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STUDIES ON THE LOCAL IMMUNOGLOBULINS IN GASTRIC
MUCOSAL BIOPSIES IN ENDEMIC HEPATOSPLENOMEGALIC SYNDROME

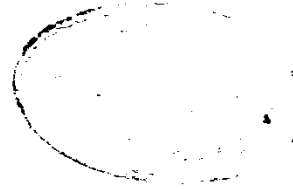
T H E S I S

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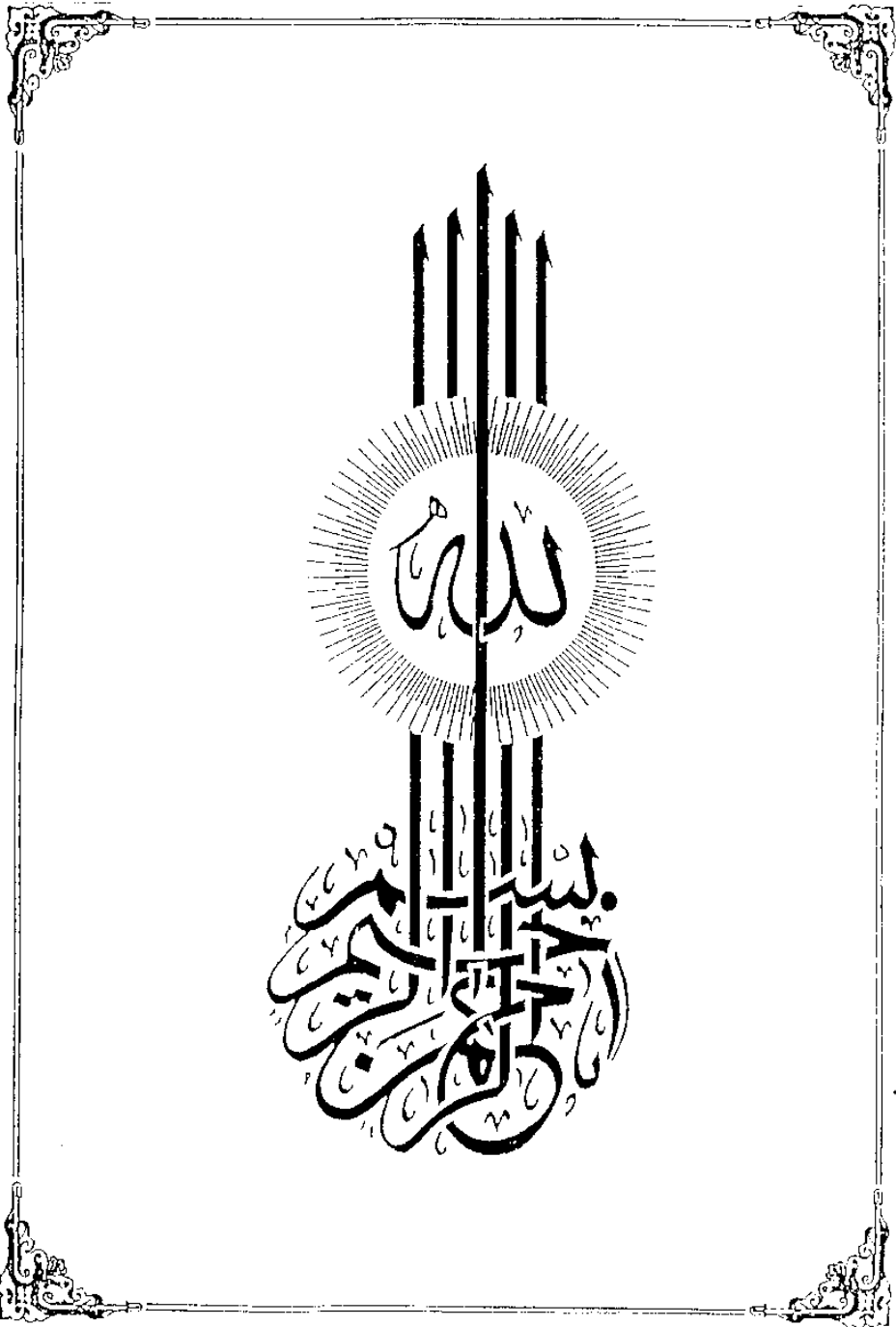
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INTRODUCTION

Endemic hepatosplenomegalic syndrome is one of the most important health problems in Egypt.

Changes in both cell mediated and humoral immunity were demonstrated in this syndrome.

Gastric disturbances are among the common presentations in endemic hepatosplenomegaly. Local immunological changes in the gastric mucosa could be one of the aetiologic factors contributing for the production of those symptoms.

The Aim of the present work is to study the local immunoglobulins in gastric mucosal biopsies in the syndrome of endemic hepatosplenomegaly.

BASIC IMMUNOLOGY

Functional anatomy of the immunologic apparatus:

Lymphoid tissues subserving the immune system can be subdivided into the central and peripheral components. The central lymphoid tissue consists of the thymus and the bursa equivalent, the cloacal lymphoid appendage in birds and probably the bone marrow in man. These two sites are responsible for the development of the two major population of the lymphocytes, the thymus dependent T cells and the bursa dependent B cells.

The peripheral lymphoid tissue consist of spleen lymph nodes and mucosal associated lymphoid aggregates in intestine, respiratory tract and genito urinary system (Chandra R.K., 1983).

Component of the immune system:

Four main immune systems assist the individual in the defence against a constant assault by viral, bacterial, fungal, protozoal, and non replicating agents that have the potential of producing infection and disease. These systems consist of antibody mediated (B cell) immunity, cell mediated (T cell) immunity, phagocytosis and complement. Each system may act independently or in concert with one or more of the others (Amman & Fundenberg, 1983).

1. T cell system:

Cell mediated immunity is the product of lymphoid cells developed through the influence of the thymus gland. T cell system is responsible for a variety of host defence activities. Control of viral and fungal, infections, rejection, graft versus host reactions, tumour immunity, delayed skin hypersensitivity and regulation of B cell function (Roper M. and Cooper M. D. 1983).

T cell development:

Precursors of both B & T lymphocytes arise from pleuripotential stem cells that may appear first in the blood islets of the embryo and yolk sac at about the fourth week of gestation, such cells later migrate to the fetal liver and then to the bone marrow, when these tissues become hemopoietic. Bone marrow precursor cells migrate to the thymus where they are induced to become lymphoid cells (Moore & Owen, 1967; Stutman, 1977).

At eight to nine weeks in human gestation, lymphocytes appear in the outer areas of the thymus may occur later in life, but this flow of stem cells into the thymus is thought to slow with ageing. (Kay et al., 1962; Papierink, 1970).

T cell differentiation within the thymus:

Approximately 90% of the thymocytes are located in the thymic cortex, and only 5-10% are in the thymic medulla.

Outer cortical thymocytes are the most immature lymphoid T cells (Stutman & Good, 1971). They exhibit a rapid rate of proliferation and DNA synthesis (August et al. 1971).

Many of these young thymocytes die in the cortex (Matsuyama et al. 1966) while others migrate from cortex to medulla as they undergo further differentiation (Owen & Raff, 1970; Prindull, 1974).

With maturation and migration to the medulla thymic lymphocytes slow their rate of cell division. The majority of cortical thymocytes can bind sheep erythrocytes to form rosettes (E-rosette). E rosette forming cells can be detected as early as 11 weeks of gestation in the thymus (Stites et al., 1972; Wybrun et al., 1973; Stites & Pavia, 1979).

During migration to the medulla, maturing thymocytes become resistant to the lytic effects of corticosteroids and acquire immuno competence (Cohen & Claman, 1971).

Medullary thymocytes can recognize & respond with proliferation to alloantigens in a mixed lymphocyte culture (Raff & Cantor, 1971), to antigens such as salmonella flagellin (Dwyer & Macaky, 1970) and to the polyclonal T cell nitrogen concanavalin A & phytohemagglutinin (Jones, 1969; August et al., 1971; Carr et al., 1973). Cortical thymocytes lack these capabilities.

T cell circulation:

Mature T cells leave the thymus by passing through the walls of medullary venules into the peripheral circulation lymphocytes can be detected in the peripheral circulation at 7 to 8 weeks of gestation. By the tenth week, these cells constitute over 50% of the circulating white cells (Playfair et al., 1963). Many of these circulating lymphocytes have been shown to have T cell characteristics.

Circulating T cell exits from the blood via high cuboidal endothelial cells lining the venules of the paracortical areas of the lymph nodes and peyer's patches, and enter the periarteriolar areas of the spleen (Weiss, 1964; Weissman, 1967; Hoywerd et al. 1972).

After a period of residence in lymph nodes, lymphocytes enter the lymphatic system via afferent channel and travel to the thoracic duct, from which they re-enter the peripheral circulation. (Fish et al., 1970).

T cells have highly variable life spans. Many die before leaving the thymus (Matsayama et al., 1966), while others may circulate for over ten years. (Buckton & Pike, 1964).

Cell mediated lympholysis:

Cytotoxic T cells can be found in the neonatal blood, but there are no reports yet of their presence in fetuses (Stites & Pavia, 1979).

In the presence of PHA, lymphocytes from 16 week old fetuses and from cord blood can lyse xenogenic cells (Stites et al., 1972).

Fetal bone marrow cells are able to produce xenogenic target cell lyses, fetal thymic cells can not. These results emphasize the functional heterogenicity of developing T cells populations. (Roper, M. & Cooper, M. D., 1983).

II. The B cell system:

This system of cells is primarily responsible for antibody production and humoral immunity. B lymphocytes are characterized by their expression of surface immunoglobulins like T cells, they have unique surface antigens, responds to a specific group of mitogens, and reside in designated areas of peripheral lymphoid tissues. (Roper, M. & Cooper, M. D. 1983).

B cell origin:

B cells arise from the same pluripotential stem cells in embryo as do T cells. Early in embryonic life they are present in blood islands of the yolk sac, later migrates to the fetal liver and finally home to the bone marrow when hemopoiesis shifts to that tissue, beginning around the 10th week of gestation. (Roper, M. and Cooper M. D., 1983).

The sites of B cell generation differ according to age during embryonic life in mice rabbits and humans, B cells are generated in the liver. The results of one study suggest

that stem cells are committed to development along B cells line even before they migrate to the liver (Melchers, 1979). Later in life, B cells are produced in the bone marrow (Osmond & Nossal, 1974; Melchero et al., 1975; Gathings et al., 1977).

Pre B cells:

The earliest cells of B cell lineage, called pre-B cells, have first been seen in the human fetal liver at 8 weeks of gestation (Gathings et al., 1977).

These cells express cytoplasmic IgM determints (CIGM⁺), but lack detectable amount of surface IgM (SIgM⁺). The earliest description of pre-B cells were based on the observation that IgM component synthesis by mouse fetal liver could occur several days before cells bearing surface IgM were detectable (Owen et al., 1974; Melchers et al., 1975). Recognizable pre B cells are heterogenous in size. Roughly they can be divided into large cycling lymphoid cells & post mitotic small lymphoid cells. Both of which contain M chains in their cytoplasm but lack surface Ig molecules, C₃ receptors & FCIgG, receptors (Roper M. & Cooper M. D. 1983).

Large pre B cells preceed small ones during ontogeny & during regeneration of bone marrow (Burrows et al., 1979). Large pre-B cells are only found in fetal liver and bone marrow whereas small pre-B cells may occur in low frequency in the fetal circulation & peripheral lymphoid tissues (Gathings et al., 1977).

Although the initial work in mice suggested that pre-B cells synthesized both heavy and light chains of immunoglobulin (Melchers et al., 1975; Cooper et al. 1978), It has now been demonstrated that the vast majority express M chains only (Burrows et al., 1979; Levett & Cooper, 1980), and only a few small pre-B cells in human express light chains also (Kubagawa et al., 1981).

Young B lymphocytes:

The next stage of B cell development is characterized by the expression of surface immunoglobulin (SIg⁺). Cells bearing SIgM have been detected as early as nine weeks in the fetal liver (Lawton et al. 1972; Gathings et al. 1977).

The Co-expression of SIg D begins around 12th week at which time subpopulations of SIgG⁺ & SIgA⁺ cells appear. Young B cell may lack the C₃ surface receptor (Gelfand et al. 1974) but express as much SIgM as can be seen on older B cells (Raff et al., 1975).

Young B lymphocytes demonstrate an interesting property lost by their more mature successors, young B cell have an increased sensitivity to modulation of their surface Ig receptors. On exposure to multivalent anti immunoglobulins or antigen, the surface Ig receptors of adult B lymphocytes form patches which migrate to one pole of the cell and then are endocytosed. This process, called modulation and is reversible. In young B cell, modulation occurs on exposure

to much lower doses of antigen or antibody and is irreversible (Raff et al., 1975; Bruyns et al. 1976).

Nossal & Pike (1975) have suggested that this mechanism may function to remove clones of B cells bearing antibodies to self antigens.

Virgin B cells:

Virgin B cells, untouched by antigen circulate through blood and lymphoid channels. At this stage in development, B cells lack cytoplasmic immunoglobulin but may express other classes of surface immunoglobulin in addition to IgM (Roper, M. & Cooper M. D., 1983).

Most B cell simultaneously bear SIgD (Rowe et al. 1973; Vossen, 1975). A small number of B cells at this stage of development may additionally express IgG or IgA (Gathings et al., 1977; Gandini et al., 1980).

In addition to surface antibodies, most virgin B cells express Fc & C₃ receptors (Warner, 1974).

The development of SIgM⁺ B lymphocytes from CM⁺ pre B cells and the switch from cells with SIgM to those having additional isotypes appear to result from intrinsic cell signals and may be independent of antigenic stimulation (Lawton & Cooper, 1973).

Plasma cell maturation and immunoglobulin secretion involves stimulation of B lymphocytes by antigen presented

by adherent cells and helper T cells (Roper, M. & Cooper, M. D. 1983).

Memory B cells:

When virgin B lymphocytes are induced to divide by appropriate contact with antigen, the clonal size is amplified and daughter memory cells are produced. These memory cells circulate more and are more readily triggered by antigen than their immediate lymphocytes precursors (Roper, M. & Cooper, M. D., 1983).

Memory cells induced by T cell independent antigens express primarily SIgM; memory cells produced by interaction with T cell dependent antigen often express SIgA (Davie & Paul, 1973).

Plasma cells and serum immunoglobulins:

Development of immunoglobulin secreting plasma cells lags behind that of B lymphocytes by several weeks (Van Furth et al., 1965; Lawton et al. 1972; Vossen, 1975).

IgM plasma cell can be identified by immunofluorescent staining of tissue from most features beyond the 15th week of gestation, while IgG plasma cells are generally not seen prior to the 20th week and IgA plasma cells have rarely been noted before 30 week of fetal life (Roper, M. & Cooper, M. D., 1983).

Adult levels of IgM, IgG and IgA are usually reached by 1,3-6 & 9-12 years, respectively (Stiehm & Fudenberg, 1966; Buckley et al., 1968).

Immunoglobulins:

Antibodies are specialized serum proteins capable to react specifically with antigens that stimulated their production or with antigens of similar chemical determinants. Physico-chemically they are special class of globulins called immunoglobulins (El Batawi, 1983).

Structure of immunoglobulins (Antibodies):

Immunoglobulins (Ig) have a basic 4 peptide structure of two identical heavy and two identical light chains joined by interchain disulphide links (Roitt, I. M., 1980).

The different immunoglobulins classes (IgG, IgA, IgM, IgD & IgE) are characterized by their heavy chain types, known as γ , α , μ , δ & E, respectively. The various heavy chains have different numbers of interchain disulphide bonds. The final shape of the molecule is modified by inter-chain disulphide bonds to form series of loops.

There are two types of light chains K or λ , but only one of these occurs with any single pair of heavy chains (Hayward, 1977).

Classes of Immunoglobulins:

I. Immunoglobulin G (IgG):

During the secondary antibody response IgG is probably the major immunoglobulin to be synthesized. Through its ability to cross the placenta it provides a major line of defence against infection for the first few weeks of a baby's life (Roitt, I. M., 1980).

It has a molecular weight of 160,000. The major part of immunoglobulins in serum belongs to this type. It is a divalent antibody. (El-Batawi, 1983).

IgG diffuse more readily than the other immunoglobulins into the extravascular body spaces where it carries the major burden of neutralizing bacterial toxins and of binding to micro organisms to enhance their phagocytosis (Roitt, I.M., 1980).

There are 4 subclasses of the heavy chains, numbered IgG 1, IgG 2, etc, the first three of these carry two special sites, one adapted to bind complement and another by which the molecule can bind to receptors on phagocytes and some lymphocytes (Hayward, 1977).

Papain splits the molecule at the exposed flexible hinge region to give 2 identical univalent antigen binding fragment (Fab) and a further fragment (Fc). Pepsin proteolysis gives divalent Ag binding fragment $F(ab')_2$ lacking the Fc (Roitt I.M., 1983).