CELL MEDIATED IMMUNITY

IN

DIABETES MELLITUS

Thesis

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By

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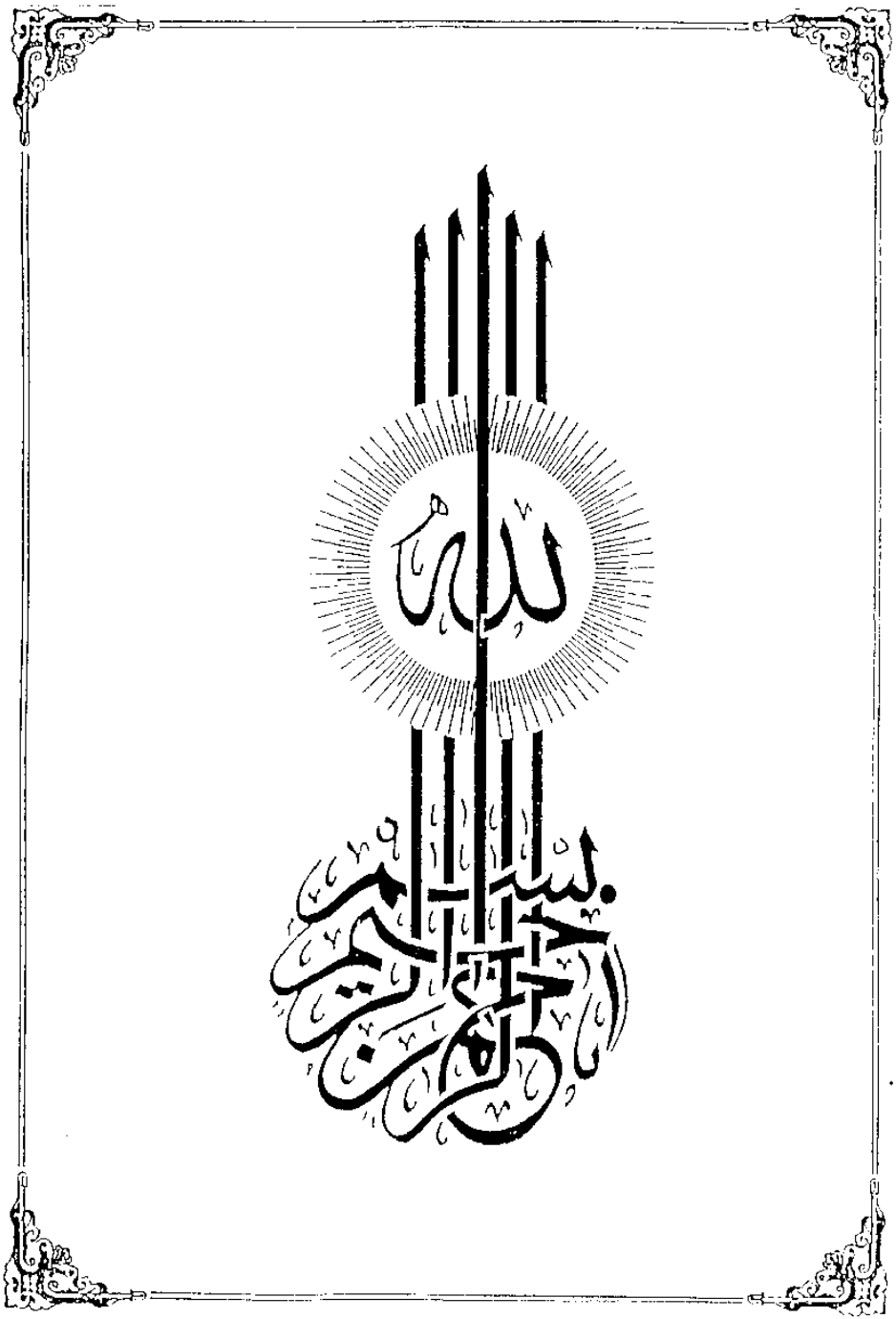

I N D E X

INTRODUCTION AND AIM OF WORK

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It has long been a clinical observation that patients with diabetes mellitus are more susceptible to infection than non-diabetic patients of similar age, sex and socioeconomic background. It is also generally accepted that infections in diabetic patients are more severe and often more difficult to control. The susceptibility of diabetics to tuberculosis, mycosis and staphylococci is well decumented to be highest in poorly controlled patients. (Joslin et al, 1959 and Lisert, 1965). This may be ascribed to many factors as for example impairement of certain aspects of host defences such as the local exudative response (Perillie et al, 1962) or neutrophilic phagocytosis (Bybee and and Rogers, 1964).

The susceptibility to staphylococcus infection has been ascribed to impaired leucocytic function (Rohmann 1966; Mowat and Baum, 1971). On the whole, immunodeficiencies are often invoked to explain the increased incidence of infections and marked complications i

in diabetics. Although humoral immunity appears to be normal in most diabetic patients(Lipscomb, Dobson and Greene, 1959), several types of functional abnormalities have been demonstrated in polymorphonuclear leucocytes, particularly when the patients are in ketroacidosis (Petillie et al, 1962; Bybee et al, 1964; Mowat et al, 1971 and Bagdade et al, 1974).

Studies of cell mediated immunity of the delayed type (CMI) have shown conflicting data. In patients with diabetes mellitus (Ragab et al, 1972; Delespesse et al, 1974 and Mac Cuish et al, 1974) cell mediated immunity appears to be important in host defences against certain infections, especially those caused by fungi and mycobacteria (Nelson et al, 1957; Rosen et al, 1968; Hart et al, 1969 and Kirkpatrick et al, 1971).

The aim of this work is to investigate the cell mediated immunity in diabetic patients by performing the migration inhibition test and comparing

this with a healthy non-diabetic control group. This is done as a trial to demonstrate the relation between cell mediated immune response and diabetes mellitus.

REVIEW OF LITERATURE

SHORT REVIEW ON THE IMMUNE RESPONSE

When an antigen enters the body, two different types of immunological reactions may occure:

1-The synthesis and release of free antibody into the blood and other body fluids (humoral antibody). This antibody acts for example by direct combination with and neutralization of bacterial toxin, by coating bacteria to enhance their phagocytosis and so on.

2-The production of 'sensitized' lymphocytes which have antibody - like molecules on their surface (cell-bound antibody). These are the effectors of cell-mediated immunity expressed in such reactions as the rejection of skin transplants and the delayed hypersensitivity to tuberculin seen in individuals immune to tubercle infection (Roitt, 1977).

Primitive lymphoid cells from the bone marrow appear to differentiate into two small lymphocyte populations:

1- T-lymphocytes, processed by or in some way dependent on the thymus, and responsible for cell-mediated immunity.

2- B-lymphocytes, bursa-dependent, and concerned in the synthesis of circulating antibody.

Both lymphocyte populations on appropriate stimulation by antigen proliferate and undergo morphological changes. The B-lymphocytes develop into the plasma cell series. The mature plasma cell is actively synthesized and secreting antibody and has a well developed rough surfaced endoplasmic reticulum characteristic of a cell producing protein for export (Rott, 1977).

T-lymphocytes on the other hand, transform to lymphoblasts which in the electron microscope are seen to have virtually no rough-surfaced endoplasmic reticulum although there are abundant free ribosomes, either single or as polysomes. These cells are concerned with the synthesis of their

own components but do not secrete appreciable amounts of free antibody. This high ribosome content makes them basophilic so that they show superficial resemblance to plasmoblasts in the light microscope. However, no antibody can be detected in their cytoplasm using immunoflurescent methods (Roitt, 1977).

Cell-mediated immune response:

The existance of the delayed-type hypersensitivity or cell-mediated immune response has been known since the time of Jenner and Koch, but appreciation of its importance in disease, and perhaps more significantly in health, has only recently become possible. For many years, cell-mediated immunity has been associated with resistance to certain bacterial, mycotic and viral infections, especially intracellular parasites. Another suggested role for the delayed-type hypersensitivity response, perhaps its primary function, is that of "surveillance", i.e. the rejection of cells in the body antigenically altered by neoplastic events (Thomas, 1959; Burnet,1967). Support for these

possibilities comes from many experiments but, perhaps most impressively from the study of those conditions of man in which there is deficiency or suppression of this immune response (Peterson et al, 1966& Balner, 1970). In addition, the cell-mediated immune response serves as the principal obstacle to successful organ and tissue transplantation as well as being involved in the pathogenesis of a number of autoimmune diseases of man and experimental animals (Bloom, 1971).

Katz and Benacerraf (1972) mentioned that T-lymphocytes when stimulated by an antigen, respond on one hand, by a clonal expansion and differentiation, and on the other hand by being activated to perform their specific functions i.e. target cell killer, helper cells, etc.

Sensitized T-lymphocytes have been shown to produce more than one biologically active molecule when incubated with a specific antigen in vitro. One of them is migration inhibition factor (MIF) which acts on macrophage at least to prevent their normal migration

from a capillary tube (David, 1966). There are other factors produced by sensitized T-lymphocytes, these factors are:

- Interferon (Wheelcock, 1965).
- Blastogenic factor or mitogenic factor (Dumonde et al, 1968).
- Transfer factor (Lawrance, 1969).
- Complement (Permlann et al, 1969).
- Skin reactive factor (Turk, 1969).
- Chemotactic factor for monocytes (Ward et al, 1969).
- A factor highly cytotoxic to cancer cells (Dumonde et al, 1969).
- Proliferation inhibition factor and cloning inhibition factor (CIF and CLIF), which inhibit proliferation of cultured cells (Good and Park, 1974).

- Osteoclast activating factor (Thaler et al,1977).

Production of MIF:

David et al (1964 b) found that when small numbers of peritoneal cells from sensitive guinea pigs (2.5%) were admixed with normal peritoneal cells, they were capable of inhibiting the migration of the mixture. Later, Bloom and Bennett in 1966 tried to ascertain which cell type was responsible for this inhibition of migration in vitro. Thus, peritoneal exudate from tuberculin hypersensitive guinea pigs were separated into their component types, macrophage population of 0.5% or greater homogeneity and lymphocyte populations of greater than 94% purity. They found that purified macrophages obtained from sensitized animals were not inhibited by PPD. In contrast, purified peritoneal lymphocytes from the same exudate were able to inhibit the migration of normal macrophages. In these studies as few as 1% sensitized lymphocytes