

Immunology of Human Reproduction

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Edited by

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Foreword

by

Sir Cyril Clarke, K.B.E., F.R.S., M.D., F.R.C.O.G.
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Medicine, University of Liverpool

Administrators tidily divide up physicians doing higher medical training into “those with an interest” and “those practising exclusively in the speciality”. In real life things are different. Many doctors irritatingly get involved in several disciplines, dabbling perhaps in paediatrics or intruding into immunology, and some have the temerity to acquire their obsession only after they are consultants. Some even cross College barriers and become, for example, obstetric physicians. Long may this continue and it is good now to see that the traffic is two-way. Dr. Scott and Dr. Jones have in fact completely turned the tables and shown how wide ranging is their speciality, for it is *their* patients who hold the clues to the age-old problems of non-rejection of the fetus, toxæmia and, I would guess, congenital malformations into the bargain. The book will undoubtedly stimulate many people to ask the right questions of their antenatal patients because pregnancy is indeed a fascinating natural immunological experiment.

Preface

The recent dramatic expansion of knowledge in immunology has had a major impact on reproductive biology which in human medicine means the joint specialities of obstetrics and gynaecology. Although the field is beset with contradiction and conjecture, there are now several important areas from which sound experimental evidence and careful clinical observation have been drawn together into a discipline of reproductive immunology involving animals and man. Our aim is to provide the clinician with a guide to the subject emphasising human clinical applications both actual and potential. We also hope to help the immunologist and the experimental reproductive biologist to discover new areas of contact between their own disciplines and the clinical field; this may encourage them to respond to the need for applied research particularly in relation to infertility and fertility control.

The chapters are so arranged to provide a progressive theme for the reader wishing to cover the whole subject although each contribution has been devised as a separate entity to cater for the selective reader. This has led inevitably to overlap and to a certain amount of contradiction between chapters dealing with similar subjects from different viewpoints. No apology is made for this as it allows the reader a wider view of evolving knowledge and concepts while stressing the many unanswered questions and controversies in the field.

No attempt has been made to provide more than a brief outline of immunological techniques and experimental methods but with the help of the introductory chapter and the glossary it is hoped that readers will find the accounts intelligible. Many assays relevant to different aspects of obstetrics and gynaecology depend on immunologic or radio-immunologic techniques; they are not dealt with specifically in this book as they relate to laboratory practice whereas this text is primarily written from a clinical standpoint.

We are grateful to our contributors for producing what we believe are balanced accounts of current knowledge of subjects which are, at least in some instances, difficult and controversial. We acknowledge our great indebtedness to Miss Bronwen M. Johnson, Miss Zena Broughton, Mrs. Pauline M. Milson, Miss P. Neill and Miss M. Smith in relation to preparation of the manuscript. Mr. H. G. Lumby, Mr. J. E. Wood and Miss Renée Bailey have given particular help with regard to the illustrations. Drs. K. W. Hancock and Pamela V. Taylor have been responsible for producing the index, a task for which their specialised knowledge of the field has been a great asset and for which we are extremely grateful.

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Glossary

Allogeneic

Genetically dissimilar within the same species.

Allogeneic Inhibition

In vitro damage to cells caused by contact with genetically dissimilar lymphocytes. The lymphocytes do not apparently need to be primed but it is still not clear whether the phenomenon is non-specific or is due to an immune reaction.

Agglutinin

- (1) An antibody that reacts with surface antigens of particles, e.g. red cells and bacteria, to agglutinate them. See *Agglutination*.
- (2) Any substance, not necessarily antibody, capable of agglutinating particles, e.g. *Lectins*.

Agglutination

Clumping of particulate antigens (e.g. on red cells, bacteria, etc.) by reaction with specific antibody which forms bridges between antigenic determinants on contiguous cells. As agglutination is easily visible, it forms the basis of many serological tests.

Allograft

Graft exchange between two genetically dissimilar individuals of the same species, i.e. members of an outbred population, or of two different inbred strains.

Allotype

Genetically determined antigenic determinants on serum protein molecules varying in different members of the same species, i.e. serum protein isoantigens. On human *Immunoglobulin* molecules the Gm, InV and Oz allotypes are found.

ALS

See *Anti-Lymphocyte Serum*

Anamnestic Response

A Secondary Immune Response. This term is often applied to an unexpectedly powerful antibody response following what is assumed to be an initial administration of antigen. In fact, the animal in question has probably been stimulated by that same antigen or by a cross reacting antigen in the past.

Anaphylaxis

An acute immediate hypersensitivity reaction following administration of antigen to a *Primed* subject. The reaction is caused by release of histamine or

other vasoactive substances when antigen combines with antibody on the surface of cells.

Antibody

An *Immunoglobulin* capable of uniting specifically, by a defined part of its molecule (*Combining Site*), with a certain antigenic determinant.

Antigen

Any substance capable of reacting specifically with antibody. When used in the context of antibody stimulation and production it is usually called an immunogen.

Anti-Lymphocyte Serum

An immunosuppressive agent, prepared by injecting lymphocytes into a different species. Can suppress all reactions of *Cell-Mediated Immunity* and also humoral immunity to some antigens.

Autoantibody

Antibody capable of specific reaction with an antigen possessed by the individual in whom the antibody was formed.

Autoantigen

An antigen that is a normal body (self) constituent but against which an immune response may be mounted by the lymphoid tissues of the same individual as occurs in *Autoimmune Disease*.

Autochthonous

Derived from self. (Syn. *autologous*).

Autograft

Graft originating from, and applied to, the same individual.

Autoimmune Disease

Clinical disorder resulting from an immune response against *Self Antigens* (*Autoantigens*).

B-Cell System (B = Bursa of Fabricius)

The system of stem cells, lymphocytes and plasma cells concerned with the production and liberation of immunoglobulins and antibodies. B derives from the Bursa of Fabricius in the chicken, an organ actively associated with the production of such cells in avian species.

Blast Cell

A multiplying cell, usually large (diameter $> 8 \mu\text{m}$) with ill-differentiated cytoplasm rich in RNA and actively synthesising DNA; is the precursor of specialised cells, e.g. **Lymphoblast**, **Immunoblast**, **plasmablast**.

Blast Transformation

See *Lymphocyte Transformation*.

C (or C')

Symbol for *Complement*.

Cell-Mediated Immunity (CMI)

Specific immunity which is mediated by T lymphocytes and is dependent on the normal development of the thymus. Cell-mediated immunity is responsible for reactions such as allograft rejection, *Delayed Hypersensitivity*, tuberculin reactions and is important in defence against viral infections and some bacteria.

Central Lymphoid Organs

Those lymphoid organs which are essential to the embryological development of the immune response, i.e. the thymus and *Bursa of Fabricius* (in birds).

Chimera or Chimaera

A fire breathing monster of Greek mythology—with lion's head, goat's body and serpent's tail. The immunological connotation is of an individual with cells of different genetic and antigenic constitution, resulting from independent acts of fertilisation.

Clonal Selection Theory

This holds that each lymphocyte (or immunocyte) has the genetic information available to react to one particular antigen which selects those immunocytes with whose receptors it can unite specifically for proliferation to form a *Clone*.

Clone

A population of cells derived by binary fission from a single parental cell. When a cell of a clone undergoes somatic mutation its descendants constitute a new clone.

Combining Site

The site on the antibody molecule that combines specifically with its corresponding antigenic determinant. Present on the Fab fragment. The heavy and light chains are probably both involved and the combining site may be formed from contiguous areas of the variable regions of both chains, involving five to fifteen amino-acids.

Complement

A system of proteins in mammalian blood which unites with a variety of antigen-antibody complexes and is usually measured by its power to dissolve (lyse) red blood cells treated with antibody.

Complement-Fixation Test

A serological test system used to detect a specific antibody by allowing it to react with antigen and added *Complement*. If antibody is present, complement is fixed to the antigen-antibody complex and is unable to lyse "sensitised" sheep red cells.

Constant Region

The median half of the Fab portion of an *Immunoglobulin* molecule. So-called because the amino-acid sequence in this region is constant from molecule to molecule except for amino-acids at allotypic marker sites.

Coombs Test

An antiglobulin test used for recognising that red cells are coated with an *Immunoglobulin* (see p. 191).

Cytotoxic Antibody

Antibody which causes damage to antigen-bearing cells, especially in the presence of *Complement*. Such antibodies may be cytolytic or may cause damage to the cell membrane without lysis.

Delayed Hypersensitivity

A type of reaction mediated by primed lymphocytes seen in an individual who has been "sensitised" by previous experience of an antigen. In response to an injection, usually intradermal, of a small amount of antigen, an inflamed area appears with a characteristic delay of 12-48 hours.

Enhancement

See *Immunological Enhancement*.

First Set Rejection

The immunological rejection of an organ or tissue that has been grafted on to a previously unprimed host.

Germinal Centre

An aggregation of *Lymphoblasts*, macrophages and lymphocytes within the primary follicles of the lymphoid tissues.

Graft-Versus-Host Reaction

Reaction of a graft rich in *Immunologically Competent Cells*, against the tissues of a genetically different recipient.

H-2 Histocompatibility Antigens

Cell-surface isoantigens in mouse, corresponding to *HL-A Antigens* in human.

Hapten

Any substance of relatively low molecular weight which can react as antigenic determinant with antibody but can only act as immunogen (i.e. induce the formation of antibody) when combined with a carrier protein.

Heterophil Antigens

Antigens occurring on the surface of tissue cells of many different animal species, plants and bacteria and showing extensive interspecies cross-relationship. Introduction of heterophil antigen into the tissues of a species which does not carry it stimulates the formation of heterophil antibody.

Histocompatibility Antigens

The antigens in tissue cells which determine the rejection response when the tissue is grafted on a genetically distinct animal of the same species.

HL-A (Human Leucocyte) Antigens

A group of isoantigens on human tissue and white blood cells belonging to a single genetic system. This group of antigens appears to be the most important in tissue transplantation.

Immune

A state in which, following contact with antigen, there is a specific alteration in reactivity to subsequent exposure to that antigen, humoral or *Cell-Mediated Immunity* being exhibited against it.

Immune Complex

An antigen-antibody complex.

Immunoblast

A large pyroninophilic *Blast Cell*, the precursor of *Immunocytes*.

Immunocyte

Any cell which can be shown capable of producing antibody or reacting specifically with an antigen.

Immunoglobulins

Antibodies regarded from the point of view of their structure as proteins (see pp. 12-19).

Immunological Enhancement

An increased rate of foreign cell growth in animals immunised to the antigens of the cells. Seen especially in experimental tumours transplanted to animals which have antibody to the tumour. Attributed to the coating of antigens with antibody which prevents access of lymphocytes.

Immunological Inertia

A specific depression of immunity towards the *Histocompatibility Antigens* of a partner in viviparity, i.e. of mother or of fetus.

Immunologically Competent Cell

Any cell capable of specific recognition of, or specific response to, an antigen.

Immunological Surveillance

A physiological capability of the immune system for the recognition and removal of potentially malignant or other mutant cells in the body.

Immunological Tolerance or Unresponsiveness

A state of specific unresponsiveness in an animal or individual resulting in failure to produce an immune response when challenged by a potentially immunogenic stimulus; immune response to unrelated antigens is not affected.

Kallikreins

Enzymes with direct activity in increasing vascular permeability, vasodilatation and smooth muscle contraction.

Kinins

Peptides formed by action of *Kallikreins*. Kinins have activity as vasodilators.

LATS

See *Long Acting Thyroid Stimulator*.

Lectin

Substance derived from plants that may influence the activity (usually *in vitro*) of animal cells by binding to their surface determinants.

Long Acting Thyroid Stimulator

Serum protein with thyroid stimulating effect, found in patients with thyrotoxicosis. An *Immunoglobulin* of IgG class whose activity is related to the Fab fragment. May be an *Autoantibody*.

Lymphoblast

A *Blast Cell* of the lymphoid cell series with a nuclear pattern characterised by fine chromatin and basophilic nucleoli.

Lymphocyte Transformation

The name given to the change in morphology seen when peripheral small lymphocytes are cultured in the presence of *Phytohaemagglutinin* or an antigen to which they are primed; the transformed lymphocytes are *Lymphoblasts*.

Lymphokines

Substances liberated from stimulated lymphocytes which can influence vascular and cellular activity in the local region.

Macrophage Migration Test

An *in vitro* test used to detect and measure *Cell-Mediated Immunity*.

Memory Cells

Immunocytes (lymphocytes) whose presence in the body is responsible for the rapid secondary response to an antigen which the individual has previously experienced; the phenomenon of immunological memory.

MIF

See *Migration Inhibition Factor*.

Migration Inhibition Factor

Factor (*Lymphokine*) which inhibits migration of macrophages.

Mixed Lymphocyte Reaction

The formation of *Blast Cells* when equal numbers of lymphocytes from two individuals are cultured together for about five days. The number of blast cells appears to be directly related to the degree of incompatibility present between the *Histocompatibility Antigens* of the two cell donors.

Opsonin

An antibody which, after combination with an antigen, facilitates the phagocytosis of that antigen by a polymorphonuclear leucocyte or macrophage. Non-antibody heat labile opsonins which also facilitate phagocytosis are found in the blood plasma. These are probably products of activated complement components, especially C3.

Peripheral Lymphoid Organs

Those lymphoid organs that are not essential to the ontogeny of the immune response, i.e. spleen, lymph nodes, pharyngeal tonsils, Peyer's patches. Their development is secondary to that of the *Central Lymphoid Organs*.

PHA

See *Phytohaemagglutinin*.

Phytohaemagglutinin (PHA)

A kidney bean extract (*Lectin*) which is capable of agglutinating red cells and stimulating lymphocytes to *Blast Transformation* and mitosis.

Plasmapheresis

The technique of obtaining large volumes of plasma without causing anaemia; this involves the return to the patient of erythrocytes separated from withdrawn blood.

Primary Immune Response

The response of an individual on first encountering an antigen. Characteristically, low levels of antibody are produced slowly but the lymphoid tissues have been primed so that a *Secondary Immune Response* can be evoked on subsequent challenge.

Primed Lymphocyte

(Syn. *sensitised*) Lymphocyte primed to respond specifically to an antigen.

Privileged Sites

Sites in the body lacking normal lymphatic drainage and into which antigens, or tissue grafts, can be placed without stimulating an immune response, e.g. the central nervous system, the anterior chamber of the eye and the cheek-pouch of the hamster.

Prozone

In *Agglutination* tests, agglutination may not occur in the tubes containing the highest concentration of antibody but becomes obvious when the antibody is diluted. This absence or weakness of agglutination in the presence of the highest level of antibody is known as the prozone phenomenon.

Runt Disease

(Syn. *homologous disease*) Disease which develops after injection of *Allogeneic*

lymphocytes into immunologically immature experimental animals. Characterised by loss of weight, failure to thrive, diarrhoea, splenomegaly and often eventual death. An example of a *Graft-Versus-Host-Reaction*.

Second Set Phenomenon

The immunological rejection of a graft by a host that has already rejected either tissue from the same donor, or tissue carrying similar *Histocompatibility Antigens*.

Secondary Immune Response

Secondary response of the body to an antigen with which it has already been primed.

Secretor

Person who secretes ABO blood group into mucous fluids such as gastric juice, saliva, ovarian cyst fluid. Over 80% of humans are secretors, this status being genetically determined and related to the Lewis blood group system.

Self Antigen

Any substance occurring as a normal constituent of an individual's or animal's own tissues which is capable of stimulating autoimmunity.

Self Tolerance

Immunological Tolerance to Self Antigens. Tolerance to self antigens, which are accessible to the lymphoid tissues, is thought to be acquired normally during fetal life.

Syngeneic

Genetically identical, usually applied to grafts exchanged within an inbred strain of experimental animals.

T-Cell System

Immunocytes and their progenitors which, before becoming functionally active, require either to multiply within the thymus or be influenced by a thymic hormone. T-immunocytes do not liberate antibody and are responsible for delayed hypersensitivity, rejection of foreign tissues and other functions.

Transplantation Immunity

The study of the immune response following transplantation of tissue from donor to recipient. Very largely, the study of *Cell-Mediated Immunity* in this situation.

Xenograft

(Syn. *heterograft*) A graft from a donor of a dissimilar species.

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