"T" AND "B" CELL IMMUNODEFICIENCY DISEASES

THESIS

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Presented By
NAHED ABD-ALL EL-HARRASS
M. B; B. Ch.

Under Supervision of
Prof. Dr. SALAH AWAAD
Professor of Pediatrics

Faculty of Medicine
Ain Shams University

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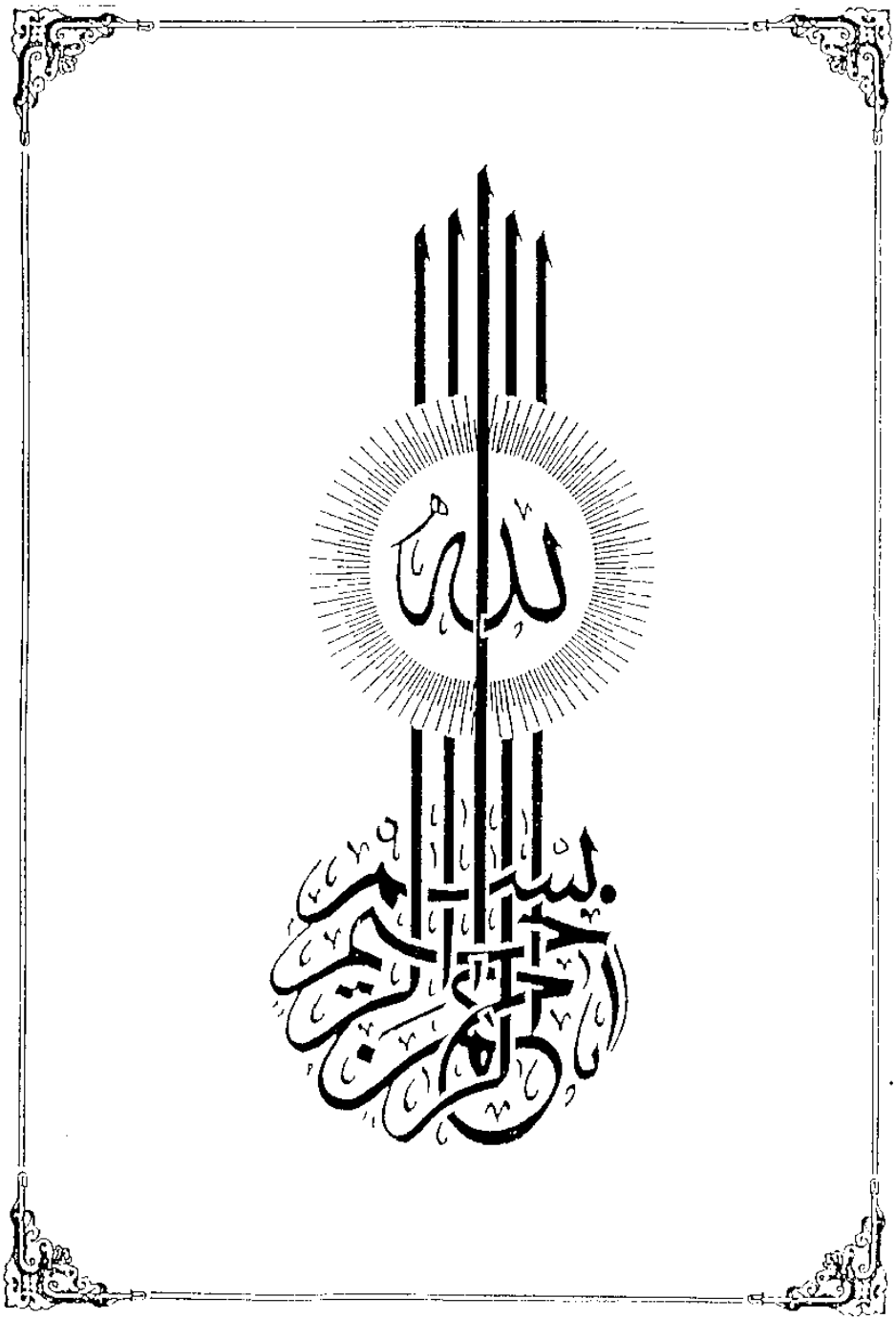

CONTENTS

B- And T-cell Immunodeficiency Diseases:

I- Introduction

The immunodeficiency disorders are a diverse group of illnesses which, as a result of one or more abnormalities of the immune system have increased susceptibility to infection. Although the possibility of an immunodeficiency should be considered in any individual with "too many infections", these are relatively uncommon disorders, so it is important to consider other conditions that lead to infection. When there is no apparent explanation for the recurrent infections, a primary defect in the immune system of the host must be considered.

The immune system includes the B-cell system (antibody), the T-cell system (cellular immunity), the phagocytic system (polymorphonuclear and mononuclear) and the complement system.

Immunodeficiencies involving the B-cell system, the antibody immunodeficiencies, are the most common and comprise about half of the primary immunodeficiencies.

T-cell (cellular) immunodeficiencies are the next largest group, comprising about 40% of the total primary immunodeficiencies. Three fourths of these patients have associated B-cell deficiencies, so they are combined immunodeficiencies.

Many of these occur in conjugation with distinct clinical features as part of asyndrome ,(e.g., ataxia telangiectasia, Wiskott Aldrich syndrome) or are associated with thymic hypoplasia or dysplasia.

Phagocytic immunodeficiencies, comprising about 6 percent of the total, involve either the polymorphonuclear phagocytic or the mononuclear phagocytic system (monocyte/macrophage).

Disorders of the complement system are also recognized in 4% of the total,

Classification and frequency of the primary immunodeficiencies: (Table 1)

	Approximate % of total
(1) Antibody (AB)* immunodeficiencies. (B-Cell)	50
(2) Cellular immunodef. (T-cell	40
a) With AB. immunodef.	(30)
b) Isolated cellular immunodef.	(10)
(3) Phagocytic immunodef.	6
a) mononuclear phagocytic immunodef.	(1)
(4) Complement immunodef.	4

* AB = Antibody

The secondary immunodeficiencies result when there is interferance with immune function by some disease or injury . These secondary forms of immunodeficiency are considered more common than primary immunodeficiencies.

The aim of this essay is to study the following:

1) The events involved in B-and T-cell maturation as well as regulatory cell interaction.
2) The pathogenic factors leading to B-and T-cell primary immunodeficiency diseases.
3) Clinical and laboratory approaches to the evaluation of the patient suspected to have B or T-cell immunodeficiency disease.
4) The major primary B and T-cell immunodeficiency diseases and immunodeficiency disorders associated with malignancies of the T- and B-cells.
5) The important conditions leading to secondary immunodeficiency of B- and T-cells.

II- The Development And Maturation of B- and T-cells.

A) The Development And Maturation of B-cells:

The development of antibody-producing lymphoid cells is best understood in birds. Studies in the chicken have shown that noncommitted lymphocytes, derived from bone marrow stem cells, mature to B-lymphocytes, under the influence of the bursa of fibricius (Cooper et al, 1965). The situation in man is less clear. The location of the mammalian bursa is yet to be fully appreciated but probably is in the bone marrow and foetal liver. (Owen et al, 1974). Lymphocytes with markers characteristic of B-cells are abundant in lymph nodes, spleen, tonsils, appendix and peyer's patches. They are also present in the peripheral blood.

The B-cell is a small, mobile, non phagocytic and has immunoglobulin on its surface. The B-cells make up 20% of the peripheral blood and thoracic duct lymhocytes, 20-30% of the lymphocytes of lymph nodes and spleen, a majority of the lymphocytes in the bone marrow but are not usually present in the thymus, (Cooper et al 1965).

Early B-cell Development:

The first cell that can be identified as a cell of the B-cell lineage makes its appearance in the foetal liver during the seventh weak of gestation in man. These cells, called pre-B cells, are initially recognizable as large, rapidly dividing cells containing small amount of intracellular immunoglobulin (IgM). Later, they also occur as small resting cells. (Owen et al, 1977). Some believe that these cells lack surface immunoglobulin, where as others believe that small amounts are present and are turning over rapidly, (Raff et al, 1976, Melchers, 1976). All would agree that the pre-B cell is not reactive to stimuli that require binding to an Ig receptor and that the pre-B cell lacks other surface characteristics of mature B cells, including Fc. receptors and complement receptors.

The next identifiable step in B-cell development occurs some two weeks after appearance of pre-B-cells in man.

The pre-B-cells (probably from the small resting cell compartment) develops into small lymphocytes that bear a single immunoglobulin (IgM) on their surface. These cells, Variously called "Immature B-cells" or

progenitor B-cells are similar to mature B-cells in that they can interact with antigen but are dissimilar in that they are exquisitely susceptible to tolerization. (Nossal et al, 1975).

Late B-cell Development:

The final stages of developmental of B-cells involve the differentiation of immature B-cells into cells capable of responding to antigen with the production of antibody of specific class (isotype). Such differentiation occurs largely in the bone marrow, although some differentiation also probably occurs in the spleen and in other peripheral lymphoid organs.

Using techniques in which developing cells are labelled, by the sequential application of two different fluoresent anti-Ig reagents, it has been shown that immature B-cells bearing only IgM develop into cells bearing IgM and IgD on the surface from which cells which produce IgM arise, similarly, other immature B-cells with IgM, develop into cells bearing IgA and IgD on the surface or cells bearing IgG_{1-4} and IgD on their surface, from which cells which produce IgA and IgG_{1-4}, respectively arise. (Abney et al 1978, Gathings et al, 1977).

Important features of this scheme of B-cell development are that:-

1) IgM bearing cell preceede IgD bearing cells in order of appearance.

2) Ig_A bearing cells destined to produce Ig_A arise mainly, if not exclusively from IgM-bearing cells and not IgG bearing cells. and

3) Terminal stages of B-cell development can occur in peripheral lymphoid tissues including peyer's patches and spleen.

B) The Development and maturation of T-cells:

The cells that provide the host with the necessary machinery for cell-mediated immune reactions arise in the bone marrow. This site is also the origin of the cells of hematologic system and may explain the clinical association of certain hematologic disorders and bone dyscrasias with immunodeficiency syndromes. Beginning in intrautrine life, some of the bone marrow cells mature under the influence of the thymus (T) gland and are known as T-lymphocytes or T-cells. Migration from bone marrow sites into the thymus gland begins in early foetal life and persists for several years, at least into adolescence. After this thymic interaction, the cells, termed post-thymic cells, take up residence in the periarteriolar sheaths of the spleen, peyer's patch tissue, and paracortical (thymic-dependent) area of the lymph nodes. In these sites they have the appearance of small lymphocytes with dark pyknotic nuclei and a high nuclearcytoplasmic ratio. It is also possible that cells pass directly from the bone marrow to the thymic-dependent lymphoid areas and "mature" under the influences of humoral factors elaborated by thymic epithelium. Experiments by(Gowans and Knight 1964); have shown that

the cells do not remain sessile, from the lymphoid organs they enter the blood stream and thoracic duct and constantly circulate throughout the lymphoid system. They do not return to the thymus, however.

Microenvironment:

T-cell differentiation shares with B cell differentiation the necessity for an appropriate microenvironment, which in this case, of course is the thymus. Bone marrow cell precursors migrate to the thymus at a low rate through out the life of the animal and once in the thymus are induced to become mature T-cells (Ford and Micklem, 1963). The induction process involves interaction between thymus epithelium and the bone marrow cells which is mediated. (Dosch et al 1974), in part by humoral factors such as polypeptide thymopoietin (Basch and Goldstein 1974). That the thymic epithelium is the origin of differentiation factors is shown by studies by Pyke et al. (1975), wherein supernatants from human thymic epithelial cultures were shown to induce bone marrow cells to form rosettes with sheep erythrocytes, a property of T-cells.

Thymic Hormones:

A product of the thymus which has been partially purified and characterized is able to exert an influence

upon the thymic-dependent population of cells both as induces, conferring onto bone marrow cells the capability of post-thymic cells, and as an expander or stimulus to proliferation. It seems most likely that there are many factors elaborated by the thymus which play a role in T-cell maturation, differentiation, and perhaps proliferation. The best discribed are thymic factor (Bach et al., 1975), Thymopoietin (Basch and Goldstein, 1974), thymic humoral factor (Trainin et al 1975), and thymosin (Goldstein et al 1975). Following treatment with crude calf thymosin, peripheral blood mononuclear cells from immunodeficient patients can be shown to develop E-rosetting characteristics (Touraine et al, 1974 and Wara et al, 1975). A preparation from calf thymus can convert bone marrow (stem) cells of normals to E-rosetting cells (Horowitz et al ,1977).

T-lymphocytes:

Lymphocyte life span:-

There are long-lived and short-lived T lymphocytes. Studies of peripheral blood lymphocytes from patients receiving X-irradiation as long as ten years prior to time of testing have shown the persistence of radiation induced chromosomal damage. These studies imply that

at least some lymphocytes have a life span of 10 years or more, such cells would be ideally suited for the carriage of immunologic memory. The long-lived lymphocytes form the major portion of the thoracic duct cells (90%), whereas the short-lived T- lymphocytes are mainly located in the thymus, spleen, and bone marrow.

T-cell circulation:

The thymus continuously resupplies the peripheral lymphoid tissue with T-cells, and thymectomy is ultimately followed by lymphocytopenia and lymphoid depletion of the thymic dependent areas of the lymph nodes and spleen. However, since the peripheral T-cell pool is long-lived, post-thymectomy lymphoid depletion may take some time to develop. A majority of thymocytes entering the peripheral pool are short-lived, these cells are non recirculating and are made up in part of a population of immature T-cells that may depend on thymic factors to complete their development. A minority of the cells entering the peripheral pool are long-lived, these are mature cells that are continuously replenishing a large pool of circulating T-cells.

Lymphocyte circulation:

The control of lymphocyte flow is probably dependent upon cell membrane receptors, because treatment of the