IMMUNOSUPPRESSIVE THERAPY IN RENAL DISEASES

THESIS

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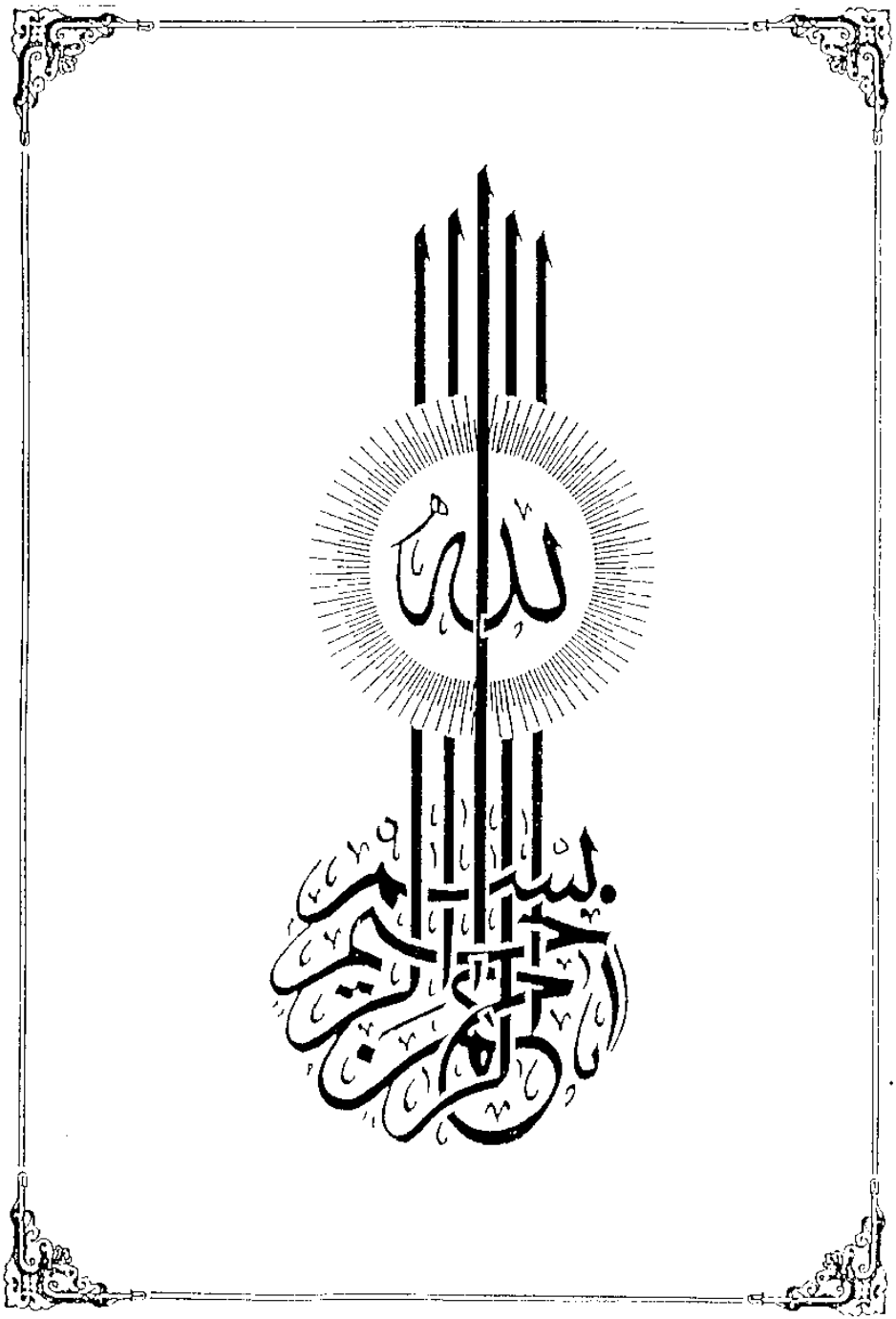

C O N T E N T S

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CHAPTER ONE

IMMUNOSUPPRESSION

CHAPTER I

IMMUNOSUPPRESSION

The conception of immunosuppression has come to the fore recently. It originated from the discovery of certain biological phenomena as allograft rejection, and at the same time from the introduction of new synthetic and natural drugs in the treatment of cancer. It has since appeared that most of these drugs, in addition to their antiproliferative action, frequently exert a remarkable action in immunopathological syndromes.(81)

For several years after the features of allograft rejection mere defined, it was assumed that this process was one of nature's most powerful weapons for preserving the body's integrity. Only by severely crippling the host's immune defence could this process be prevented.(123)

The first clue that host death was not the requisite penalty for allograft protection come from observations that acceptance of adult donor tissue could be induced in fetuses of newborn animals. As a result, it was suggested that exposure of the fetus to donor tissue might similarly confer protection persisting after birth to subsequent grafts from the same donor but not those from other donors.

The hypothesis was confirmed by injecting allogenic lymphoid cells into mouse fetuses and subsequently demonstrating that these mice accepted grafts from the same donors when they become adults.(157) It was hoped that a similar sequence of events, termed acquired immunologic tolerance, could be duplicated in adult recipient of allografts. The search was stimulated for immunosuppressive agents or techniques with which it might be feasible to induce acceptance of allografts.(9, 16, 147)

Immunosuppressive agents are precisely what their name implies: agents that weaken or abolish the immunologic response. The term itself promises more than any such agent has, in fact, achieved. An immunosuppressive drug or treatment should theortically be one that inhibits the immune response only and no other physiologic function. Unfortunately, no therapy presently available fulfills the requirements of this definition except perhaps certain preparation of ALS. The immunosuppressive action of all other agents in common use is a by-product of some much more general toxic influence that happens to affect, among many others, the cells involved in the immunologic response. For this reason immunosuppressive agents are dangerous, and their use at present is only justified for life threating conditions .(123)

The activity of immunosuppressive agents can be related to the cellular events involved in developing an immune

response,(151) therefore, explanation of the details of the immune mechanism is necessary in begining this review.

THE IMMUNE MECHANISM

Although some of the details of the over all immune mechanism are still uncertain, a general scheme of the steps involved in the genesis of specific immunity can be sketched (Figure 1) as a means of placing the effects and toxicities of immunosuppressive agents in perspective.(143)

Specific immunity appears to result from the interaction of antigens (substances the host normally recognizes as foreign) with mononuclear cells that circulate in the blood and lymph. The nature of self recognition, or "tolerance" is complex, but it appears to be defined in utero, during development of the lymphoid tissues. An initial "antigen-processing" step seems to occur in the mononuclear phagocyte (blood monocyte or the tissue macrophage), which then makes the antigen more readily recognizable or available to lymphoid cells. Macrophages or supernatants from macrophage cultures also can stimulate or inhibit immunoproliferative reactions. Recently it has been established that macrophages secrete large amounts of thymidine, apparently because they lack thymidine kinase. Local excess thymidine concentration can blook proliferative reactions in vitro.

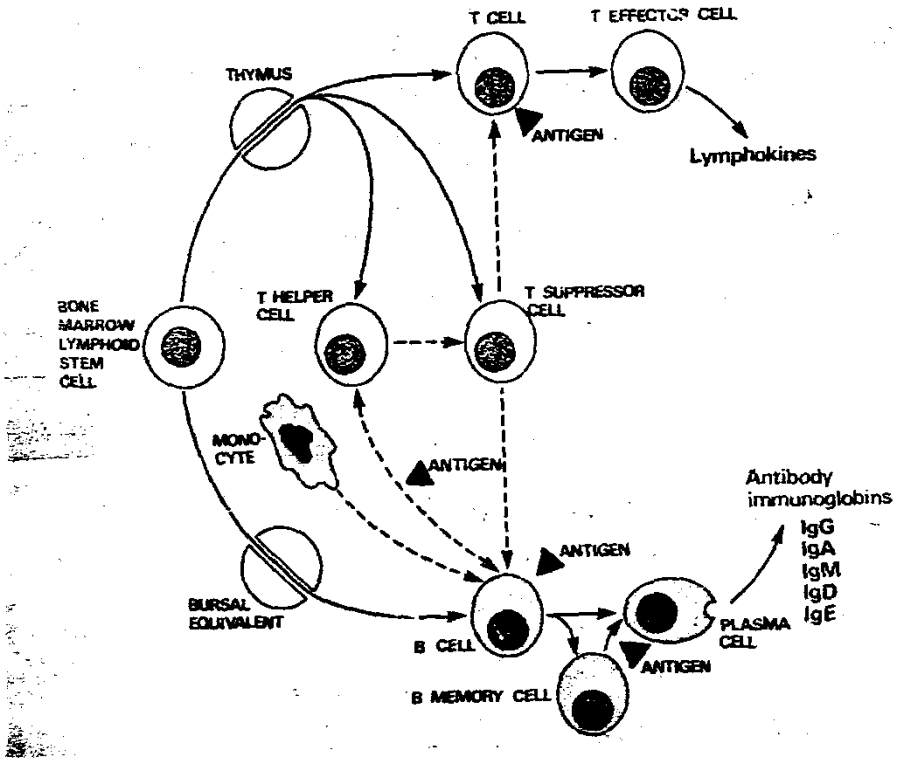

Fig. 1: Genesis and interactions of the immune system. (Adapted from Salmon S.E.: Drugs and the immune system. In Review of Medical Pharmacology. Sixth edition. F.H. Meyers and others (eds), 1978, p. 517).

A basic dualism seems to govern the function of the lymphoid cells-T-and B cells-mediate cellular immunity and humoral immunity, respectively. Both types of cells are found in the blood as well as in peripheral lymphoid tissues. Both B and T cells appear to have microvilli on their surfaces when examined by electron microscopy. Long lived clones of small lymphoid cells derived from or influenced by the thymus (T cells) appear to recognize the antigen and bind to it. The T cells specificity of this line of cells appears to arise from a bone marrow progenitor under the influence of thymic hormone, which is produced by the epithelioid component of the thymus. T cell function seems to be modulated also by histamine, and T cells bear a histamine type 2 receptor which can be blocked with burimamide or metiamide but not with "classical" antihistamines such as diphenhydramine. The proliferation of clones of antigen recognition T cells, which occurs after contact with antigen is responsible for the development of "cellular immunity" which can be demonstrated in delayed hypersensitivity reactions and is important in tissue graft rejection. The T cells appear to exert their effects by direct cytotoxic interaction (e.g., with tumour cell, or transplants) and by release of various effector substances, or lymphokines (Table 1). The genesis of specific antibody

Table 1: The lymphokines produced by lymphocytes[§]

Substance	Effect
Transfer factor (TF)	Transfer of cutaneous hypersensitivity.
Migration inhibitory factor (MIF).	Inhibits macrophage migration
Lymphotoxin (LT)	Cytotoxicity against target cells.
Mitosis-stimulating factor (MSF)	Stimulates proliferation of unsensitized lymphocytes.
Chemotactic factor	Stimulates chemotactic migration of macrophages.
Interferon	Inhibits intracellular viral replication.
Immunoglobulin (Ig)	Specific antibody molecules.

§ Salmon, S.E.: Drugs and the immune system. Review of Medical Pharmacology, 6th ed., 1978, p.517.

immunoglobulins resides in the progney of the second type of lymphoid cell, the antibody precursor cell (B cell), derived from the bone marrow. B cell can identified by the presence of monoclonal immunoglobulins on their surfaces which are located in "spots" or the cell membrane, and through their antibody function, appear to serve as antigen receptors, B cells also have receptors for complement components and immune complexes. Intimate cell-cell interaction between macrophages bearing the antigen in an immunogenic form on the cell surface and complementary colones of T cells and B cells is thought to be required before the clonal proliferation of T cells can develop cellular immunity and B cells can form antibody - forming cells. The primary immunoproliferative response is augmented or inhibited by T cells with helper or suppressor function. Antibody forming cells can increase their synthetic capacity by further differentiation into plasma cells, clones of which specifically secrete large amounts of antibody of one of the immunoglobulin classes - IgG, IgA, IgM, IgD, or IgE. Finally, specific antibody binds to the foreign antigen, leading to its precipitation, inactivation (e.g., virus), lysis (e.g., red cells), or phagocytosis (e.g. bacteria). In some of these circumstances, complement is bound to the antigen-antibody complex and facilitates the destruction or phagocytosis of the antigen. Once an antibody

response is established, reexposure to antigen leads to an immediate chemical combination of antigen antibody and also serves to provide a "booster" for a rapid secondary wave of cell proliferation and antibody synthesis, this is the secondary response.(27)

Normally, most components of the lymphoid system remains in a highly "repressed" state until they are selectively activated for a specific immune response. Briefly the cellular events involved in immune response, is divided into 4 phases, and it should be possible to interfere with each of them to obtain a state of immunosuppression.(81)

1. Afferent phase: during which most antigens, either soluble or particulate, are taken up by macrophages in order to be presented later to immunocompetent cells in an appropriate form.

2. The recognition phase: during which predetermined small lymphocytes (antigen-sensitive cells) recognize immunogenic determinants on antigens presented to them.

3. The stimulatory phase: antigen-sensitive cells trigger antibody-producing cells probably of bone marrow origin. They also generate memory cells and committed small lymphocytes responsible for delayed hypersensitivity reactions.

4. The efferent phase: where antibodies are produced by plasma cells and several factors (lymphokines) are secreted by lymphocytes which are responsible for cellular or delayed hypersensitivity reactions.

Most of immunosuppressive agents which will be discussed later, are able to suppress a primary immune response than secondary response.(147) Although most of these agents are capable of inhibiting immune response when administered before the final immune effector has been elaborated. They have relatively little effect against either the final differentiated antibody producing cell or lymphocytes which carry immunologic memory. Further, cytotoxic immunosuppressive agents do not interfere with the function of those phagocytic cells which may initiate the immune response. But the only cell vulnerable to those cytotoxic immunosuppressive agents which act to inhibit cell division are the actively proliferating immunoblast.(75)

TISSUE INJURY IN IMMUNOLOGICAL REACTIONS

Not only immunological mechanisms operate to the benefit of the host in overcoming bacterial and viral infections and in protecting him from cancer, but some forms of tissue damage may arise also from immunological responses. These damaging immunological reactions or oberrant immune responses are collectively known as hypersensitivity.(27) The term "allergy" was suggested by Von Priquet early in this century to describe a state of altered reactivity to foreign antigenic material.

In terms of aberrant immune response, one or more pathophysiologic mechanisms may be involved in an individual disease process (Table 2).(181) In the following section, each of the basic mechanisms is discussed in relationship to the possible activity of cytotoxic immunosuppressive agents in ameliorating manifestations of the aberrant response.(151)

Table 2: Immune mechanisms (151)

1. Anaphylaxis.
2. Cytolysis, agglutination and inactivation.
3. Toxic complex disease.
4. Cellular immunity (delayed hypersensitivity).