IMMUNOPOTENTIATION

THESIS

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A C K N O W L E D G M E N T

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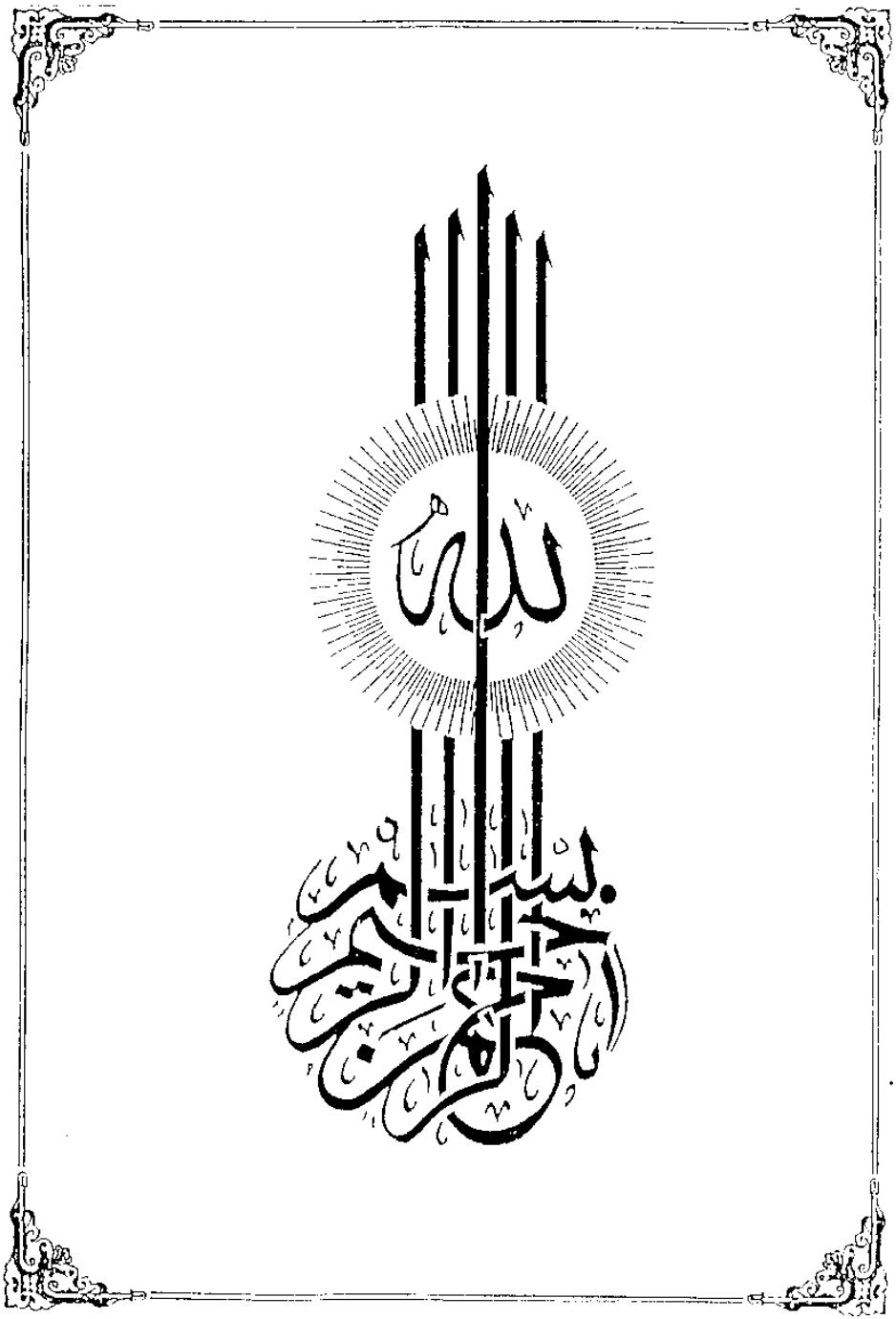

C O N T E N T S

INTRODUCTION

AND AIM OF THESIS

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It has been recognised for centuries that individuals who recover from certain diseases are protected from recurrences. In order to immitate this natural phenomena by introduction of fluid from the pustules of small pox into the skin of uninfected persons (variolation , 1721). The begining of modern immunization was done by Jenner, who introduce vaccination with cow pox to protect against small pox (1796). It was the first decumented use of a live attenuated viral vaccine. In 1876, koch demonstrated the specific bacterial cause of anthrax, and the etiologic agents of several common illnesses were rapidly identified thereafter. Attempts to develop effective immunizing agents followed. Immunization results in the production of antibodies directed against the infecting agents or its toxic products; it may also initiate cellular responses mediated by lymphocytes and macrophages. Immunization gives a good protection against many viral and bacterial diseases.

For the past thirty years, the control of immune response has been virtually equated to immunosuppression. This is due to the fact that the great goal of applied immunology has been the transplantation of tissues between individuals.

However, with the discovery of tumour immunity, the focal point of immunological control has changed from immunosuppression

to immunopotentiation & the great goal of applied immunology has become the prevention and control of malignant growth. This is currently the subject of considerable research both in the laboratory and the clinic, with a few compounds such as levamisole and Tilorone, being studied in man for antitumour activity and possible efficacy in rheumatoid arthritis. It would be premature therefore to attempt a detailed review.

By Immunopotentiation we mean the enhancement of immune response. By enhancement we may mean an increase in the rate at which the immune response develops, an increase in the intensity or level of the response and its prolongation, or the development of a response to an otherwise non immunogenic substance. The agents which enhance immune responses are generally termed adjuvants. The modern concept of the mode of action of adjuvants has evolved in exact relation to our understanding of lymphoid organ system & the complexity of the immune response and its regulation.

The literature on Immunopotentiation is-though extensive-yet widely dispersed in several branches in medicine including oncology, Rheumatology, clinical immunology, and allergy. The present thesis is therefore considered to provide a unified source for physicians and immunologists.

NATURAL REGULATION OF IMMUNE RESPONSES

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Types of Immune Responses:

When antigen enters the body, two different types of immunological reaction may occur:

1. The synthesis & release of free antibody into the blood and other body fluids (humoral antibody). This antibody acts for example by direct combination with & neutralisation of bacterial toxins, by coating bacteria to enhance their phagocytosis and so on. The B-lymphocytes which are bursa-dependent are concerned in the synthesis of circulating antibody. These antibodies are immunoglobulins. By using the technique of electrophoresis it has been possible to define five classes of this human immunoglobulin. These are referred to as IgG, IgM, IgA, IgE and IgD.

2. The production of sensitised lymphocytes which have antibody-like molecules on their surface (cell-bound antibody). These are the effectors of cell mediated immunity expressed in such reactions as the rejection of skin transplants and the delayed hypersensitivity to tuberclin (Mantoux test) seen in individuals immune to tubercle infection. The T-lymphcytes which are thymus dependent are responsible for this cell-mediated immunity.

Table (1) shows the humoral immune responses .

Table (2) Lists the types of cellular hypersensitivity & immunity (Eisen, 1979)

Table (1) : Humoral immune responses

Molecular class	Thymus dependence	Principal sites of stimulation	Principal sites of formation	Character	Prinicipal Function
IgM	0, +	S,LN	S,LN	Plymorphic, high CHO, low affinity	Rapid clearance of blood
IgG	+++	S,LN	BM,S,LN	Monomeric, low CHO, high affinity	Sustained systemic response, antibacterial immunity
IgA	+++	GALT, BALT	Mucosa	Polymeric, high CHO	Sustained-mucosal response, antiviral immunity
IgE	+++	GALT BALT	Mesentric LN,mucosa?	Monomeric, High CHO	Sustained systemic & mucosal response, antiparasitic immunity.

S = Spleen
LN = Lymph node
GALT = gut-associated lymphoid tissue
BALT = bronchus-associated lymphoid tissue
BM = bone marrow

Table (2) : Types of cellular hypersensitivity and immunity

Types of lymphocytes	principal sites of stimulation	location of effector cells	soluble mediators (b)	secondary participants	target effect
NK-Cells	B M, S	Circulation, direct contact with target cells	0	0	Killing
T-Cells					
- cytotoxic	LN,GALT,BALT	Circulation, direct contact with target cells	0	0	Killing
- Sensitized	LN,GALT,BALT	Circulation, target site	LK	0	Killing, inhibition of function.
- Sensitized	LN, GALT, BALT	Circulation, target site	LK	inflammatary Cells (c)	localisation, Killing, inhibition of function
B-Cells Antibody-forming	S,LN,GALT,BALT	S,LN, mucosa, BM	Ag Ab	K-cells inflammatory cells	Localisation, killing, ihibition of Fucnction

Abbreviations : S = Spleen , LN = lymph nod, GALT = gut-associated lymphoid tissue BALT = Bronchus associated lymphoid tissue , BM = bone marrow, NK-cells = natural Killer cells. (b) LK = lymphokines , Ab = antibody, Ag Ab = immune complexes (c) Macrophages , polymorphonuclears, basophils, eosinophils, antigen-specific B cells or cytotoxic T-cells Goblet cells.

Cells Participating in Immune Responses :

The known immune responses result from the natural function of B and T-cell populations, macrophages and the less well defined natural killer cells and killer cells (Katz, 1985).

The primitive stem cell is located in hematopoietic tissues. These cells which morphologically have not been identified are pluripotent : they can mature into either T or B-lymphocytes. However, in their native state, they are incapable of reacting with antigens or inciting an immune response. Thus they are designated as immunologically incompetent cells.

During fetal life, a proportion of these stem cells migrate directly to the thymus. In this organ , they are acted upon by local factors which direct their maturation into the T-lymphocyte lineage. After maturation, these lymphocytes leave the thymus and seed peripheral lymphoid tissues. They show a predilection for residing in specific areas of these tissues designated thymus-dependent regions. These include the paracortical zones of lymph nodes and the inner aspects of the periarteriolar sheaths of the spleen. In addition most (50-70%) of the blood lymphocytes are T-cells. Considerable information has now been gathered concerning the role of the thymus in the maturation of T-cells. This organ serves its major function during embryological life. After birth, the peripheral T-lymphoid system is already largely formed & is self-sustained even in the abscence

of a thymus. Other studies suggest that the conversion of stem cells to T-lymphocytes is controlled by thymic humoral foctors (Winkelstein, 1981). T-cells will give rise to T-cell subpopulations. They can be devided into 2 major functional categories, regulatory and effector T-lymphoyctes (David H. Katz, 1983). Regulatory T-lymphocytes may amplify (as helper cells), or suppress (as suppressor cells) the responses of other T-lymphocytes or of B-lymphoyctes. Distinct subpopulations of T-cells appear to be responsible for these activities. Effector T-lymphocytes are responsible for such cell-mediated immune reactions as delayed cutaneous hypersensitivity responses, rejection of foreign tissue grafts and tumours, and elimination of virus-infected cells. Cytotoxic T-lymphocytes commonly referred to as "Killer cells" Participate in the latter responses. Rejection of foreign tissues also involves T-cells that undergo rapid proliferation in mixed lymphocyte reaction (MLR)

The process by which mammalian B-cells are formed has not been determined. In birds, this maturation is regulated by a hindgut lymphoid organ, the bursa of fabricius. However, no equivalent structure has been identified in man and many ives-tigators now believe that this process probably occur directly in hematopoietic tissues. As would be expected, B-lymphocytes can develop in the abscence of a thymus. Moreover, these cells are present in peripheral lymphoid tissues in anatomical areas

distinct from those populated by T cells; these are referred to as the thymic-independent regions. These may include all germinal centers, plus the subcapsular regions and medullary cords of lymph nodes and the red pulp & peripheral aspects of the periarteriolar sheet of the spleen. B-cells are a minority in the blood compartements, between 5-10% . Once B cells react with an appropriate immunogen; they undergo blastic transformation and a serious of mitotic devisions, and the daughter cells then mature into the plasma cells coded to elaborate antibodies which react specifically with the inciting antigen. These may be of the IgG, IgA, IgM, IgD or IgE class; it is believed that each plasma cell elaborates only one immunoglobulin class(Winkelstein, 1981). It appears that, a large proportion of B-Cells bear surface IgD and surface IgM, probably as monomer (Ivan M. Roit, 1977).

Each step of diffrentiation for each T and B-cell precursor in the bone marrow & thymus is governed by elevation of cyclic adenosine monophosphate in cycling cells, induced by local hormones. For T cell sequence, thymopoietin plays this role ; the B cell hormone is unknown. However B-adrenergic agonists, including lipopolysaccharides and ubiquitin can indiuce differentiation in cells of both T and B lineages.

The functional subpopulations of B-lymphocytes are:

1. Precursor of antibody forming cells.
2. Memory B cells which are functionally important for devel-

opment of rapid secondary antibody responses upon subsequent antigenic exposure.

3. ? Requlatory B-lymphocytes : As yet, there is no hard evidence for the existence of regulatory B-lymphocytes - although the future discovery of such cells, would not be surprising. The capacity of antibody molecules themselves to specifically regulate immune response by "antibody feed back " is well decumented (David H. Katz, 1983).

Macrophages derived from the same pluripotent bone marrow stem cells which , after differentiation to blood monocytes, finally settle in the tissues as mature macrophages where they constitute the so-called reticuloendothelial system. They are present throughout the connective tissue and arround the basement membrane of small blood vessels and are particularly concentrated in the lung (alveolar macrophages), liver (Kupffer cells), and lining of spleen sinusoids and lymph node medullary sinuses, where they are stratigically placed to filter off foreign material. Macrophages are of primary importance; both as auxilliary cells in several phases of immune response and also as secondary cells in cell-mediated immunity (Schwartz et al., 1970).

The inflammatory cells (Polymorphs, basophils, eosinophils) play a secondary role in various cell-mediated responses. They arise as separate lineages from bone marrow stem cells. Each follows a destinctive pathway of steps of diffrentiation governed