IMMUNOLOGIC ASPECTS IN ORGANS TRANSPLANTATION

ESSAY

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master Degree of General Surgery

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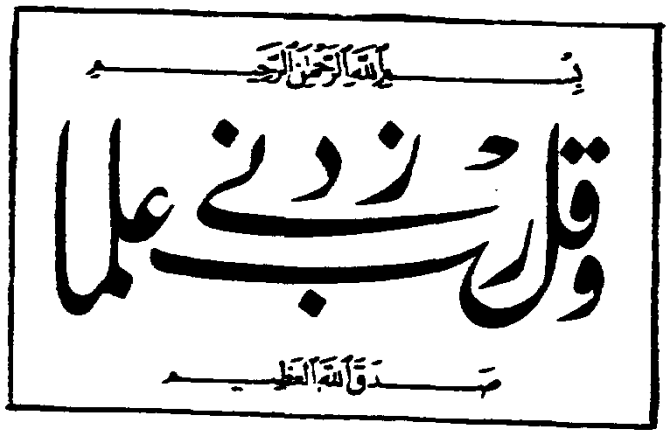

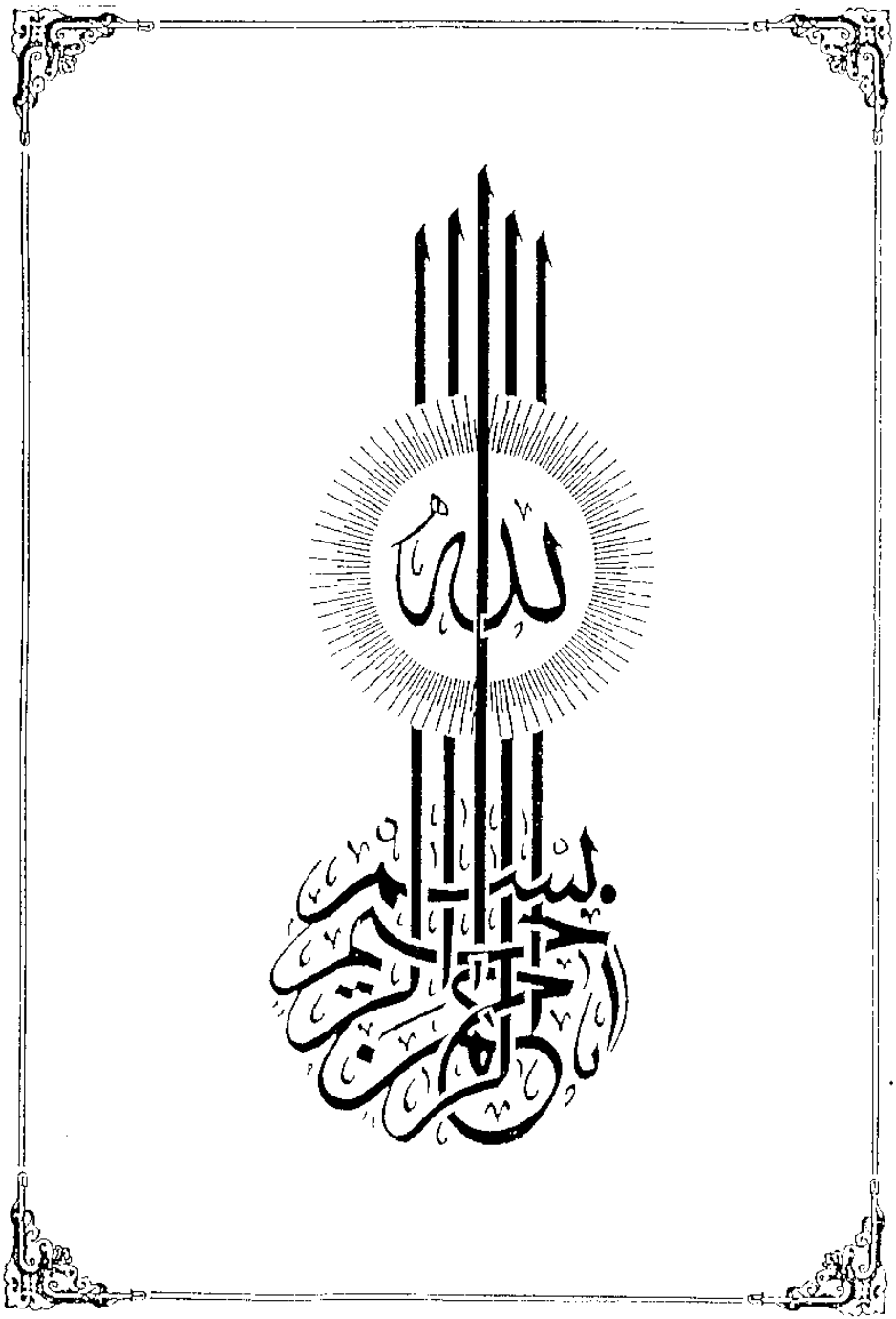

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INTRODUCTION

INTRODUCTION AND HISTORICAL BACKGROUND

Until the 1940s most cogent limiting Factors For organ grafting were surgical; since then it has become apparent that the central problem in tissue transplantation is immunologically mediated rejection.

Some of the earliest studies yielding significant information about transplantation immunology were carried out during world war II by Medawar. At that time he was asked by the British government to determine why skin from cadavers used to replace areas of burn in injured fighter pilots was rejected, and what means could be used to prevent this rejection process. By few basic experiments on rabbits, he demonstrated that the fundamental features of immune responsiveness, i.e. specific recognition and memory, apparently played a role in tissue transplantation.

A number of other early experiments by various researchers demonstrated phenomena that would later have relevance to the problems encountered in clinical transplantion. Any nucleated cells from a given donor could sensitize a host to all tissue from that donor.

In addition to the gross observations he made about graft survival. Medawar also examined the histologic nature of the rejection process. The finding of vascular degeneration with an intense infilteration of small mononuclear cells into the graft and graft bed led him to suggest that the mononuclear cell (lymphocyte) played an important part in allograft destruction just as it did in the delayed hypersensitivity to tuberculin.

Another early finding, transplanted skin grafts were rejected almost immediately such that no revascularization had occured and the graft

appeared white. This type of "hyperacute" or "white graft" reaction, was found to have a distinctive histologic paltern,with an absence of lymphocyte infilteration into the graft but instead a dense band of acute inflammatory cells, especially neutrophils, present at the graft border. One of the early misleading findings that transplant immunity was mediated by cells alone,but humoral immunity does play an important role in several types of rejection.

These early descripitive studies provided a basis for subsequent work geared to exploring the mechanisms involved in allograft recognition and response.

Transplantation has been proved technically possible for a wide variety of organs, including kidney, liver, pancreas lung, heart, and several other tissues in both animals and man. Unfortunately, uncontrollable rejection has caused the failure of a high proportion of such transplants. Immunosuppressive agents have been required for mating clinical transplantation at all feasible, and the transplantation of several tissues or organs still remains impracticaple because of the intensity of the host immune response.

IMMUNE RESPONSE

Introduction:

Immunity is concerned with the recognition and disposal of foreign or "non-self" material that enters the body whether in the form of life-threatening infectious microorganisms or life saving kidney graft. Resistence to infection may be "natural" (i.e. inborn and unchanging) or "acquired" as the result of an adaptive immune response (Playfair 1982). The immune response in relation to foreign materials has two components, humoral and cellular. Humoral immunity is related to formation of immunoglobulin antibodies. Cellular immunity is attributed to sensitized Lymphocytes (T-cells) which are activated against the foreign antigen (Walter and Israel 1979).

Antigens.

Antigens are substances of various chemical types capable of stimulating the immune system of an animal to produce a response specifically directed at the inducing substance. The specificity of the immune response for chemical structures (antigenic determinats) of the antigen molecule is an important characteristic (Weir 1978). Most proteins and polysaccharides are strongly antigenic whereas lipids and nucleic acids tend to be poorly immunogenic (Morris and Williams,1981).

Haptens:

Haptens are substances which are not antigenic in themselves but, which behave as antigens when combined with a suitable carrier protein. The hapten molecule then acts as a determinant of antigenic specificity and is referred to as an antigenic determinant (Weir 1978).

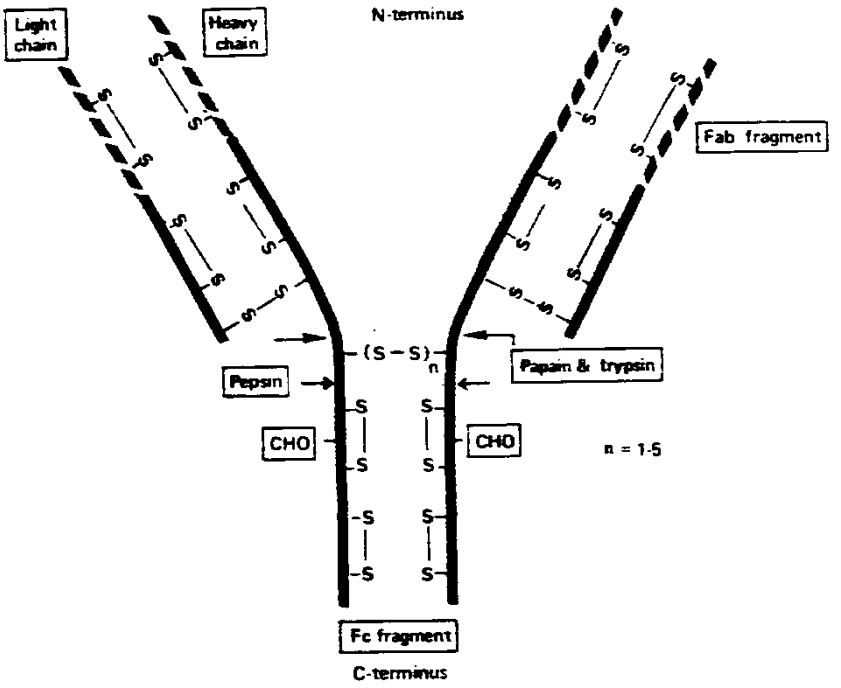
The importance of haptens may be illustrated by:

Simple chemicals may combine with body proteins, there by producing an antigenic complex. This is the basis of allergic contact dermatitis and many types of drug hypersensitivity.

* *Several important tissue antigens are either haptens or haptens combined with protein. Thus, the blood group substances (ABO system) are glycoproteins, and transplantation, Forssman, and Wassermann antigens are lipid in nature. (Walter and Israel 1979).*

The humoral immune response:

The humoral antibodies are mostly gamma globulins on electrophoresis, and by convention are called immunoglobulins (Ig).



Structure of immunoglobulins. Electron microscopic studies have demonstrated that immunoglobulin molecules are Y-shaped Solid lines indicate regions of constant amino acid sequences: broken lines indicate variable regions. Note symmetry in structure of molecule. One intrachain disulfide loop recurs for every 110–120 amino acid residues along heavy and light chains; about 60 residues are contained within each loop. From 1 to 5 inter-heavy chain disulfide bonds are present in each molecule depending on subclass of heavy chain. Points of cleavage of heavy chains by the proteolytic enzymes papain, trypsin, and pepsin, in relation to the inter-heavy chain disulfide bonds, are indicated.

Immunoglobulin diversity:

The basic unit of all immunoglobulin molecules consists of 4 polypeptide chains linked by disulphide bonds. There are 2 identical heavy chains (molecular weight 53-75,000) and 2 identical light chains (molecular weight about 23,000). There are five classes of immunoglobulin known as IgM, IgG, IgA, IgD and IgE. which differ in the amino acid sequence of their heavy chains (μ, γ, α, δ and ε respectively),in their physical characterestics and in their biological function further subdivisions of each class into subclasses is made on the basis of minor heavy-chain structural differences, there are, for example, four subclasses of IgG (IgG 1-4) and two subclasses of each IgA and IgM.

IgM:

IgM consists of a pentamer of the basic four-chain structure, linked together by disulphide bonds. It is an efficient complement fixer and is thus an excellent cytotoxin , its valency (approximetly six) also makes it a good agglutinin. In a classic primary immune response in man, IgM antibody is detectable within 48 hours of antigenic stimulation. Four to six days later, IgG antibody appears, the response peaking at about day ten. As IgG production increases, so IgM production decreases; prevention of IgG production by immuno-suppressive drug therapy leads to continued production of IgM, suggesting that IgG exerts an immunoregulatory feed back effect on IgM production.

IgG:

IgG antibodies probably form of the major line of defence against microbial infection. Most IgG subclasses fix complement and the antibody undoubtedly plays a role in opsonization. It is found in both the blood and the extravascular space and in some species can cross the placenta, thereby protecting the neonate until immuno-comptence has developed.

IgA:

IgA is synthesized by plasma cells located in submucosal areas and appears mainly in the sero-mucous secretions bathing mucous epithelial surfaces. Its most important function is to protect these surfaces against microbial invasion.

IgD:

IgD is found in only minute quantities in the circulation and its precise biological function is unknown. It is present on the surface of some B lymphocytes, where it act as a receptor for antigen.

IgE:

IgE antibodies, also known as reagins, are found in only small amounts in the circulation. They have a high affinity for mast cells and the manifestations of allergy as seen in hay fever. IgE has recently been implicated in immunity to helminthic infection (Morris and Williams 1981).

Antigen-antibody union:

When antibody is mixed with antigen a primary union occurs. Frequntly there is no visible change but if the physiochemical conditions e.g., PH, Temperature, electrolyte concentrations, etc. are appropriate, the primary union is followed by a variety of secondary phenomena, which can be seen or detected such as: Agglutination, precipitation and complement fixation are the most important. Other secondary phenomena are: Opsonins, Neutralizing antibodies and cytotoxic antibodies. (Walter and Israel 1979).

Agglutination: In this reaction the antigen is part of the surface of some particulate material such as a red cell, bacterium or perhaps an inorganic particle. Antibody added to a suspension of such particles combines with the surface antigens and links them together to form clearly visible aggregates or agglutinates. The highest dilution of serum which produces agglutination is called its titre, and a rising value is significant.

Applications:

The classical applications of the agglutination test is Widal test used for demenostration of antibodies to salmonella in serum specimen taken from suspected enteric fever cases. Agglutination is the basic technique used in blood grouping (Weir 1978).