PERIPHERAL T-LYMPHOCYTE SUBPOPULATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

Thesis

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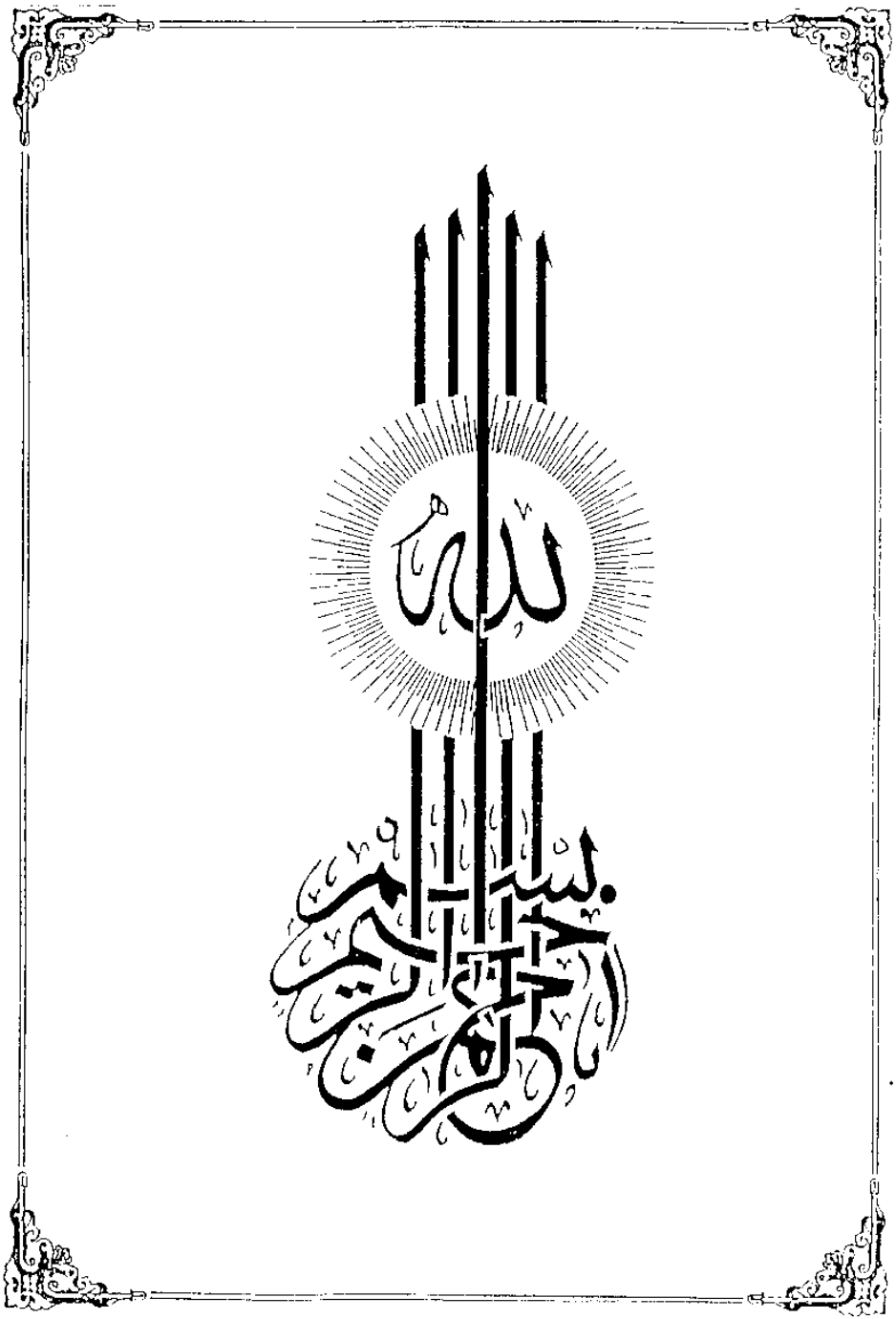

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The distinction between insulin-dependent (Type I) and non-insulin dependent (Type II) diabetes mellitus (IDDM and NIDDM respectively) as two separate disorders has been recently established beyond doubt. The finding of a definite - and essential - role for an environmental factor in 'initiating' the disease process in IDDM is an important differentiating feature which has been behind hopes of possible prevention of this disease type. The role played by genetic factors in the aetiology of IDDM (MHC phenotype susceptibility or resistance) is another differentiating feature (Adams *et al.*, 1984; Krolewski *et al.*, 1987b).

Recently, evidence has accumulated that implicates an autoimmune mechanism in the pathogenesis of IDDM. Many autoimmune changes (both humoral and cell-mediated) are characterizing the clinical onset of IDDM, and have been behind the recent interest in immunosuppressives as possible 'curative' agents in those IDDM patients who might still be at an early stage of the autoimmune disease process (Bottazzo *et al.*, 1985; Eisenbarth, 1986; Bach, 1988).

Among the autoimmune changes described in IDDM, T-lymphocyte relations with pancreatic beta cells have recently received much

attention. It has been known that different T-lymphocyte subpopulations have the capacity to magnify or diminish immune responses (helper and suppressor T cells respectively), as well as to destroy cells (cytotoxic T cells). T-lymphocyte subpopulation changes in IDDM have been recently described and suggested as having a fundamental role in the aetiology and pathogenesis of IDDM (Eisenbarth, 1986; Editorial, 1988).

The aim of this work is to study peripheral T-lymphocyte subpopulations (helper and suppressor-cytotoxic T cells, as well as the ratio between them) in IDDM, and - through this - to highlight their aetiologic role in the context of the autoimmune mechanism that ends in the destruction of the insulin-producing beta cells in the pancreatic islets of Langerhans.

LIST OF ABBREVIATIONS

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ADCC : Antibody-dependent cellular cytotoxicity.

AGEs : Advanced glycosylation end-products.

AIDS : Acquired immuno-deficiency syndrome.

APC : Antigen-presenting cell.

ARIs : Aldose reductase inhibitors.

BB : Bio-Breeding (rats).

C : 'Complement', complement component.

CD : Cluster of differentiation (T-cell differentiation antigen)

CF-ICA: Complement-fixing islet cell antibody.

DM : Diabetes mellitus.

Fab : Antigen binding fragment (of an immunoglobulin unit).

Fc : Crystallizable fragment (of an immunoglobulin unit).

2HBSS: 2-Hour Blood Sugar Screen (test).

HIV : Human immunodeficiency virus.

HLA : Human leucocyte antigen.

IAA : insulin autoantibody.

ICA : Islet-cell antibody.

ICSA : Islet-cell surface antibody.

IDDM : Insulin-dependent diabetes mellitus.

IFN : Interferon.

Ig : Immunoglobulin.

IGT : Impaired glucose tolerance.

IL : Interleukin.

IL-2r: Interleukin-2 receptor.

LAK : Lymphokine-activated killer (activity).

LGL : Large granular lymphocyte.

mAb : Monoclonal antibody.

MHC : Major histocompatibility complex.

MODY : Maturity-onset diabetes of the young.

MRDM : Malnutrition related diabetes mellitus.

NIDDM: Non-insulin dependent diabetes mellitus.

NK : Natural killer (cells).

NOD : Non-obese diabetic (mice).

OGGT : Oral glucose tolerance test.

SD : Standard deviation.

SLE : Systemic lupus erythematosus.

SRBC : Sheep red blood cells.

Tc : Cytotoxic T (lymphocytes).

TCR : T-cell receptor.

Td : Delayed hypersensitivity T (lymphocytes).

Th : Helper T (lymphocytes).

Ts : Suppressor T (lymphocytes).

REVIEW OF LITERATURE

CHAPTER I

THE IMMUNE SYSTEM

INTRODUCTION

The immune system should be thought of as an essential part of the homeostatic mechanism, continually keeping out and destroying invaders and abnormal cells as they appear. At the same time it is regulating its own cells as they develop and circulate. Immune reactions are occurring in healthy individuals continuously and, in addition, they play important roles in most disease processes (Mc Michael, 1987).

The immune responses are distinguished from the non-specific defence mechanisms, such as inflammation, by the 'specificity' of the reaction, which is not only in terms of antibody responses but is also true of the cellular immune responses. The ability to distinguish between self and non-self is a part of this specificity. Another distinguishing feature of immune responses is 'memory' by which a second challenge with a stimulus provokes a more rapid and more vigorous immune response (Paul, 1988).

Immune reactions can be divided into two: those dependent on antibody (humoral reactions) and those dependent on T lymphocytes (cell-mediated reactions); which is indicative of the basic division of lymphocytes into two types, B and T cells.

These interact with each other and with a third important cell: the 'antigen presenting cell' (Henry & Claman, 1987; Mc Michael, 1987).

Both B and T cells arise from a stem cell residing in bone marrow in postnatal life. B lymphocytes are independent of the thymus and are responsible for the release of specific antibody molecules. T lymphocytes, on the other hand, are dependent on the presence of a functioning thymus and have a high binding affinity for the antigen (Lessof, 1988; Roitt, 1988).

About 5-10% of peripheral blood lymphocytes lack the identifying features of B or T cells. These were previously called 'null cells' and are having the 'large granular lymphocyte' (LGL) morphology. They comprise both the natural killer (NK) cells and cells mediating the antibody-dependent cellular cytotoxicity (ADCC) (Haynes & Fauci, 1987; Roitt, 1988).