microbial origin, products of mammalian origin, and synthetic compounds *(Fauci, 1987).*

Non specific immunomodulators of microbial oigin have shown limited therapeutic benefit due to low purity, and lot to lot product variability. the most extenively studied is BCG. When BCG is injected directly into cutaneous melanome lesions, regression of both injected and distant, non injected lesions can be observed, but without prolonged patient survival in prospective randomized trials. However, intravesical BCG treatment of superficial bladder carcinoma is now widely accepted in the management of such patients. BCG has also been evaluated in the active specific immunotherapy of serected cancers. This involves immunization with tumor-associated antigens plus BCG or its methanol extracted residue. This approach is intended to increase host antitumor immunity as a means of preventing tumor recurrence following primary therapy *(Lamm, 1992).*

Non specific immunomodulators of mammalian origin include the thymosins, hormone like substances that are produced by the thymus gland and that have diverse biologic activities including augmentation of immune responses in both

normal and thymectomized animals. Although they are potentially useful in the treatment of selected immunodeficiency states, significant efficacy has not been demonstrated in controlled clinical trials *(Hillman, l992).*

Synthetic compounds such as levamisole, an antihelminthic drug capable of inhibiting suppressor T cell activity, constitute the third class of compounds. Levamisole given to patients with cancer has been associated with increase in delayed type hypersensitivity and in increased in vitro lymphocyte proliferative and mitogenic responses. Preliminary studies of the adjuvant treatment of melanoma and colorectal cancer show promise of clinical efficacy, as measured by disease free survival. Adjuvant refers to a therapy used following optimal local treatment of a tumor, with curative intent) *(Rumke, l992).*

Monoclonal antibodies are produced by hybridoma technology, a procedure in which a mouse is immunized with a specific antigen and its spleen cells are then fused with a continuous B-cell line, producing a hybrid antibody - secreting cell with clonal specificity for the antigen. This produces large quantities of antibodies to a single molecular epitope on the desired antigen. The early clinical trials involving cancer patients given murine monoclonal antibodies specific to human

tumor antigens have identified several problems including tumor heterogeneity, limited vascular access, non specific antibody uptake at non tumor sites, blocking antibodies, antibody-conjugate dissociation, and the development of human antimouse antibodies. These problems have significantly limited monoclonal antibody therapy of specific cancer, particularly solid tumors. However, the use of monoclonal antibodies conjugated to radioisotopes, cellular toxins, or other drugs as a strategy for targeting the conjugated drug specifically to the neoplastic cell is currently being evaluated *(Ziegler et al., 1992).*

One class of monoclonal antibody has an established role in the treatment of graft rejection. The monoclonal antibody OKT3, which has specificity for the CD3 antigen found on T-cells, compares favourably with conventional high-dose corticosteroid therapy of acute renal, hepatic, and cardiac allograft rejection. There are, however, significant side effects, including influenza like symptoms, blood pressure changes, and dyspnea (particularly following the initial dose) *(Woodle et al., 1991).*

Cytokines are hormone like proteins that are produced by immune cells and other cells and that regulate the function of the immune system. They include lymphokines and monokines,