AN ESSAY ON IMMUNOMODULATION

Submitted in Partial Fulfilment of the Degree of Master of Pediatrics.

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قالوا

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة (الآية ٣٢)

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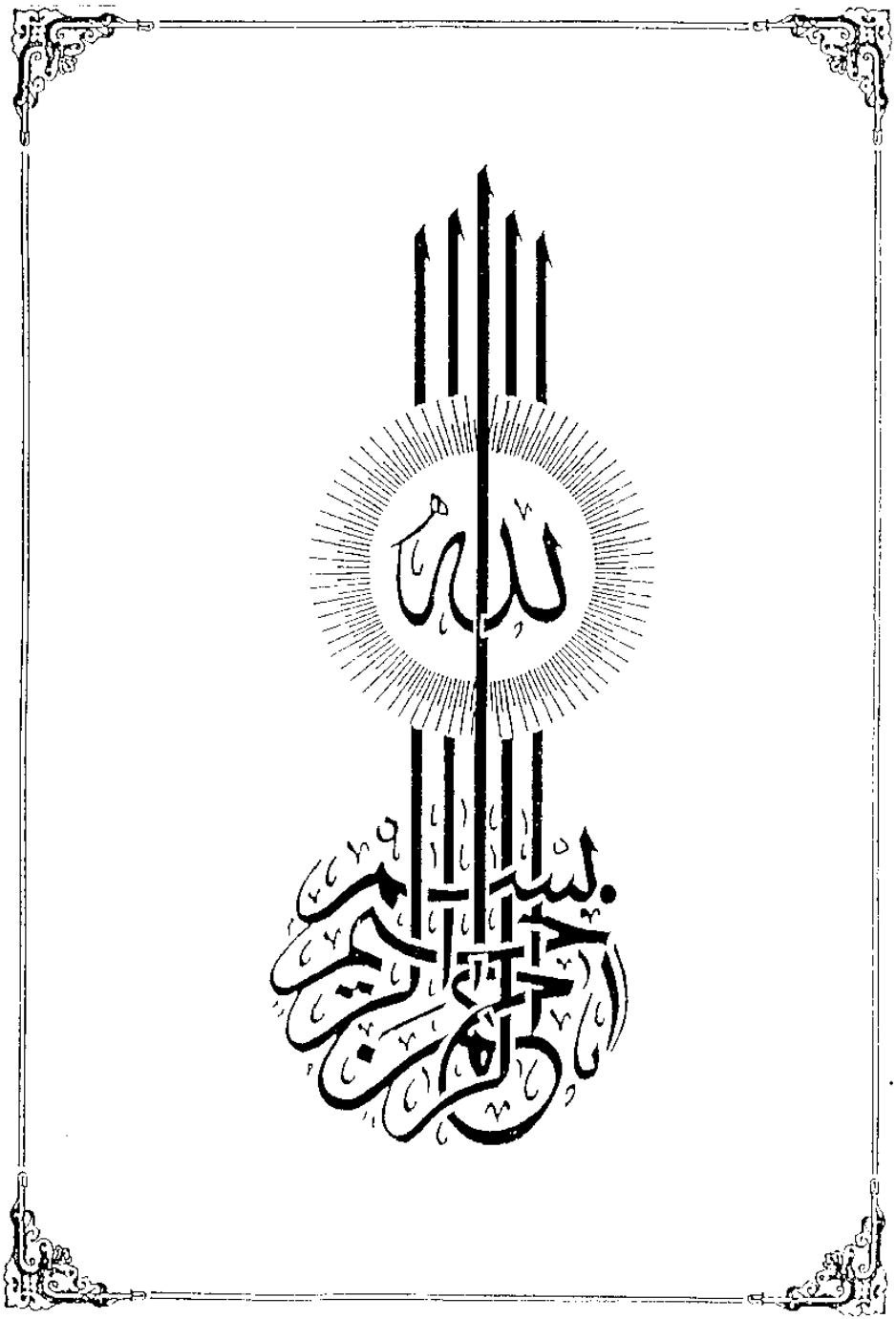

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I. INTRODUCTION AND AIM OF WORK

Immunology is a rapidly expanding field of medicine, in which new knowledge accumulated at an explosive rate during the past decade. A new frontier in immunology, still in the stage of exploration and debate, is the development of immuno-modulator agents that change or modulate the function of B and T lymphocytes and the mono-nuclears phagocytes. The rational for the development of these agents is that they can be used to modulate the immuno-responsiveness of patients who have either selective or generalized immun-deficiency.

The aim of this essay is to discuss the immuno-modulation and immuno-modulator agents, Also, their major potential uses in three essential fields of medicine namely oncology, infectious diseases and organ transplantation will be discussed.

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IMMUNE SYSTEM

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II. The Development, Structure and Function of the Immune System

An efficient immune system depends upon the interaction of many cellular and humoral componants which develop at different rates during foetal and early life.

Many cells involved in immune response are derived from undifferentiated, haemopoietic stem cells and are thought to differentiate into various cell lineages under the influence of different micro-enviromental factors (Fig. I). In mammals the adult bone marrow is thought to provide a continuous source of stem cells and most or all of other cells involved in the immune response.

The Components of the Immune System

The genetic, cellular, and molecular components of the immune system are combined in our exquisitely complex communilations net work. The relationships between these components are reciprocal and circumscribed. Regulatory control of immune mechanisms is a function of their interactions.

The Immune System Consists of the Following:

Organs, cells, and immunologically active proteins:

I. Organs and Tissues of the Immune System:

These include:

A. Primary (or centeral) Lymphoid Organs:

These include the thymus gland and the bone marrow and in binds, the Bursa of Fabricius. They are called primary lymphoid organs because they supply immune competent cells

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to all peripheral tissues.

B. Secondary (or peripheral) Lymphoid Tissues:

These include the lymph nodes, the spleen the tonsils and the Payers patches.

II. Cells of the Immune System

1) Cells of lymphocytic series T and B cells.

i. T lymphocyte

ii. B lymphocyte

2) Macrophages and Dendritic cells (Adherent cells).

iii) Macrophages.

3) Granulocytes (basophils, esinophils and neutrophils)

4) Null cells and lymphocyte traffic cells:

iv. Null cells

v. Lymphocyte traffic cells.

vi. Dendritic cells and longerhams cells.

III. Immunologically Active Proteins:

These include the following:

1. Immunoglobulins.
2. The complement system including the properdin system
3. Interferon.

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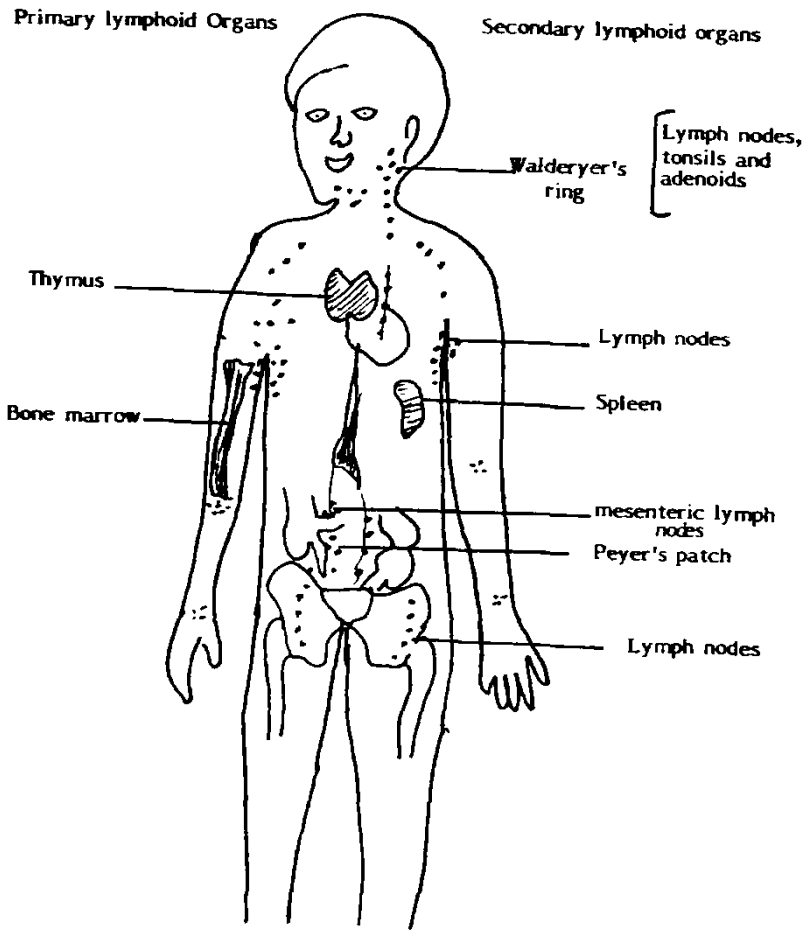

Fig. (1): Major lymphoid organs and Tissues

The thymus produces T cells and the bone marrow produces B cells. The secondary lymphoid organs and tissues contain mature T and B cells and accessory cells. In the mammalian foetus the B cells are initially generated in the liver. In man the adult bone marrow is also a secondary lymphoid organ. Lymph nodes are present through out the body and are usually found at the junctions of lymphatic vessels. The group of lymph nodes including the tonsiller and adenoidal lymphoid tissue in the area of the neck and throat is called the Waldeyer's ring of lymphoid tissue. Lymph nodes drain the tissue spaces and the lymphocytes at these sites generally respond well to lymph-born antigens whilst lymphoid cells in the spleen respond well to blood born antigens. Peyer's patches are unencapsulated masses of lymphoid tissue in the small intestine.

The central lymphoid organs are the bone marrow and the thymus. It is there that lymphocytes acquire immuno-competence. The peripheral lymphoid system consists of lymph nodes, spleen, and tensils etc. It is there that the immuno-competent lymphocytes encounter antigens and mount an immunoresponse. Antibody production occurs in the tissues of the peripheral lymphoid system, while cell mediated immune responses can be carried out - wherever needed in the body.

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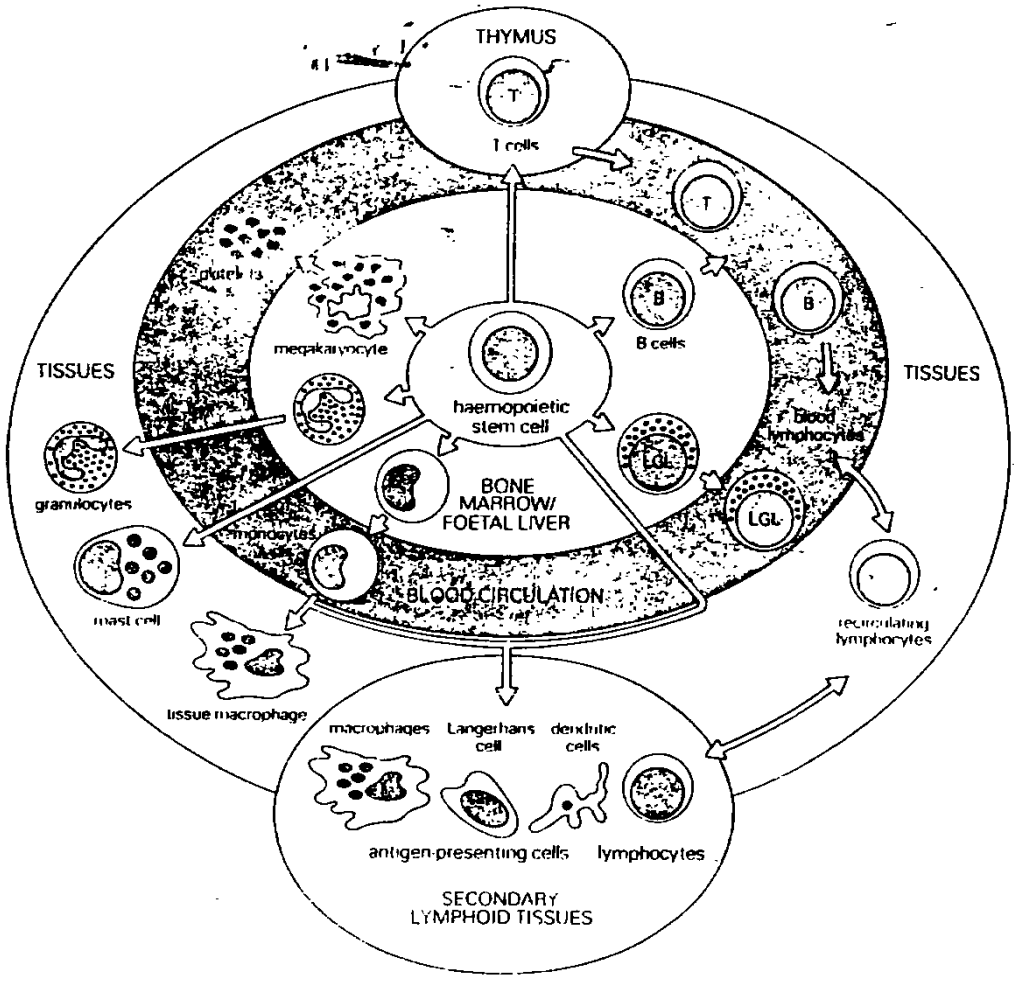

Fig.(2): Shows Origin of cells of the Immune System

All of the cells of the immune system arise from the haemopoietic stem cell. Platelets produced by megakaryocytes are released into the circulation, granulocytes pass from the circulation into the tissues. Mast cells are identifiable in all tissues. B cells mature in the foetal liver and bone marrow in mammals while T cells mature in the thymus. The origin of the large granular lymphocytes (LGL) is uncertain. Both lymphocytes and monocytes which develop into macrophages, can recircutate through secondary lymphoid tissue. Langerhans cells and dendrite cells act as antigen-presenting cells in secondary lymphoid tissue.

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A. Primary OR Central Lymphoid Organs

i. The Thymus

In mammals the thymus is a bilobed greyish orgen located high in the thoracic cavity. Until the late of 1960s the thymus function was uncertain. In 1961 Miller in Australia and Good in Minnesota revealed the importance of this organ to proper immune function. The procedure done was neonatal thymectomy which led to profound lymphopenia where circulating lymphocytes decline to very low levels with consequent failure to develop normal cell mediated immunity. (not reject allograft) (=a graft between animals of the same species) and failure to develop delayed type hypersensitivity DTH) and also with failure to develop respond to some antigens (thymus dependent antigens).

The thymus gland has also an endocrine function; secretion of thymosine hormone which can restore cell mediated immune response in Nude mice. It also secretes thymopoietin, thymic humoral factor, thymostimulin, and "Factor Thymique" (FTS). It plays an important role in the differentiation process from stem cells to thymocytes where generation and maturation of cell occur. Also the thymus is important in the process of learning to recognise self antigens in the thymus by helper T cell, rejecting allografts and developing the delayed type of hypersensitivity by thymocytes (Cooper et al. 1966).

ii) The Brusa of Fabricus and its Mammalian Equivalent:

In birds, the B cells differentiate in Bursa of Fabricus, hence, the name B cell. Bursa of Fabricus is like a modified piece of intestine

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with plicae ((folds) directed towords a central lumen. The bursal follicles are organized into cortex and medullae and lie along the margins of the plicae. Mammals have no bursa, instead, islands of haemopoeitic cells in foetal liver and in foetal and adult bone marrow, give rise directly to B-lymphocytes.

As well as being a site of B cell generation, adult bone marrow contains many mature T-cells and antibody producing plasma cells i.e. in man it is also an important secondary lymphoid orgen. The bulk of evidence suggests that in adult mammals, the cells responsible for antibody synthesis begin development in the bone marrow which may represent equivalent to Bursa of Fabricus in mammals.

iii. Bone Marrow:

The haematopoeitic bone marrow is contained largelly within the flat bones. The bone marrow is the major source of red cells, platelets, and granulocytes. It also manufactures lymphocytes and monocytes (Fig. 2). There is a single stem cell which gives rise to all the cells of the blood "pluripotent stem cell". It gives rise to red cells, gronulocytes, monocytes and megakaryocytes. The bone marrow is the source of cells which participate in cellular mediated immunity, and these cells do not gain competence until they have been exposed to the influence of the thymus.

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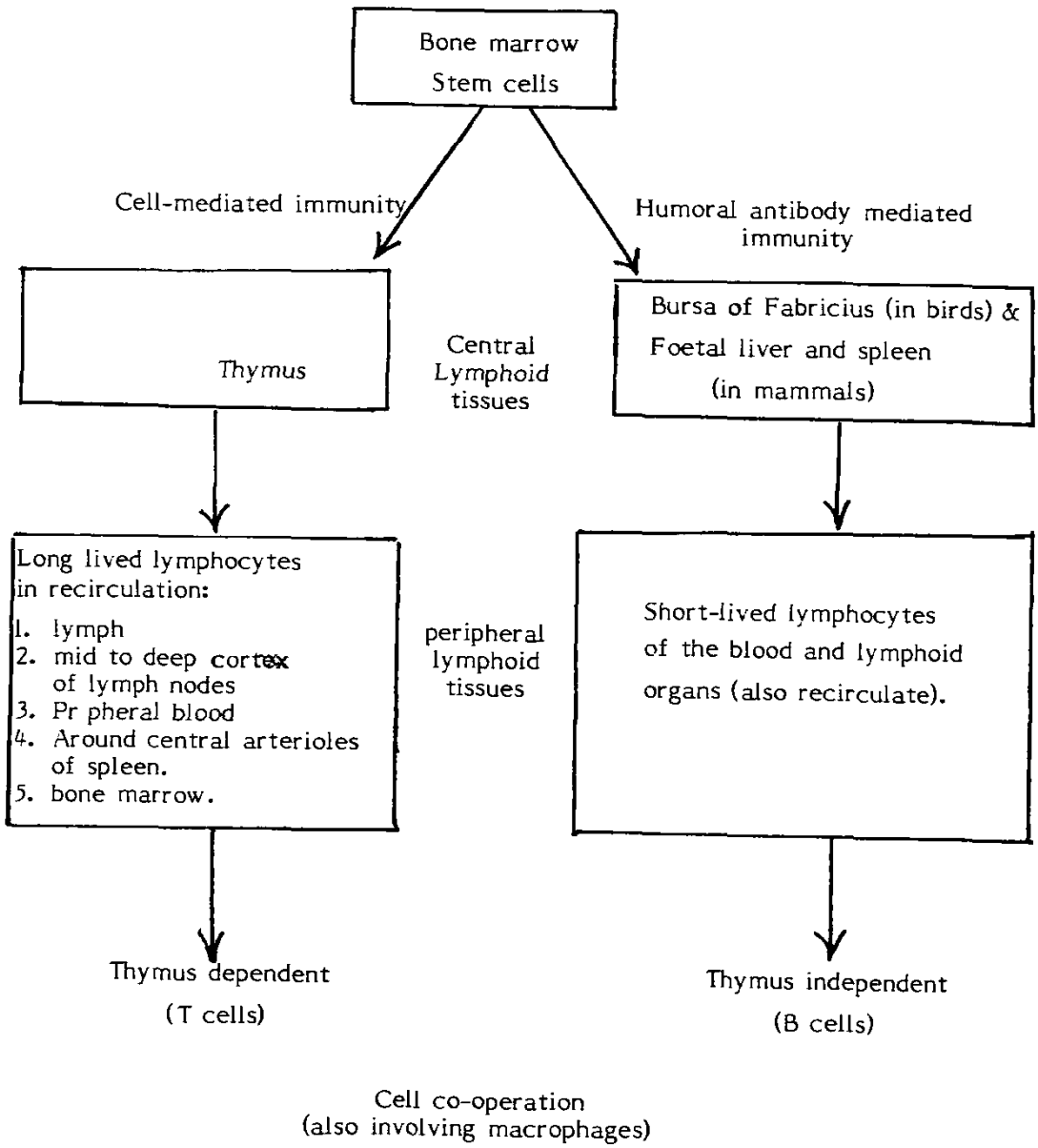

Table (I): **Scheme illustrating possible relationship between central and peripheral lymphoid tissues. (After immunology D.M. Weir, 1980).**

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