"T" LYMPHOCYTE FUNCTION IN CHRONIC RENAL FAILURE

THESIS

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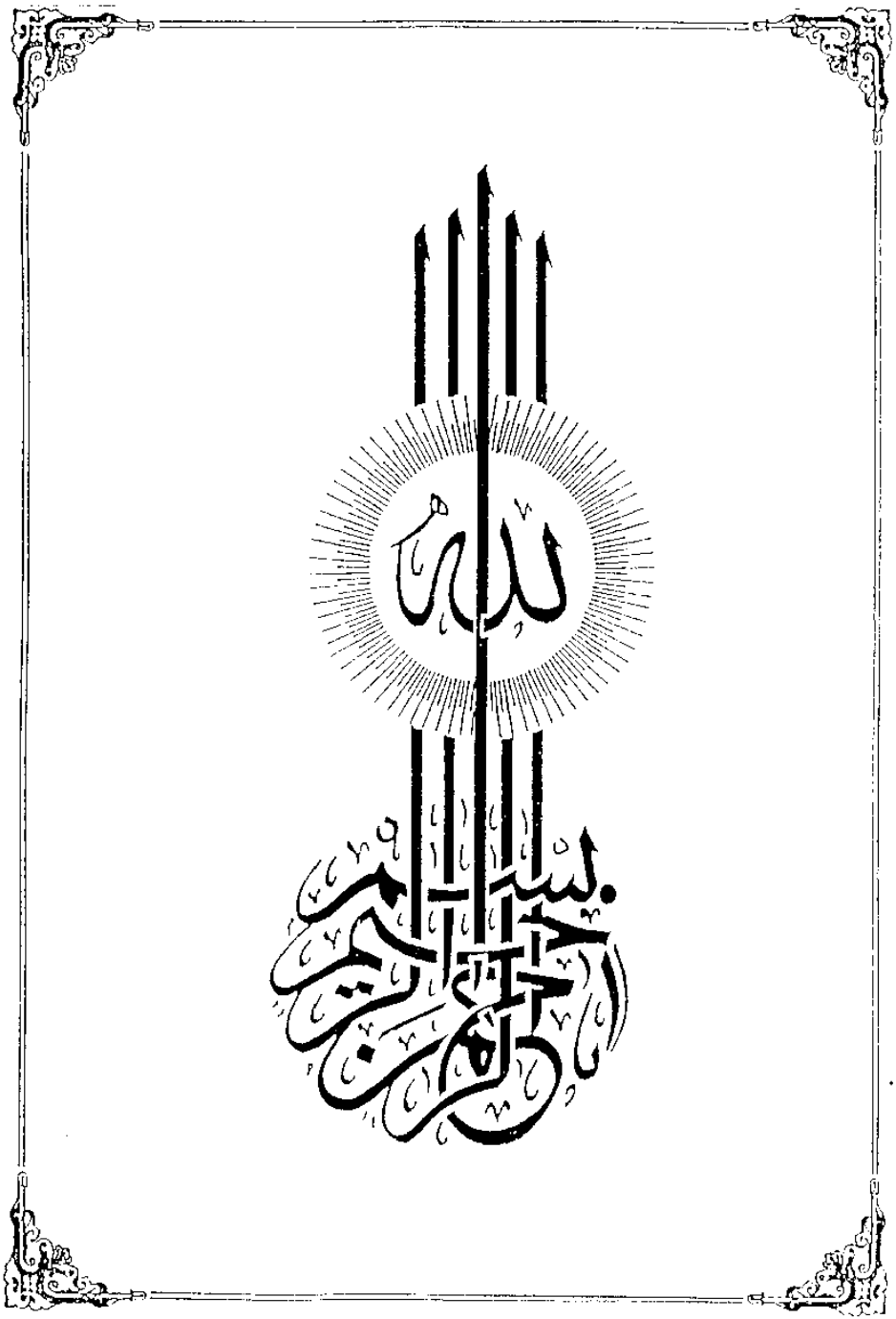

C O N T E N T S

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INTRODUCTION

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Immunological alterations in persons with non-dialyzed chronic renal failure (CRF) have been reviewed by several authors (Montgomerie et al.,1968, Lawerence H.S., 1965, Dobbelstein H. 1976).

Chronic uremia is often accompanied by depression of cell-mediated immunity (Wilson W.E.C. et al, 1965, Sengar et al., 1974), and this is manifested by cutaneous anergy (Sengar et al., 1974, Kirkpatrick et al., 1964), prolonged allograft survival (Dammin G.J. et al., 1957, Smioldy F.G. et al., 1961), lymphopenia (Quadracci et al., 1976), structural abnormalities of lymphoid tissue and thymus gland (Sengar et al., 1965, Wilson et al., 1965), and increased susceptibility to infections (Siddiqui J.Y. et al.,1970). So uremia is a reliable indicator of eventual compromised host immune status.

The etiology of these immunological abnormalities is not completely understood, but several explanation accounting for the depressed cell-mediated immune responses in uraemia have been proposed and include lymphopenia associated with uraemia (Wilson et al., 1965), Vitamin B_6 deficiency (Dobbelstein et al., 1974),

concomitant antimicrobial therapy (Munster et al., 1977) and activation of cellular immune suppressor mechanisms. Soluble factors with immunosuppressive activity have been searched for in serum of uraemic patients (Hanicki et al., 1976).

The pathogenesis of lymphopenia is not apparent. uraemic serum has an inhibitory effect on lymphocyte function, certain metabolites referred to as middle molecules, including methylguanidine and guanidino-succinic acid are known to accumulate in the face of renal insufficiency and suppress PHA-induced transformation (Bergtrom et al., 1976), it may cause or contribute to impaired immune response in uraemia (Abiko et al., 1980).

Impaired cellular immunity is also a manifestation of zinc deficiency (Fraken P.J. et al., 1977, Gross, R.L. et al., 1979, Atoniou L.D. et al., 1981).

Zinc dificiency disorder is characterized by thymic atrophy, lymphatic hypoplasia (Haas et al., 1976, Fernandes G et al., 1979), and lymphopenia (Golden M.H. N et al., 1977).

So our aim of work is to study T-lymphocyte function in chronic renal failure patients and its relation to serum zinc level in uremic patients.

T-CELL REGULATION, ANTI-IDIOTYPIC IMMUNITY

T-CELL REGULATION, ANTI-IDIOTYPIC IMMUNITY AND NEPHRITOGENIC IMMUNE RESPONSE

It is generally agreed that most forms of nephritis probably have an immunologic basis. This belief is supported by a large number of studies focusing on the nephritogenic immune response as it occurs locally within the kidney. One outogrowth of these immunologic investigations is the classical subdivision of renal histopathology into the effector pathways of antibody (Unanue E., Dixon F.J. 1967, Mccluskey R.T., Clovin R.B. 1978), immune deposit (Cochrane C.G., Koffler D. 1973, Wilson C.B., Dixon F.J. 1981), and cell-mediated disease (Nelson E.G., Phillips M. 1980, Mccluskey R.T., Bhan A.K.1982).

The thorough study of these effector pathways has greatly enhanced our understanding of inflammatory mechanisms directly involved in developing immunopathology (Wilson C.B. 1979).

There is, however, another aspect to immune-mediated renal disease which is the rapidly growing area of immune regulation.

In the contex of renal disease, immune regulation can be viewed as a complex network of antibody and cell mediated circuits operating together to produce feed

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back suppression and down regulation leading to the eventual control of on going renal injury.

The modern study of immune-mediated renal disease was primarily influenced by Burnet's theory of clonal selection (Burnet F.M. 1972). This theory predicted that a new antigen bound to pre-existing lymphoid cells would cause them to proliferate and secrete antibodies. In competition for antigen only those cells with high affinity receptors for the antigen continued to proliferate.

Free high affinity antibody united with antigen preventing the further stimulation of antigen reactive clones. In this way antibody removed antigen, thus acting as a negative feedback system, and the lymphocyte clones with high affinity receptors remained as a memory for long lasting immunity (Burnet F.M.1972).

Now it is clear that the humoral and cell mediated immune responses are closely interrelated at many functional levels.

Regulatory networks may provide new and additional pathogenic pathways for immune mediated renal disease (Fig.1).

That is, defects or alteration in regulatory systems may create a permissive environment for the uncontrolled expression of effector responses producing renal injury (Contal H, Gershon R.K. 1979, Bach M.A., Droz D. 1980), so we correlate recent observations in the area of immune regulation and the development of nephritis, and we will focus on the concepts of T-cell function and the role of anti-idiotypic immunity in the control of nephritogenic immune response.

Immunologic circuits and network theory of immune regulation

A normal individual does not destroy his own parenchymal tissues because immune mechanisms capable of producing such injury as specifically inhibited by regulatory systems aquired during ontogeny (Allison A.C. 1977, Weigle W.O. et al. 1979).

Regulatory systems during life are activated after exposure of the immune system to new antigens. The actual mechanism regulating the immune response to complex antigens is determined to a large extent by the T cell repertoire.

T cells can be divided into subpopulations that can be distinguished by cell surface markers encoded by genes activated during Thymic differentiation (Cantor H, Gershon R.K. 1979, Cantor H., Boyse E.A. 1977, Huber B. et al., 1976, Swain S.L., Dutton R.W. 1980).

Helper/inducer T cells ($Ly1^+$ in mouse; OKT_4+ in human) can induce B cells to make antibodies, other mononuclear cells to participate in delayed hypersensitivity reactions, and killer precursors to become cytotoxic effector cells.

Suppressor T cells ($Ly2,3^+$ in mouse; OKT5/8 in human) can inhibit both humoral and cell mediated immunity. A third type of T-lymphocyte ($Ly1,2,3^+$ in mouse $OKT_4^-,5^-,8^+$ in human) appears to be intermediate amplifier cell that can differentiate into more mature helper or suppressor cells (Reinherz E.L. et al.,1980).

The helper T cell is the pivotal cell required for activating and expanding the immune response. Once this process is begun all three groups of cells subsequently function as a dynamic modulating unit which normally feeds back to down-regulate or suppress the antigen induced immune response (Fig.2).

Is an expample, a helper T cell activated by a conventional antigen stimulates the development of a variety of effector cells for the purpose of carrying out the immune response.

A subset of these helper cells, also induces a suppressor cell from intermediate pool of cells (Cantor H, Gershon R.K. 1979, Eardley D.D. 1980). This new suppressor cell inhibits the immunologic activity stimulated by the original helper cell. While some of these immunologic cirauts may operate through cell to cell contact, there is growing evidence that much of network communication is accomplished by soluble lymphokines released by activated cells.

There are two general groups of lymphokines; those which are antigen-specific and those which are not of the latter group the interleukins have received much attention.

Interlukin 1 is an accessory cell-derived peptide which prepares a T cell to respond to antigen (Mizel S.B. 1982). It also induces the secretion of helper T cell-derived interleukin 2, a soluble lymphokine which can amplify an antigen-reactive immune response by recruiting other helper T cells (Farrar J.J. et al., 1982).

These nonspecific lymphokines are essential for successful T cell activation.

Immune response genes that are carried in major histocompatibility complex (MHC) determine an individuals ability to immunologically respond to complex antigens (Back F.H, Van Rood J.T. 1976, Benacerrof B, Germain R.N. 1978).

Immune response genes exert their influence by providing gene products for modulating two basic lymphocyte functions: those of intensity and those related to restriction.

The intensity of an immune response is genetically determined not only by the presence of antigen reactive lymphocytes but also by the relative balance between helper and suppressive influence (Bancerrof B, Germain R.N. 1979). For example, if T-helper cell is going to respond to its antigen, this antigen must be processed by an accessory cell and seen in association with certain class II MHC antigens (HLA-D/DR region in the human), which are also expressed on the surface of these antigen presenting cells (Pierce W. 1980).
N.B. (1) MHC major histocompatability complex in humans it is designated HLA. Genes in this complex provide