# Immunosuppression and Renal Transplant Follow-up

An Essay

Submitted for partial fulfilment

of Master Degree in

Urology



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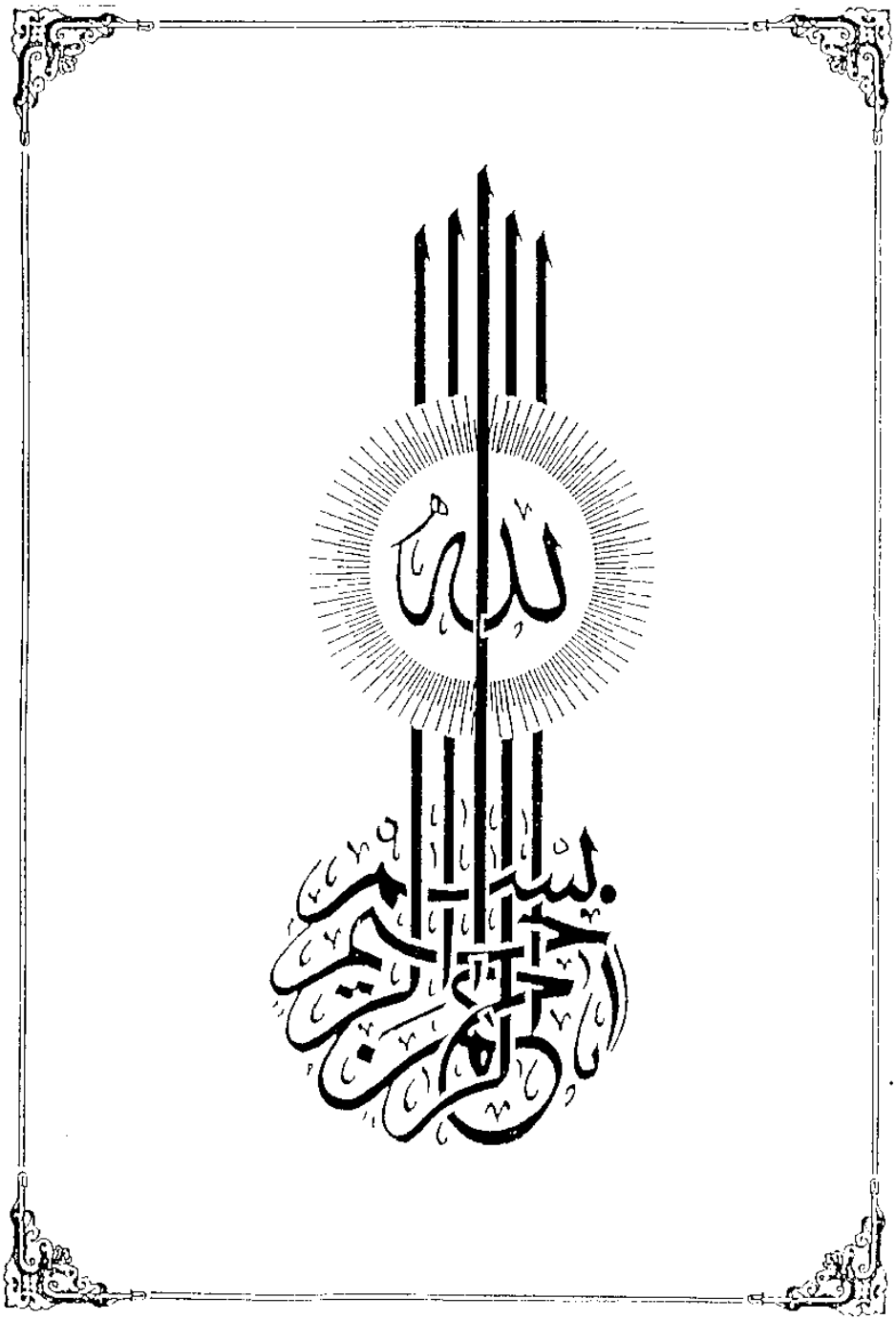
بسم الله الرحمن الرحيم

To my daughter Heba
& my son ALI...



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# Introduction

Renal transplantation has advanced from the realm of surgical research to a point where it is currently the preferred treatment for most patients with end-stage renal failure .

Young men and women die every day because their kidneys are destroyed by disease , although the rest of their body is perfectly sound . Faced with this situation , it is hardly surprising that nephrologists have been preoccupied with the idea of saving these young lives by kidney transplanation .

The problem didn't lie in the actual surgery . The operative technique had been established by many surgeons , but it was known that the transplant was inevitably recognised as foriegn and as such rejected . Unfortunately the body has no discriminating powers in its natural mechanisms for eliminating foriegn invaders .Potientially lethal bacteria and viruses are dealt with in the same way as life-saving tissue grafts . However , rejection of the transplanted kidney by the recipient still remains the major problem to be overcome .

If immunosuppression is neverthlesss increasingly used , it is for the following reasons :-

A} Transplantation is proving unfeasible without immunosuppressive therapy in almost all conditions , except the transplantations of organs between identical twins .

B} In a number of clinical conditions it has been found that mild immunosuppression alleviates immunopathological

conditions without producing the related hazard of infection.

In recent years , investigation on cellular and molecular events of immunization have made it possible to study different ways and means of interfering with the immune response .(P.A. Mieschen , 1974).

Therefore , this is an attempt to throw light on and summarize collectively the different aspects of immunosuppression and its role in the field of renal transplantation . Immunosuppression is classified into non-specific and specific .

Non-specific immunosuppression includes methods and drugs . These methods are either surgical , such as thoracic duct drainage , or non-surgical such as pre-transplant blood transfusion and irradiation .

Immunosuppressive drugs comprises ,steroids azathioprine (immuran) , Cyclophosphamide , antilymphocytic globulin (ALG) , Cyclosporine A and others .

Specific unresponsiveness , selective for the major transplantation antigens of a donor , remains the ideal goal of efforts in clinical transplantation . Specific methods of immunologic modification involve exposure to antigen in such a way that a graft will be tolerated instead of rejected . (Charles B.Carpenter and Terry B.Strom , 1980).

The aim of my essay necissitated a trial to understand the immunologic aspects of graft rejection and its regulation , its clinical types and its early diagnosis .

This is to be able to evaluate the effect and control the usage of immunosuppressive regimens .

The historical background of each of the immunosuppressive agent as regards the field of renal transplantation is mentioned in the appropriate situation in this essay .

To achieve an alert and competent renal transplant Follow-up , it was found important to be well oriented with the post operative complications of renal transplantation , their clinical picture and their proper diagnosis . The management of these complications is accounted for shortly.

And GOD is the most helpful.

# PHYSIOLOGY OF BODY IMMUNE RESPONSE

* Definition:

Immunology concerns itself with functions involved in the differentiation of self from non-self thus detecting that which is foriegn ; with the specificity of this recognition mechanism and with the laying down of immunological memory of the past experience of foreingnness.

(Geoffry Taylor , 1975)

* Immune response:

The reaction to foreign substances involves elimination of the foreign material , and is an important homeostatic mechanism . It results in the formation of antibodies . These may be either immunoglobulins (Ig) or cell-bound . (Walter & Israel , 1979).

* Antigens:

The material against which an animal mounts an immune response is usually referred to as an antigen . This is defined as a molecule which is capable of inducing an immune response in an animal and which is further able to react specifically with the products of the response .

(Geoffrey Taylor , 1975)

Or it may be defined as a substance , which when introduced into the body of a susceptible animal leads to an immune response which results in a specific change such that when the antigen is introduced on a subsequent occasion there is a response differing from that seen when the substance was first introduced (Walter & Israel , 1979).

## Characteristics of Antigens:

* Protien in nature .

* Of high molecular weight .

In fact , immunogenic molecules can have MW. as low as 450 (Edwin L.Cooper , 1982). Polysaccharides of trough high M.W. have antigenic properties .

It must be noted that antigenicity is not an absolute quality . A substance can be considered antigenic only in relation to a specific host . (Walter & Israel and Geoffry Taylor).

The antigenic specificity of each protien is due to specific areas of the molecule called determinant sites or epitopes . The response to such antigens is influenced by helper T cells.

The majority of naturally occuring antigens are T-dependent and stimulate an immune response by evoking T-B cell co-operation T-independent antigens can initiate an antibody response in thymectomized animals these are molecules which have a large number of identical antigenic determinants (W.M.G . Amos . Fimls , 1981)

(Edwin L.Cooper , 1982)

## Natural kinds of Antigens:

** Blood cell antigens:

* Blood leucocytic antigens .

* Erythrocyte antigens (ABO Bl.groups).

** Viruses and bacteria.

** Protiens .

** Carbohydrates : If they occur as integral components of bacterial cell walls , they are immunogenic , but when alone they behave as haptens .

** Lipids & nucleic acids:

Lipids are unable to induce immune response when they occur alone .

** Transplantation antigens:

These induce allograft immunity humoral allo-antibodies and cutaneous hypersensitivity reactions . They are generally present on all cell surfaces.The greatest amount of extractable antigen is found in lymphoid tissue , while kidney , lung , adrenal and liver contain moderate amounts ; the brain , placenta and muscles are poorer sources.

Polypeptides must be present if transplantation antigens are to be active . Antigenic activity ceases irreversibly if cells are exposed to denaturation as by : 50 % urea , 90 % phenol , aqueous alcohol , heat and ph values less than 4 and greater than 9 .

Haptin:

This is a non-protien substance which has little or no antigenic properties itself , but which combines with a protien to form a new antigen . The latter is capable of stimulating the production of specific immunoglobulins , the specificity of which depends upon the hapten fraction rather than the carrier protien . (Walter & Israel , 1979).

Adjuvants:

Substances that when combined with soluble antigens , enable them to induce more effective antibody synthesis . ( Edwin L.Cooper , 1982 ).

Notes on physiological anatomy :

Two separate systems are involved in the immune response :

* The lymphoid tissue associated developmentally with the thymus is responsible for the production of cell-bound antibodies .

* Cells which are dependent developmentally on lymphoid tissue associated with gut , in birds . This is the bursa of fabricius . They are responsible for synthesis of immunoglobulins . ( Walter & Israel , 1979 )

Three cell types play a critical role in the initiation of an immune response , T lymphocytes , B lymphocytes and macrophages ; these cells also play vital functional roles , assisted in final stages by neutrophils and to a lesser extent by other granulocytes . ( W.M.G. Amos,1981).

The immunocompetent T cell:

Precursor T cells migrate from the bone-marrow to the thymus where they acquire T cell characteristics . A small minority leave the thymus as short - lived rapidly dividing T cells and most spend their life circulating between the lymph , blood and tissues , large concentrations accumulating in the lymph nodes . T cells can recognize and

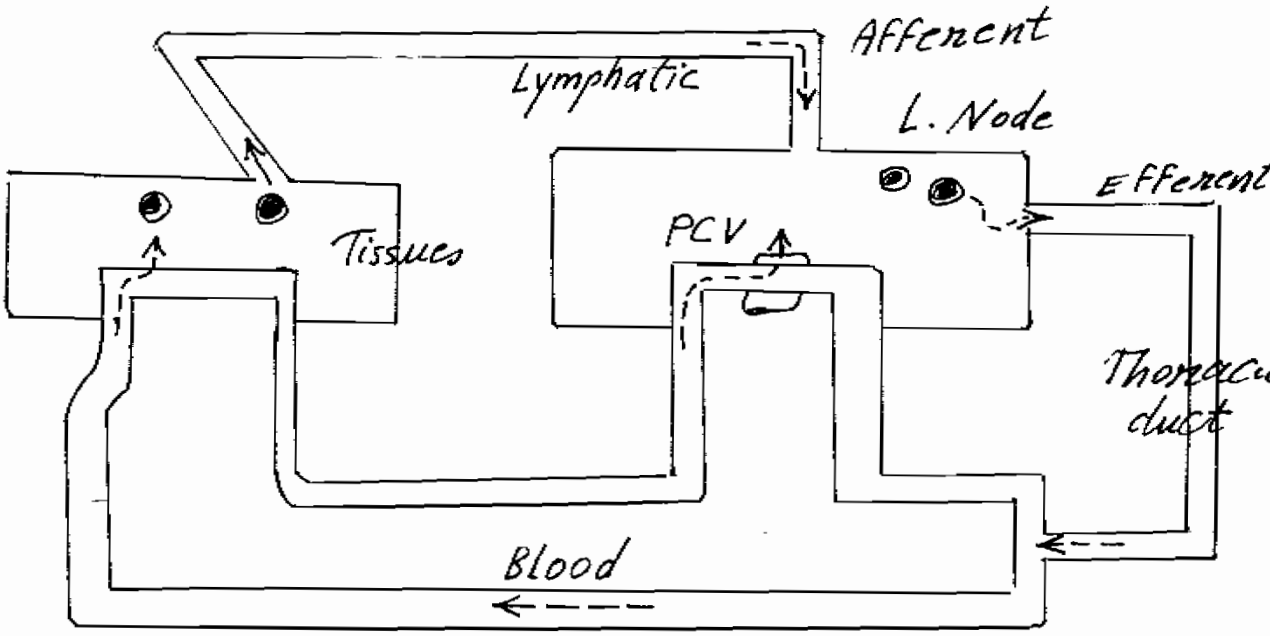
bind to antigen , proliferate in response to antigen and in addition attach to other cells , using the Fc receptor on antibody -antigen complexes as a link . They mediate cellular immunity ; graft rejection is a cell-mediated immune response . Recognition molecules present on T cells are the product of genes within the major histocompatibility complex (MHC). These are the group of genes that controls an individual's capacity to reject of foriegn tissue graft . (Edwin L.Cooper , 1982).

T cells are currently divided into several populations :

* A population mainly responsible for cytotoxicity .

* Another one responsible for blast transformation.

* A third class of T-cells is responsible for inhibition of B-cells and probably also of T-cell activity (suppressor T-cell). (Jean Francois , 1974).




Traffic & recirculation of lymphocytes

Blood-borne lymphocytes enter the tissues and lymph nodes passing between the high cuboidal cells of the post-capillary venules (PCV) and leave via the draining lymphatics . The effernt lymphatics finally emerging from the last node in each chain join to form the thoracic duct which returns the lymphocytes to the blood stream where it empties into the left subclavian vein (in the human) . In the spleen , lymphocytes enter the lymphoid area (white pulp) from the arterioles , pass to the sinusoids of the erythroid area (red pulp) and leave by the splenic vein.

(Ivan M.Roitt , 1978).

## Immunocompetent B cells:

Bursa - dependent and concerning in the synthesis of the circulating antibody . They develop into the plasma cell series . As a response to specific antigenic stimulation it undergoes blast cell transformation and functional differentiaion into a memory cell or plasma cell .(W.M.G. Amos , 1981 & Ivan M. Roitt , 1978).

## Macrophages :

The large mononuclear cells of the monocyte - macrophage series play a central role in the induction of the immune response .(Ivan M.Koitt , 1978).

Various theories suggest that macrophages are:

1) Antigen - trapping cells . This is thought to make antigen particularly accessible to lymphocytes , causing their activation.

2) Cells that digest large molecules of particles into smaller antigens that are more capable of initiating immune responses .

3) Cells that possess antigen that has been complexed with RNA or other substances , producing a very potent " Super antigen".

4) Cells that are involved in the act of antigen recognition .

The most widely accepted view of how macrophages may function assumes that the macrophage is an antigen - concentrating cell which capable of capturing antigen on its surface . (Edwin L.Cooper , 1982).