An Essay

ON AUTOIMMUNITY

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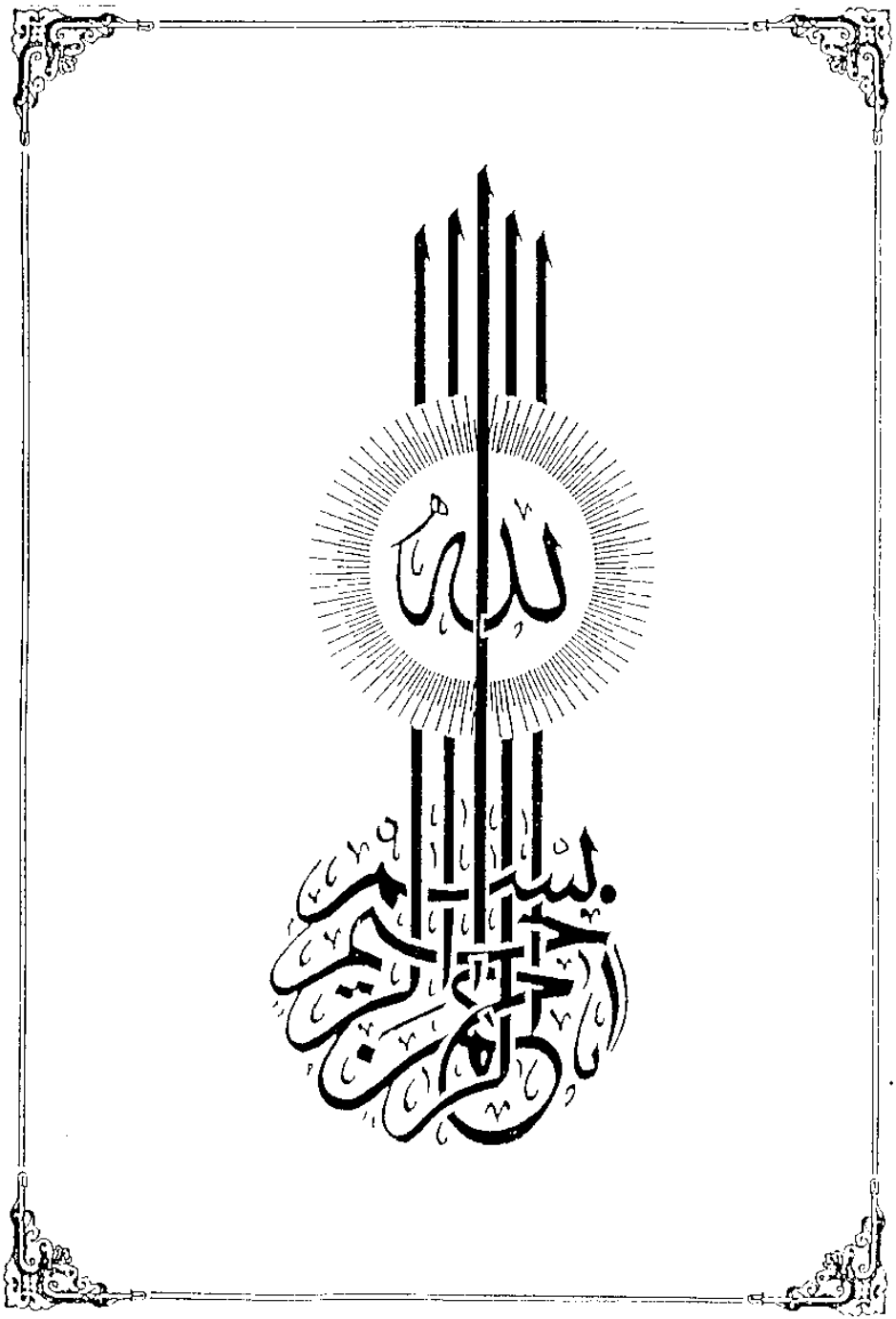

C O N T E N T S

I N T R O D U C T I O N

INTRODUCTION

In the early days of the study of the subject of autoimmunity, it was thought that an animal was incapable of forming antibodies which would combine with its own tissues. This concept was called "horror autotoxicus" by Paul Ehrlich who in 1900 considered this was the means by which the body protected himself from self destruction by autoantibodies. (52)

In his clonal deletion and/ or clonal abortion theory, Burnet spoke of potentially self-reactive "forbidden clones" that were eliminated as the organism developed. As common as autoimmune diseases are the autoimmune phenomena, without any clinical manifestations, are even more prevelant. More than 50 % of people in their seventh decade have at least one type of autoantibodies readily detectable in their serum. The existence of autoimmune phenomena is a major reason for believing that Burnet's deletion and/ or clonal abortion theory may not be able to account for the full expression of tolerance. As autoantibodies do exist which can react against self-constituents, they must therefore be actively maintained in a state of unresponsiveness throughout life. The development of autoimmunity can thus be viewed as an escape from the mechanisms by which self tolerance is maintained (88).

T lymphocytes which send on and off signals to these effector cells. Control, manifested in the appropriate initiation and termination of the immune responses involving T and B lymphocytes, in the switch from IgM to IgG production, and in the general utility of theses responses to the host, who is protected from infectious agents and possibly from neoplasia. When this system is functioning abnormally, however, the immune response appear chaotic. (82)

Autoimmunity is marked by an abnormal or excessive activity on the part of immune effector cells. This activity can include the production of autoantibodies by B lymphocytes and tissue infiltration or destruction by T lymphocytes and macrophages. These effector cells may not be deranged primarily, but may be merely responding to an aberrant set of regulatory signals received from a disordered control system.

The word autoimmunity is used to indicate immunologic self-injury and is not intented to imply an etiologic mechanism. For example, the destruction of normal tissue by the host's immune system in its response to a viral immunogen is considered an "autoimmune phenomenon" even though the immune response is triggered by a foreign antigen.

Autoimmunity plays a role in a wide range of clinical situations, including aging, response to viral and other infections, organ-specific immunologic diseases (e.g. thyroiditis), and non-organ specific immunologic diseases (e.g. systemic lupus erythematosus). Autoimmunity can be either transeint and reversible or persistent and life threatening. An entire area of clinical medicine, the autoimmune diseases, of which rheumatoid arthritis is an important example, is concerned with illnesses in which autoimmunity plays a dominant pathogenic role. (82)

THEORIES OF PATHOGENESIS

OF

AUTOIMMUNITY

Before begining a detailed discussion of autoimmunity in all its various manifestations, it seems well to review certain major theories proposed to explain autoantibodies and antiself reactivity.

I. The Forbidden Clone Theory:

Burnet postulated that during the early embryonic development, the self antigens are recognised by the immunological tissues and that self-reactive clones "forbidden clones" are eliminated in the thymus or at other sites by cells derived from the thymus and a state of immunologic tolerance is developed to these self antigens, as a result of which, the immune system was unable to react to these self antigens when the animal became immunologically mature. So autoimmunity was thought to follow the proliferation of the forbidden clones of lymphocytes with specifity for autoantigens. (17)

This theory of clonal selection has to be modified in the light of recent findings.

Some evidences against the Burnet's theory:

1. Autoreactive cells and propably autoantibodies exist in low concentrations in normal individuals; lymphocytes

capable of binding thyroglobulin, DNA, and erythrocyte antigens are easily demonstrated in normal healthy individuals. (11)

2. Polyclonal B. cell activators such as lipopolysaccharide (LPS) induce normal B cells to produce a variety of autoantibodies both in vitro and in vivo. Lambert and his colleagues observed that several strains of normal mice respond to repeated injections of LPS by producing antibodies to DNA and even, in some circumstances, developing immune complex glomerulonephritis. (43) Talal N. have been able to confirm the development of autoantibodies to polynucleotides (IgM but not IgG antibodies for polyadenylic acid), although these antibodies disappeared rapidly following discontinuation of LPS. (71)

3. Additional evidence against the forbidden clone theory is the autosensitization of normal lymphocytes by exposure to syngeneic fibroblasts or thymic reticulum cells. (8)

4. As Burnet's clonal selection theory stated that precursors of lymphocytes reactive with self-antigens are eliminated during embryonic and fetal life, (17) , the basis of the elimination of this self reactive clones was not clearly stated, but it rests on the supposition that

large amounts of antigens given prematurely may lead to functional abortion of the committed clones.(59) More recent information on cellular interactions in the immunologic response has provided alternate ways of visualizing clonal elimination. It is quite possible that only one of two (or more) populations of cells necessary for antibody production has been eliminated. Weigle and his colleagues (91) demonstrated that smaller amounts of antigen inactivate T Lymphocytes as compared with B lymphocytes. (91) Small quantities of circulating self antigens may lead in some manner to T cell elimination, leaving precursors only of self reactive B cells.(7) Supported evidence for this hypothesis is proved by experiments showing that thyroglobulin reactive B cells are present in the peripheral blood of normal animals and humans. These B cells can be triggered into action when suitable T cells are provided, either by activation of T cells with a cross-reactive antigen, or by giving antigen with adjuvants that act as non specific T cell stimuli. (50)

One explanation of clonal inactivation states that antigen impinging on only one of the two cooperating cells required for antibody production may result in unresponsiveness rather than a positive response. Since

self antigens are present at all times, they would be present whenever self-reactive lymphocytes arise by somatic mutation. Such single self-reactive lymphocytes would be easy prey to elimination, whereas foreign antigens would usually encounter two or more committed cells and therefore elicit a positive immunologic response. (50)

The theory outlined above accord with the general notion of clonal elimination, that is, the view that self-reactive lymphocytes are inactivated when they arise during embryonic life or even in later life. However, they fail to account for the finding that self reacting T cells, as well as, B cells, can readily be induced to self antigens like thyroglobulin.

2. Sequestered Antigen Theory:

Another early theory suggested that certain antigens are isolated from the blood and lymphatic circulation, so secluded from the immune system i.e. non accessible antigens. So once these sequestered antigens suddenly come in contact with the immuno-competent cells i.e. become accessible, they are recognized as foreign antigens and elicit autoantibody production. Example of the so-called sequestered antigens have been identified; the lens of

of the eye is well shielded from the blood stream and inaccessible to the entibody-forming cells, if rabbit lens crystallines are extracted and injected into a rabbit, antibody production results, however, these autoantibodies do not harm the intact lens in the living animal. As well if a rabbit was injected with bovine lens material, it would develop autoantibodies which would react with its own lens in vitro, but would not cause any disease of the animal's lens in situ. (36)

Spermatozoa behave in a similar manner, they elicit autoantibodies when injected even into the same animal from which they came. (78)

The brain also behaves as if it is sequestered, because brain suspensions obtained from foreign species elicit autoantibody production. (66) However, brain suspensions of the same species do not elicit antibody production unless altered in some way. It is necessary to combine brain extract with foreign protein carrier (such as hog serum), culture brain cells with vaccinia virus, permit autolysis to occure, or combine the extract with complete Freund's adjuvant, a mixture of mineral oil and acid fast bacilli (45). Under these conditions the brain demonstrates its autoantigenic

capabilities in the same animal.

Thyoglobulin, the major protein of the thyroid antigen, was long thought to represent an anatomically isolated substance confined to the follicles of the gland. Thyroglobulin is not completely sequestered within the gland but gain access to the extracellular fluid around the follicles and leaves via the thyroid lymphatics reaching the serum in normal human subjects at concentrations of approximately 0.01 - 0.05 ug/ml. (42) Concentrations of this order produce "low zone tolerance" probably by affecting T lymphocytes. (67) In man, T cells are tolerant to thyroglobulin and B cells are not. Indeed a small proportion of the B cells in normal individuals bind human thyroglobulin. In terms of autoantibody production there are only four antigenic determinants on human thyroglobulin, mol. wt. 650,000, and these may behave merely as haptenic groups in the sense that the non tolerant B cells can only be stimulated by these groups through T cell cooperation. Because the T cells are tolerant to thyroglobulin, the B cells will not normally be activated. (6)

3. Cross-Reactive Antigens:

Modified cross reactive antigens or related foreign antigens can terminate a state of specific unresponsiveness,