IMMUNE COMLEXES IN AGING

THESIS

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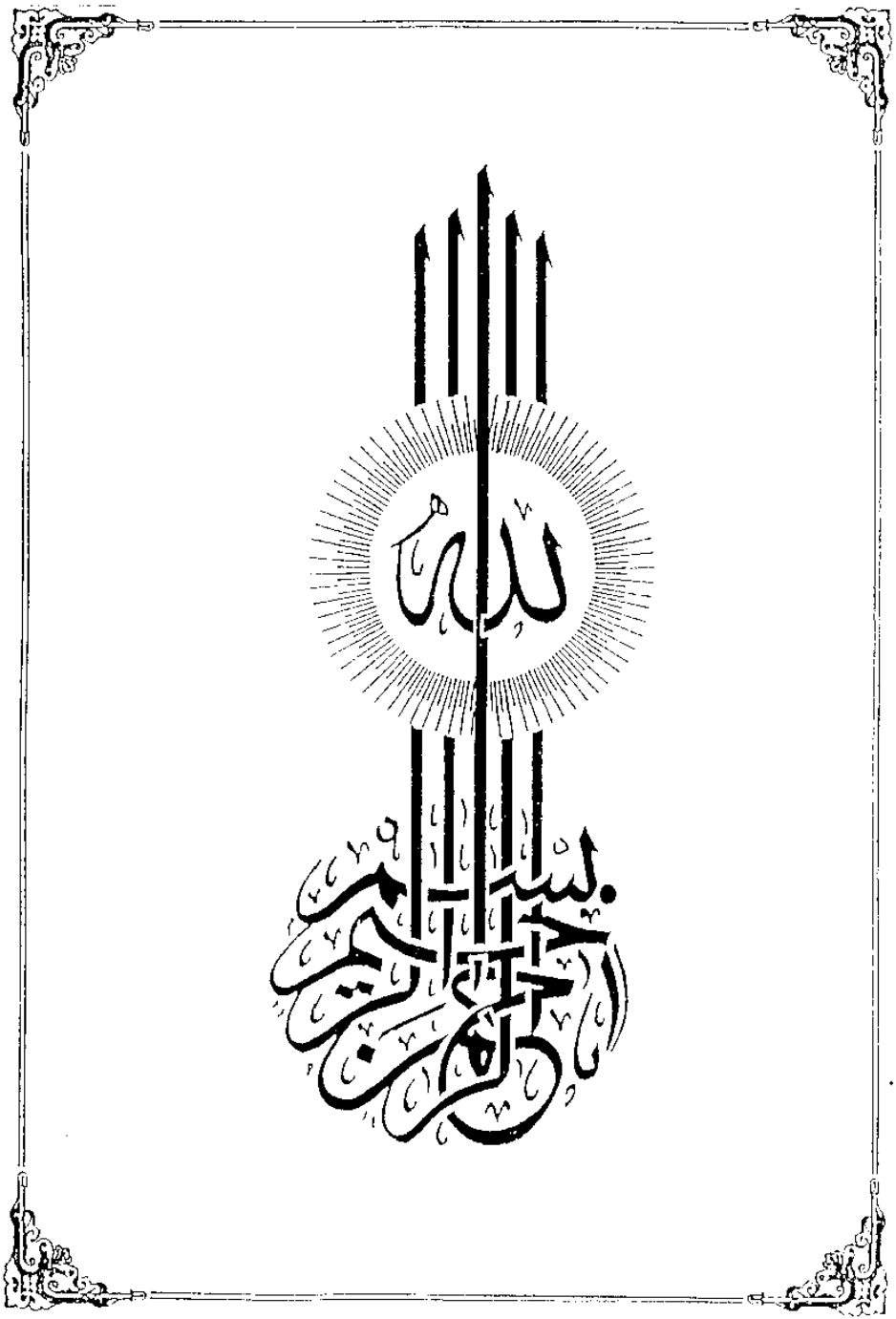

CONTENTS

AIM OF THE WORK

The study of immune function in aging mammals is currently attracting a great deal of interest. The findings that, in some instances, certain functional characteristics of the immune system decrease with age have spurred these studies. One reason that these studies are pursued with enthusiasm is the belief that an age-associated immune deficiency may have a causative role in the pathogenesis of age-related diseases, and the correction of this immunodefficiency may result in the modulation of aging phenomenon, so that some of the manifestations of aging can be changed.

The aim of this work is to study the age-associated disorders of the immune system by detecting the incidence of circulating immune complexes (CIC), rheumatoid factor (RF), and serum level of IgM in different age groups.

REVIEW OF LITERATURE

Chapter 1

Aging and Immune Dysfunctions

Introduction

The study of immune function in aging mammals is currently attracting a great deal of interest .

The ma jor role of the immune system in man appears to be the maintenance of the biological identity of the individual. It does this by eradicating any substance recognized as "foreign" to the individual whether it is of endogenous or exogenous source. In other words a defence system which is not only directed against micro organisms but also involved in the surveillance of malignant cell clones and autoimmune phenomenon (Thomas 1959, Burnet 1967, Klein et al ,1975) Certain functions of this immune system decline with age in humans ,guinea pigs, hamsters , rats and mice.(Walford 1969).

The age associated immune deficiency may have a causative role to play in the pathogenesis of age related diseases since,with a decrease in immunologic vigor , the incidence of infections,autoimmune and immune complex diseases and cancer increases (Walford 1969, Mackay 1972, Good and Yunis, 1974).

Many aging theories propose the existence of a biological clock in the organism which paces the changes of senescence. This has been overtaken by increasing attention to the immune system (Walford, 1974).

Age assotiated changes in the human immune system are complex , but in general are dominated by a decline in T-cell function with relatively well preserved B-cell function (Makinodan et al,1976).

The onset of the T-cell decline begins at sexual maturity with the involution of the thymus which is,therefore seen to be as the main pacer for senescence.

Roberts Thomson et al (1974) showed that the evidence of reduced T-cell function in the elderly persons was assotiated

with subsequent mortality . But whether impaired T-cell is a cause of death or merely a sign of its imminence is an open question.

Mackay et al (1976) demonstrated an increase with age in various autoantibodies with increased autoimmune manifesta--tions . Cells of the immune system lose the ability to re--cognize "self" and a low grade histoincompatibility reac--tion sets in analogous to a chronic autoimmune state mani--fested as aging.

Thus we can see that changes in the immune system are an index of aging, and the correction of such immune deficien--cy may result in the modulation of aging phenomenon so that some of the manifestations of aging can be changed.

The increased occurrence of immune dysfunctions in rela--tion to aging has been amply documented. These dysfunctions have been defined as quantitative, qualitative , functional , or descriptive or simply as deviation from the normal sit--uation. They can be classified into three groups :

(1) Immune deficiency .

(2) Auto-immunity .

(3) Idiopathic paraproteinaemia .

(abnormal serum components)

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(1) Immune Deficiency

There are two types of immune responses , humoral immune response (B-system) and cellular immune response (T-system).

B cells can be distinguished from T cells by the presence of membrane immunoglobulins and Fc and complement receptors on their surface.

Functionally B cells differentiate into cells which synth-etize and secrete antibody and therefore are responsible for humoral immunity (immunological responses which can be transferred by serum).

The bone marrow is considered to be a major site of anti-body prodction (Benner et al ,1974).

The thymus is essential for the full development of cellu-lar immunity . This system has been termed T-system.

It plays a major role in the delayed type of hypersensit-ivity, including the graft versus host transplantation reac-tions. It can also modify the activity of Bcell system in a helper or a suppressor function.

The T cell system has a separate influence on the degree of avidity of antibodies (Katz & Stewards , 1975).

The decline in normal immune functions with age may be due to changes in the cellular environment (extrinsic) ,changes in the cells of the immune system (intrinsic) or both. Price and Makinodan(. 1972 ab)found that only about 10% of the normal age-related decline can be attributed to changes in the cell-ular environment , while 90 %of the decline can be attributed

to changes intrinsic to the old cell :

Cellular Environmental Changes (extrinsic factors)

The responsible factors in the cellular environment was shown to be systemic and non cellular (Price and Makinodan, 1972b). Spleen cells from young mice were cultured with the test ant-igen either in the young or old recep ient"s spleen by the cell transfer method or in the recep ients' peritoneal cavity by the diffusion chamber method. A two-fold difference in response at both sites was observed betw-een young and old recep ients indicating that the factors are systemic .

Cellular changes (intrinsic factors)

Three types of cellular changes could cause a decline in nor-mal immune functions ;

(a) An absolute decrease in cell number through death caused possibly by autoimmune cells.

(b) A relative decrease in cell number as a result of an inc-rease in the number of suppressor cells.

(c) A decrease in functional efficiency possibly caused by so-matic mutation . All three types of interactions can occur (Peter ,1971 & Makinodan et al, 1976).

These interactions account for the fact that although the-re may be a dormant underlying mechanism responsible for the loss of immunolgic vigor with age, it is expressed differen-tly between aging individuals and this fact contributes to the increased variability of immunologic performance with age.

Also probably reflecting intrinsic cellular defects with age is the fact (according to Award & Walford, 1980) that the number of doublings human peripheral T-cell will undergo upon culture in the presence of T-cell growth factors, declines with the aging of the lymphocyte donor

Macrophages:

Macrophages confront antigens before T and B cells, any defect in them could decrease immune functions without appreciable changes in the antigens specific T and B cells. It has been found that macrophages are not adversely affected by aging in their handling of antigens during both the induction of immune responses and phagocytosis.

The in vitro phagocytic activity of old mice was equal to, or better than that of young mice (Perkins and Makinodan, 1971). The activity of at least three lysosomal enzymes in macrophages, increased rather than decreased with age (Weidrick, 1972)

The capacity of splenic macrophages and other adherent cells to cooperate with T and B cells in the initiation of antibody response in vitro was unaffected by age (Weidrick and Makinodan 1973). On the other hand when their antigen processing ability was assessed by Price & Makinodan (1972a) it was found that it is reduced. Associated with reduced antigen processing is the failure of antigens to localize in the follicles of lymphoid tissues of antigen stimulated old mice (Metcaff et al 1966: Legge and Austin 1968). One clinical implication of these results is that the ability of individuals to detect low doses of antigens

especially (weak) antigens such as syngenic tumor antigens can declines with age-due to poor immune surveillance noted against low doses of certain syngenic tumor cells in aged mice . It also could explain why the resistance to allogenic tumor cell challenge can decline more than hundered fold with age in mice manifesting only a fourfold decline in T- cell mediated cytotoxic activity against same tumor cells(Goodman and Makinodan1975)

B-CELL :

Inhumans:studies on circulating B-cell indicate that their number remains relatively constant(Diaz Jouanen et al 1975). In contrast to the constancy with age in the total B-cell population;subpopu-lations of B-cell may fluctuate with age .The number of B-cell responsive to a T-cell independent antigen is decreased slightly with age in long lived mice (Price and Makinodan1972a) and the level of serum IgG and IgA tends to increase with age while that of serum IgM tends to decrease(Haferkamp et al 1966) .

Shwick and Becker (1969) reported a rise in IgG and a significant fall in the level of IgM concentrations with age. Classidy et al (1974) found that the concentrations of IgG and IgA increased with age where as IgM did not change .Weksler and Hutteroth(1974)found that Ig-bearing cells in humans peripheral blood decreases,increases or remain constant with age .These discripancies probably reflect the considerable variability among individuals and techniques used to identify B-cells or Ig-positive cells in human peripheral blood.

The previously mentioned variations in the level of serum immunoglobulins may be explained by the fact that in a devel--oping organism the response to many different antigens results in competition with varying responses to antigens during a pa--rticular time interval.

It is also well documented that after immunization the ser--um antibody level can rise , descend and then repeat, this cyclical pattern for an extended lenghth of time .

(Romball and Weigle , 1973 , Macario and De Macario, 1975).

Therefore the particular level of an antibody may depend on the point during such a cycle that the serumis sampled rather than on the age of the organism.

Thus it can be concluded that B-cell functions appear to be relatively well preserved with age and the increase in the propotion of B to T cells is due to a fall in the propotion of T-cells.(Diaz-Jouanen et al 1975).

T -CELL

P resent evidence suggests that the decline in the immune functions which accompanies aging is due primarly to changes in the T-cell component of the immune system. The thymic lymphatic mass decreases with age primarily as a result of cortical atrophy in both humans and laboratory animals begi--nning at the time of sexual maturity .

(Good et al 1964).The number of circula-ting lymphocytes decreases progressively during or after middle age in humans to a level that is about 70%

of that of a young adult by the sixth decade(Diaz-Jouanen et al 1975,Augener et al 1974,Alexopolos and Babitis 1976).

A proportional decrease in the number of T-cells is observed while the number of B-cells show little change.Heidrick(1973) suggested that the defect in T-cells is intracellular and may be hormone -dependent.He found that cyclic nucleotide 3,5 gu--anosine monophosphate-which has been shown to increase when T-cells are stimulated by mitogens-is present in relatively low concentrations in mitogen-stimulated T-cells of old mice and it is known that the levels of cyclic nucleotides are ho-rmone-dependent.

There are indications,however that in humans the level of ci--rculating thymic hormone does decrease with age.Perhaps this reflects a decline in one form of thymic influence and this results in a decrease of functional T-cells(Van Bekkum 1975). Thus shortly after the thymus begins to involute and atrophy the level of serun thymic hormone(s) decreases with age (Bach et al 1973).It would be reasonable to assume that this hormone(s) is necessary for terminal differentiation of T-cells. This could lead to a decrease in effector cells for certain immune functions and thus to a deficit in T-cell responsiveness. Others found that with age in splenic T-cells of mice,the resting cyclic AMP level is five times decreased,cyclic GMP seven times increased and the cAMP /cGMP ratio to be 50 times lowered than in young(Award & Walford , 1980). Also ultrac--entrifugation studies have revealed different patterns of sub-cellular distribution of cyclic nucleotides and of adenylate