IMMUNE RESPONSES TO VARICELLA-ZOSTER VIRUS IN THE AGED

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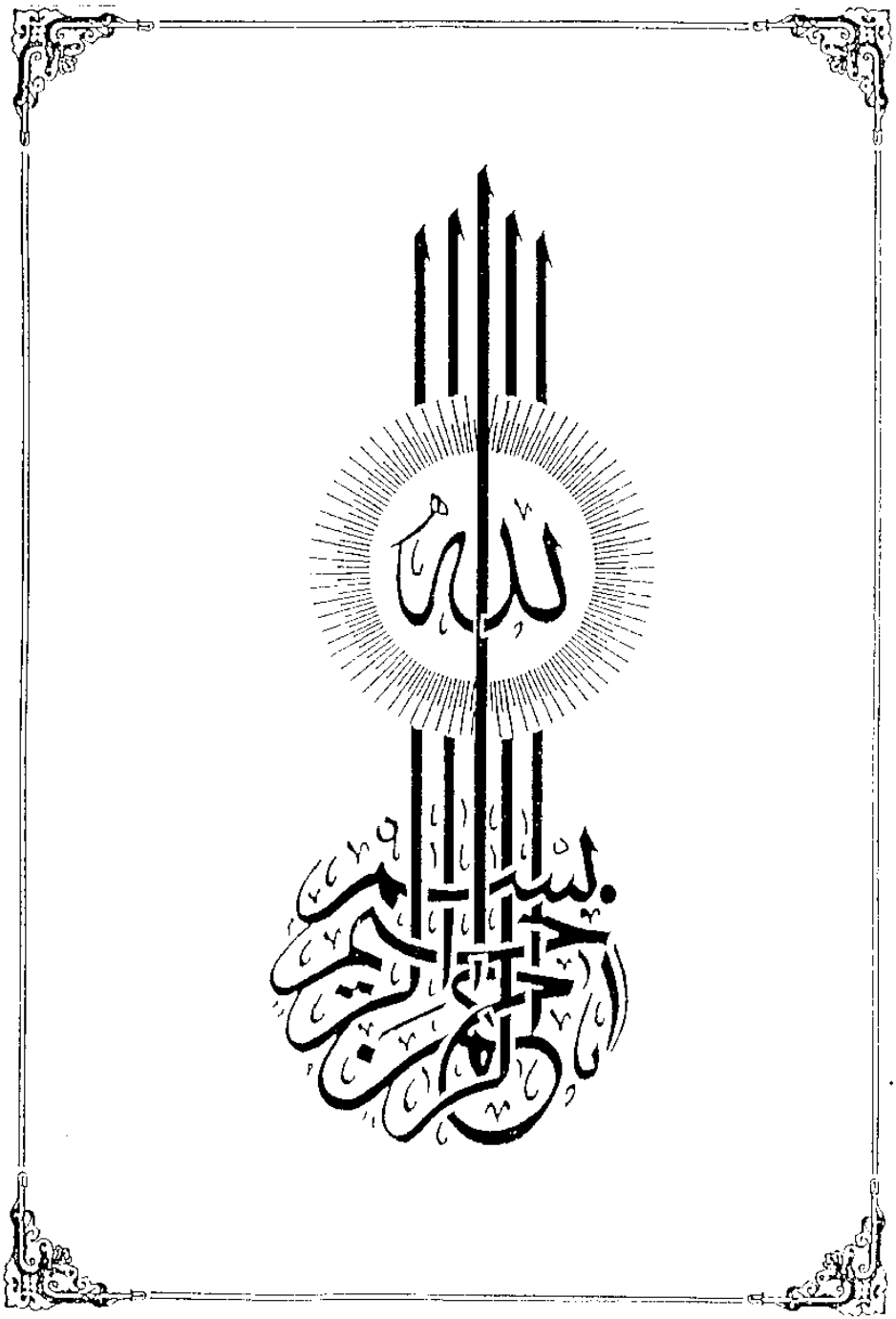

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ABBREVIATIONS

ADCC	Antibody-dependent cellular cytotoxicity
AP	Alkaline phosphatase
BMT	Bone marrow transplant
CFT	Complement Fixation Test
CMV	Cytomegalo-virus
EBV	Epstein-Barr virus
ELISA	Enzyme-linked immunosorbent assay
FAMA	Fluorescent antibody to membrane antigen
FCS	Fetal calf serum
F/H	Ficoll/Hypaque
GVH	Graft versus host
HBSS	Hank's balanced salt solution
HHV-6	Human herpes virus-6
HSV	Herpes simplex virus
IAHA	Immune adherence haemagglutination
IHA	Indirect haemagglutination
K	Killer
MHC	Major histocompatibility complex
NK	Natural killer
NT	Neutralization test
PBS	Phosphate buffer saline
PHA	Phyto haem agglutinin
PWM	Pokeweed mitogen
RIA	Radioimmunoassay
SRBc	Sheep red blood cells
VZV	Varicella-Zoster virus.

CONTENTS :

1

Introduction And Aim Of Work

Varicella (chickenpox) and zoster represent different clinical manifestations of infection with the same virus. Varicella constitute the primary infection whereas zoster occurs in individuals with partial immunity resulting from a prior Varicella infection. Reduced immunity to Varicella zoster as a consequence of aging seems likely to contribute to the reactivation of Varicella zoster in the elderly *(Hayward and Herberger, 1987)*. It has long been thought that intact cell-mediated immunity (CMI) is crucial for recovery from Varicella-zoster (VZ) virus infections. This thought has developed largely from clinical observations on patients with agammaglobulinaemia who have been observed to recover normally from both Varicella and Zoster and patients with deficiencies in cell-mediated immunity who are prone to develop severe Varicella-zoster infections *(Gershon and Steinberg, 1979)*. The age-related decline of thymus regulated lymphocyte (T-lymphocyte) function is a well documented finding in experimental animals. Although immunocompetence in humans also changes with age, there exists a large amount of conflicting data about precisely what changes do occur. Decrease in the number of T-cells activated by plant lectins and the failure of these cellular subpopulations to subsequent divide are reported to be characteristic of older individuals *(Inkeles, 1977)*. However, despite this reported decline in the number of responding cells, certain studies indicate that the representation of peripheral blood T-lymphocytes, enumerated

by sheep erythrocyte (SRBC) rosetting techniques, does not change with age *(Davey and Huntington, 1977)*

However, other investigators have reported age-associated decline in peripheral blood T cell numbers *(Angener et al., 1974)*. There is also unclear picture of the age-related changes occurring in human regulatory T-lymphocyte subpopulations with helper or suppressor activity. Using monoclonal antibodies that are capable of identifying surface membrane markers associated with functional subsets of human T-cells, one can characterize peripheral blood lymphocytes from young and old individuals to determine the changes that occur with aging *(Nagel et al., 1981)*.

AIM OF THE WORK:

Reduced immunity to Varicella-zoster as a consequence of aging seems likely to contribute to the reactivation of Varicella-zoster in the elderly.

The aim of the study was to assess humoral immune response to Varicella-zoster virus and cellular immunity in aged persons through evaluation of the following parameters:

1] IgG antibodies to Varicella-zoster antigen.

2] The percentage of peripheral blood T-lymphocytes.

3] The percentage of T-lymphocyte subsets (helper and suppressor).

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Review of Literature

A. INTERACTION OF MICROBIAL AGENTS WITH THE IMMUNE SYSTEM

The vital importance of the immune system for host defences against microbial infection has been recognized for a long time. However, it seems clear that such mechanisms are dependent on highly complex interaction between a number of different cell types *e.g.;* B-lymphocytes, plasma cells, T-lymphocytes with T-helper and T-suppressor subpopulations, cytotoxic K cells and NK cells, monocytes and macrophages, neutrophilic and eosinophilic granulocytes as well as their molecular products *e.g.;* immunoglobulins, lymphokines and interleukins *(Froland, 1984)*. In addition, the various components of the immune system interact with the complement system which also has important antimicrobial functions *(Johnston and Stroud, 1977)*. Furthermore, immune reactions apparently modulate many physiological and pathological non specific phenomena regularly seen during host responses to microbial infection *e. g.;* fever and acute phase reactions of serum proteins which possibly enhance specific antimicrobial effector mechanisms *(Duff and Durum, 1982)*. As regards the B-cell system, the hallmark of B cell-mediated antimicrobial functions is the production of immunoglobulin molecules with specific antibody activity directed against microorganisms and their products *(Froland, 1984)*. Antibodies play an important role in protection against and recovery from certain virus infections. The

neutralizing effect of antiviral antibodies depends upon several mechanisms *(Buchanan et al., 1979)*. The interaction of antibody with virus often prevents adherence and subsequent penetration of viruses into host cells. Antiviral antibodies sometimes affect lysis of virus particles, usually in cooperation with complement. Furthermore, antibodies may have important antiviral effects in cooperation with cytotoxic K cells *(Froland, 1984)*.

The other major branch of the immune system, the T-cell system, is highly specialized to combat many microorganisms which are not effectively handled by B-cells and phagocytic cells. One important consequence of antigen stimulation of the T-cell system is the induction of cytotoxic T-cells having the ability to attack and destroy other cells carrying the corresponding surface antigen *(Hahn and Kaufmann, 1981 and Wagner et al., 1982)*.

Crucial steps in the induction of cytotoxic T-cells are activation of T-helper cells and the participation of interleukins *(Wagner et al., 1982)*. The cytotoxic reaction usually requires histocompatibility for class I *Major Histocompatibility Complex* (MHC) antigen between the cytotoxic T-cell and the target cell *(Biddison, 1982)*. Cytotoxic T-cells are thought to be important in the defense against a number of virus infections where infected host cells carry viral antigens on the membrane *(Biddison, 1982 and McMichael et al., 1983)*. Additional antiviral mechanisms are

necessary to inactivate virions released from the dying host cells. These include antibodies and macrophages attached to the infected site *(Froland, 1984)*. Activated T-lymphocytes also contribute to antiviral immunity by means of other mechanisms *e.g.;* the production of gamma interferon which is also called immune interferon *(Buchanan et al., 1979)*.

In addition, other important cells in viral immunity are K cells and NK cells which are lymphocytic cells mediating cytotoxicity against target cells. The former functions with and the latter without antibodies *(Figure 1)*. K cells mediate antibody-dependent cellular cytotoxicity and they resemble natural killer cells. Comparative experiments indicate that a single cell can mediate both *Antibody-dependent cellular cytotoxicity* (ADCC) and the NK function. Very likely, the K-NK system represents a heterogeneous population of cells in which some cells are more inclined to carry out ADCC and others tend toward NK activity. K-cells carry receptors for the Fc fragment of the IgG molecule and it is by means of this receptor that they bind the antibody-coated target cells *(Klein, 1982)*. K cells can destroy host cells infected with certain viruses as *Herpes simplex* and *Measles (Froland, 1984)*.

The interest in NK cells has particularly been stimulated by the possibility that they may have important functions in host

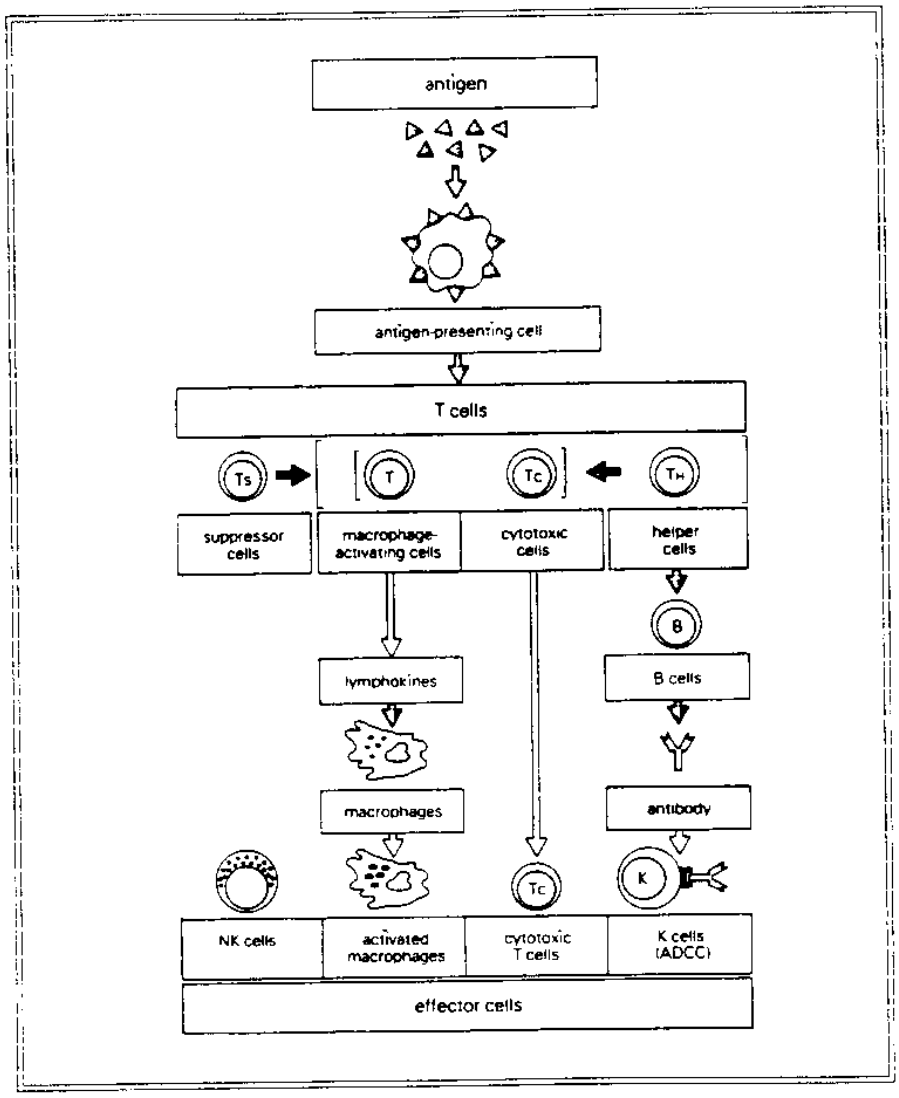

Fig. 1: SCOPE OF CELL-MEDIATED IMMUNITY