ACTIVITY OF NATURAL KILLER CELLS IN DEPRESSED PATIENTS

THESIS

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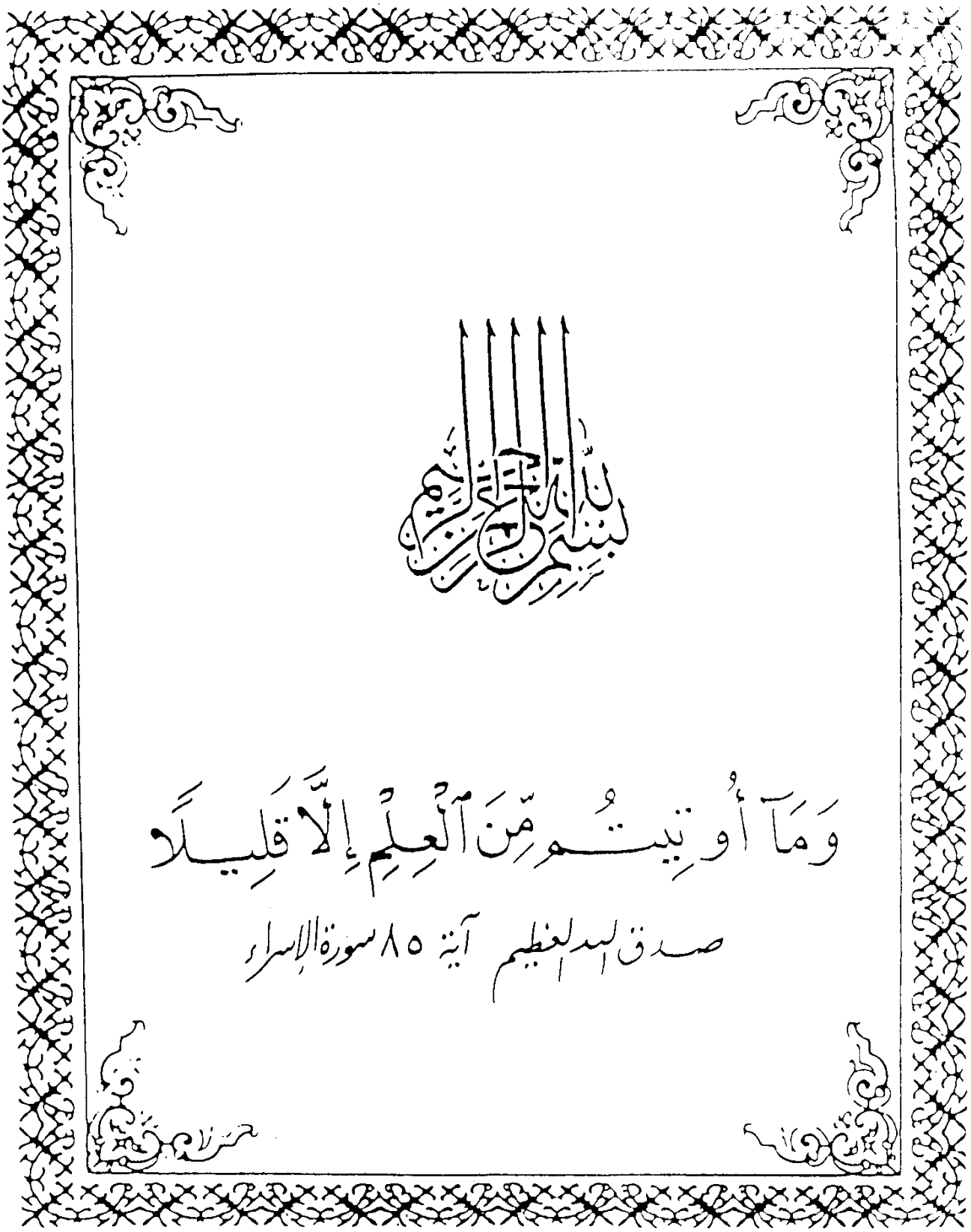

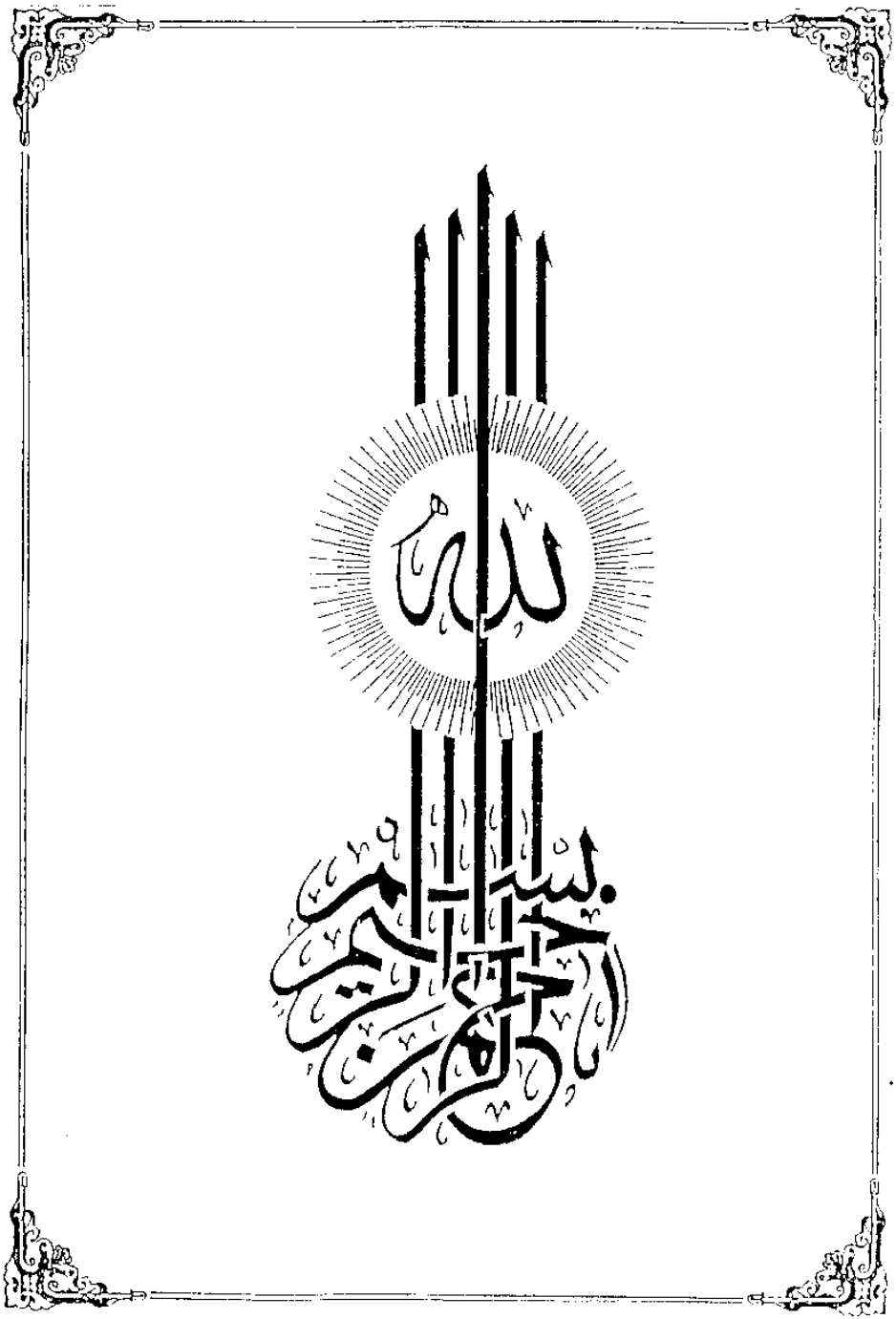

THIS WORK IS DEDICATED

TO

MY FATHER, MOTHER, WIFE

AND MY DAUGHTER SARA

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Natural killer (NK) cell activity is important as its primary function is to guard against cancer and viral infections. Natural killer cells comprise a defense system in which the effectors appear to have an innate ability to recognize and kill neoplastic cells **(Herberman and Ortaldo, 1981).**

Due to this immunologic surveillance function, it is considered to be an important line of defence in the human body. Its activity measures the ability of particular type of immune cell to destroy tumour cells, and for this reason natural killer cells are being used clinically as lymphokine-activated killer (LAK) cells in the treatment of advanced cancer **(Mule et al., 1986).**

A number of clinical studies have shown that many people who has become severely depressed tend to develop declining health, high mortality and increased susceptibility to cancer.

Recently, there are many studies dealing with the interrelationship between psychological trauma and alterations in brain function and their combined effect on the activity of immune system. A growing number of researchers and clinicians believe that both stress and

depression trigger chemical changes in the brain that can suppress the immune system.

The aim of the present work is to determine if natural killer cell activity is different among subjects with major depressive disorders and if treatment has any effect on modulating the function of this component of the immune system.

REVIEW OF LITERATURE

PHYSIOLOGY OF NATURAL KILLER CELLS

1- Definition :

The search for cytotoxic T-cells led to the discovery of another cell that can kill a variety of tumour cells. These cells comprise a discrete population of large lymphocytes that can be distinguished by characteristic azorophilic granules in their cytoplasm. They have been termed natural killer (NK) cells or large granular lymphocytes (LGL) **(Stite, 1987).**

Oldham (1983) reported that the population of cells in an unimmunized host that are capable of lysing certain tumour cell lines in vitro have collectively been designated "natural killer" cells.

2- Origin :

Despite the intensive study of NK cell population, it is still unclear whether these cells are in the lymphoid, myeloid, or other undefined lineages **(Lewis et al., 1983).** However, **Tizard (1988)** reported that natural killer cells originate in bone marrow, and that they are probably derived from the same stem-cell pool as are T cells since they carry low levels of thy-1 on their surface.

3- Properties of NK cells :

Natural killer cells are large granular, non-adherent, non phagocytic lymphocytes constituting about 5% of blood or

splenic lymphocytes. They have low affinity FC receptors, so that they can bind antibody coated target cells and participate in antibody-dependent cell-mediated cytotoxicity (ADCC) **(Rowlands and Daniele, 1975)**. However, **Stite (1987)** reported that NK cells comprise from 10 to 15% of the peripheral blood lymphocytes.

They show some relationship to T cell, for example, about half of the human NK cells form E rosettes (they possess CD2). However,they don't carry CD4, CD8, or CD3. Nor do they express the peptide chains of the T-cell receptor. NK cells don't reticulate like T cells and are not found in the thoracic duct **(Kimball, 1983)**.

Lighthart et al. (1989) reported that most of the natural killer cell population express CD16 antigen which could be demonstrated by specific monoclonal antibodies.

4- Classification of NK cells :

Minato et al. (1981) reported that several distinct NK-cell population do exist, and these differ not only in their antigenic phenotype but also in their biological activities. They classified natural killer cells as: NK_1 or classic NK cells, NK_T or killer cells resembling classic cytotoxic T cells in expressing Thy-1 antigen, TK which are Thy-1 positive cells not found in nude mice, NK_M or cells which are

found only in bone narrow and NC cells or natural cytotoxic cells with specific activity against solid tumours.

Abo et al. (1982) reported that the majority of LGL expressed the Leu-7 antigen which was also identified on 10 to 25% of other peripheral blood lymphocytes.

Lanier et al. (1983) found that some cells that lack the Leu-7 antigen, however, can also mediate a significant proportion of NK activity, ranging from 10 to 40% of the total NK activity in normal blood. These cells were found to express the Leu-11a antigen **Phillips and Babcock (1983)** reported that, in contrast to Leu-7, the Leu-11a antigen is expressed on essentially all functional NK cells in the peripheral blood and on neutrophils.

Lewis et al. (1983) classified NK cells into four lymphocyte subsets according to the expression of Leu-11a and Leu-7 antigens. The Leu-11a^{+},-7^{-} cells which were highly active in 4-hr NK assays, the Leu-11a^{-},-7^{+} cells demonstrating weak activity, the Leu-11a^{-},-7^{-} cells which demonstrated no activity and the Leu-11a^{+},-7^{+} cells which varied considerably in activity among several individuals examined.

Antiviral activity of NK cells :

Herberman (1986) reported that NK cells recognize structures on high molecular weight glycoproteins on the surface of virally infected cells. Activation of the NK cell ensues and leads to extracellular release of granule contents into the space between NK cell and the target cell. Perhaps the most important of these is a perforin or cytolysin bearing some structural relationship to C9; and it can insert itself into the target cell membrane to form a transmembrane pore with an annular structure which induces cell death.

Anti-tumour activity of NK cells :

NK cells comprise a defense system in which the effectors appear to have an innate ability to recognize and kill neoplastic cells **(Herberman, 1981).**

Natural killer cells are being used clinically as lymphokine-activated killer (LAK) cells in the treatment of advanced carcinoma **(Mule et al., 1986).**

Krim (1981) reported that natural killer cells attack and destroy tumour cells, and in contrast to cytotoxic T-cells, whose function requires recognition of specific viral or tumour antigens, NK cells can attack tumour cells and virus-infected cells directly without prior antigen interaction. This direct cytotoxic property is believed to be