IMMUNE COMPLEXES IN DERMATOLOGY

THESIS

Submitted for Partial Fulfilment of

Master Degree in

(Dermatology and Venereology)

By

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M.B., B.Ch.

Supervised by

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Faculty of Medicine

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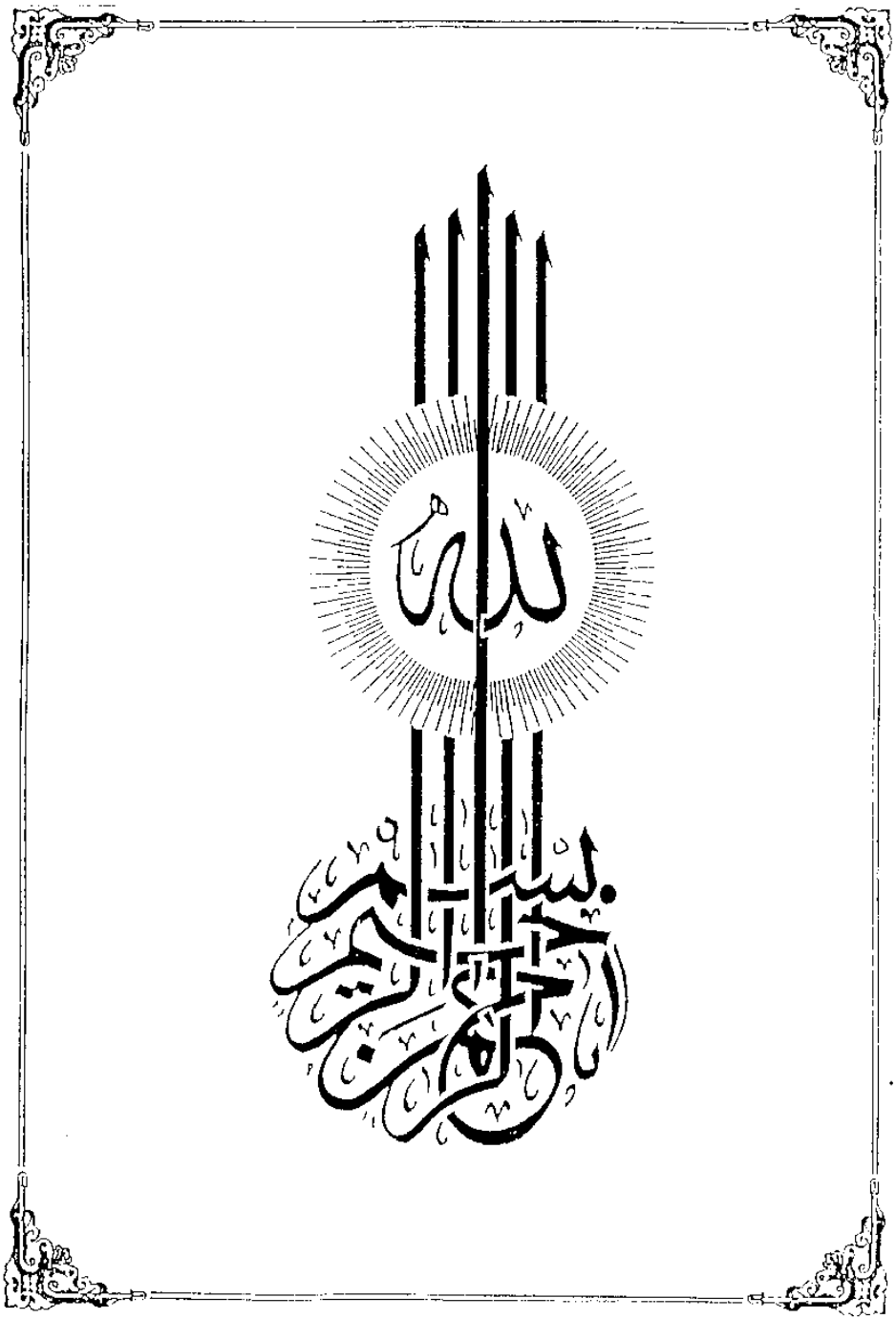

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INTRODUCTION

INTRODUCTION AND AIM OF THE WORK

Immune complexes (ICs) are a heterogenous group of immuno-reactants formed by the interaction of antigen and antibody. They are either formed locally in the tissues or exist as soluble complexes in various body fluids.

Generally, this immune mechanism usually results in elimination of noxious and foreign antigens from the circulation, but in many instances immune complex formation can cause tissue damage and many clinical diseases result.

For immune complexes to become pathogenic, they must become lodged in the blood vessel wall or in tissues. In local formation of immune Complexes the antigens are part of the organ or unrelated antigens are selectively deposited in the organ and antibodies from the circulation react with these antigens. In this pathogenic mechanism characteristically one organ system is involved and immune complexes are not present in the circulation. On the other hand, when immune complexes are present in the circulation usually more than one organ is involved resulting in multisystem disease.

The recent development of sensitive assays for the detection of circulating immune complexes (CICs) and the capability to assess immune complex clearance mechanisms in humans in vivo have expanded our understanding of these mediators in many disease states.

In the present study we aim to review fully the various aspects of the diseases caused by formation of immune complexes and to discuss the views of previous authors. This will entails: historical review, immunochemistry, biology, clearance and detection of immune complexes and their role in selected dermatologic diseases.

REVIEW OF LITERATURE

Immune Complex as a type of hypersensitivity reactions:

Four types of hypersensitivity reactions are recognized:

Type I is the immediate hypersensitivity reaction or anaphylactic reaction. It is mediated by IgE which becomes fixed on the cell membranes of mast cells and basophils if an antigen is injected for the first time. The first dose of antigen is called sensitising dose. If another dose of the same antigen is given after ten days from the sensitising dose, severe symptoms of shock develop which are called anaphylactic shock. After injection of this shocking dose, the antigen will react with mast cells previously fixed by IgE leading to release of several mediators. Among the numerous preformed mediators are histamine, serotonin, eosinophil chemotactic factor of anaphylaxis (ECF-A) and neutrophil chemotactic factor of anaphylaxis (NCF-A), slow reacting substance of anaphylaxis (SRS-A), platelet aggregating factor (PAF), Bradykinin and prostaglandins. Histamine causes increase vascular permeability, constricts smooth muscles, stimulates respiratory irritant receptor and chemoattractants for eosinophils. Serotonin (in rodents but not in man) causes stimulation of smooth muscle and increase vascular permeability. (SRS-A) causes contraction of smooth muscle, enhances vascular permeability and decrease pulmonary compliance. (PAF) mediates serotolnin release from platelets. Bradykinin causes bronchoconstriction, vasodilatation, pain, hypotension and bradykinin chemotactic for neutrophils. Prostaglandins cause local vascular leakage and potentiation of oedema in skin, pain and induce fever. These substances lead to appearance of the symptoms of anaphylactic shock which vary from a fatal shock to some respiratory distress. This reaction occurs also in urticaria, angioedema, atopic diseases such as atopic dermatitis, bronchial asthma, allergic rhinitis and hay fever.

It also occur after insect stings or bites, skin tests, injection of therapeutic sera or drugs, anaesthetics and radiological contast media.

Type II is the cytotoxic reaction. The antigen is either a part of cell membrane such as ABO antigens of red blood cells or is attached to the cell membranes as bacteria or a drug acting as a hapten. The antibody is usually IgG and sometimes IgM. The antigen antibody reaction leads to activation of the complement system which cause destruction of the cells. Examples of the cytotoxic reaction are mismatched blood transfusion, RH incompatibility, drug sensitivity causing haemolytic anaemia, thrombocytopenia and agranulocytosis, autoallergy in generalized eczema and in rejection of homografts.

Type III is the immune complex reaction. The antigen reacts with specific circulating antibodies resulting in activation of the complement system. If the antibody is of IgG or IgM class complement is activated via the classical pathway. IgA containing complexes are effective in activating complement via alternative pathway. Activation of complement leads to formation of anaphylatoxins C5a, C4a and C3a resulting in migration of neutrophils to the vessel wall. Neutrophils release lysosomal enzymes including elastase, cathepsins, cationic proteins, kinin activating enzymes and thromboplastin activator that cause blood vessel and active tissue destruction. The complexes are then ingested and lysosomal enzymes are released which promote furthur complex disposal and damage the vessel wall. Examples of the immune complex reaction are systemic lupus erythematosus and necrotizing vasculitis.

Type IV is the delayed hypersensitivity reaction or cell mediated reaction. It is mediated by the specifically sensitized T lymphocytes. Lymphokines are released from the sensitized lymphocytes at the site of the antigen and produce tissue damage. Example of this reaction is allergic contact dermatitis.

HISTORICAL REVIEW

The first description of immune complexes in man was made by Von Pirquet and Schick in (1905) during their studies of the disease following the injection of horse diphtheria antiserum in children. The investigators found that after eight to twelve days following the injection, a clinical syndrome appears as fever, arthralgia , albuminuria, edema, urticaria associated with severe pruritus, marked leukopenia with granulocytopenia and local then more widespread lymphadenopathy, occasionally a morbilliform rash was noted. The authors also observed that when a second injection was given twelve to forty days following the first one, edema fever and urticaria developed within a day. Contrary, when the second injection given six weeks to six months after the first an immediate reaction as before occured followed by an accelerated reaction within eight days. They suspected that this reaction was not due to a toxic effect of the serum but to an immune response in the recipient and the formation of antigen-antibody complexes.

Von Pirquet and Schick (1905) recognized that the initial latent period was due to the time required for the development of antibody in the recipient which react with horse antigens and deposited in the tissues resulting in tissue damage after formation of immune complexes, and the immediate reaction was due to the presence of circulating antibody. The accelerated reaction was like the reaction to horse serum in the virgin recipient but it was more violent, appeared after a shorter latent period and required smaller doses of serum.

Von pirquet and Schick (1905) suggested that the incidence of this reaction which was called serum sickness was directly related to the amount of horse serum injected.

Germuth (1953) observed the development of lesions in cardiac, vascular and renal systems of rabbits after injection with a single dose of crystallized bovine albumin. The lesions were rheumatic fever, polyarteritis nodosa and acute glomerulonephritis. He found also granulomatous lesions, consisting of epitheloid cells and foreign body giant cells in the spleen and lymph nodes of the animals receiving the antigen and this was attributed to hypersensitivity.

Dixon et al., (1961) recognized the deposition of antigen antibody complexes along the renal capillary basement membranes causing acute, subacute and chronic glomerulonephritis by daily injection of a foreign serum protein in rabbits. The amount of antibody formed in rabbits determined the occurance and the type of the disease, more antibody caused acute self limited glomerulonephritis and if the amount of antibody is lower and sufficient to neutralize the non glomerular antigen, subacute and chronic glomerulonephritis developed.

THE NATURE AND PROPERTIES OF IMMUNE COMPLEXES

The size and composition of immune complexes depend on many factors, including antigen size, antigen valence, antibody class, antibody valence, molar ratio of antigen and antibody and interaction of the immune complex with the complement system (Theofilopoulos & Dixon, 1980).

Antigens and antibodies are the essential constituents of all immune complexes. Antigens are defined as substances that interact specifically with available antibodies or sensitized lymphocytes. The actual portion of an antigenic molecule that react with the antibody combining site is defined as antigenic determinant. The number of antigenic determinants on a molecule defines its valance for the interaction with a specific antibody, valence of antigen and antibody is the numerical measure of their capacity to combine (Mannik, 1980).

Finbloom et al. (1981), defined immunoglobulins as a set of heterogenous molecules which upon reacting with antigen can transmit common effector messages to complement, to macrophages, to lymphocytes and to other cells. Antibodies may belong to IgG, IgA, IgM, IgD or IgE class of immunoglobulins. IgG, monomeric IgA, IgD and IgE have a valence of 2, i.e., each of these molecules have 2 binding sites for a given antigen. Dimeric IgA has a valence of 4. IgM has a valence of 5 or 10 depending on the nature of antigen molecules

Hyslop et al. (1970) mentioned that most antibodies have valence of 2 and detailed studies with polymeric IgA and IgM have not been conducted. The valence of antigen molecules influences the lattice of immune complex that can be formed with given antibodies. The lattice reflects the number of antigen and number of antibody molecules in each complex. Monovalent antigens combine with only one antibody binding site and form relatively small complexes which are soluble. Multivalent antigens can form large latticed immune complexes and undergo immune precipitation.

Theofilopoulos & Dixon (1980) reported that the critical immunochemical factor in immune complex formation is the molar ratio or relative concentration of the reacting antigen and antibody. At equivalence the number of antigenic sites is equal to the number of antibody combining sites and immune complexes are large. Addition of excess antigen beyond the point of equivalence leads to formation of small immune complexes because all antibody combining sites are saturated and chances for lattice formation are limited. Complexes with a moderate antigen excess are large enough to efficiently activate complement and not rapidly cleared from the circulation, so these complexes are the most pathogenic to man.

Koyama et al, (1978) found that antibody affinity will influence the interaction between antigen and antibody. Antibody affinity is the strength of interaction between antibody and a single antigenic determinant. The higher the affinity of a given antibody for antigen, the lower the concentration of free antigen required for saturation