PROGRESS IN OBSTETRICS AND GYNAECOLOGY

Volume Five

EDITED BY

JOHN STUDD

PROGRESS IN OBSTETRICS AND GYNAECOLOGY

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Preface

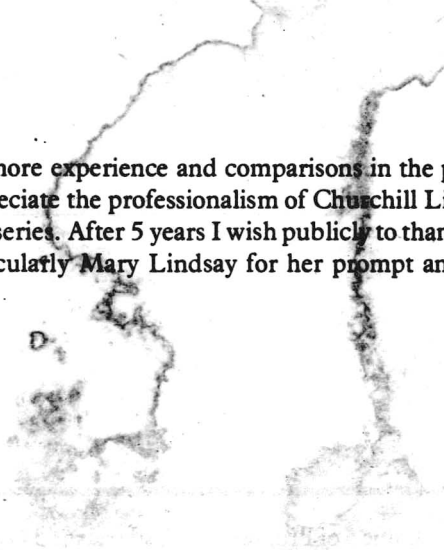
I cannot hide the fact that Volume 5 of Progress in Obstetrics and Gynaecology is 'a posy of other men's flowers with nothing but the string that binds them my own'. Looking at the contents it is certainly no worse for that. The alpha to omega has been covered. From the immunology of pregnancy to post-partum problems in obstetrics. From puberty and intersex to the climacteric in gynaecology.

It is hardly possible to express my gratitude to those who have been willing to write for this series during the last five years. Perhaps one should not be surprised at the young lions in training anxious for recognition who produce excellent and punctual chapters. But it is a mystery why senior colleagues invariably accept these invitations for a fee that hardly covers secretarial expenses. It is a tribute to the academic and teaching instincts that heads of departments should be willing to spend so much of their spare time distilling in these reviews their vast experience and enthusiasm into the wisdom of some of the truly marvellous reviews in this volume. The adage that if one wants a job done give it to a busy man is well taken. I and the readers are greatly in their debt.

Of all the variables of training — location of jobs, research, Third World experience, etc — I am of the belief that the most important is to have the good fortune to fall under the influence — the spell — of a great teacher. Some never have that luck. I have had the good fortune to experience this on three occasions with three very different individuals. To the brilliant and eccentric Hugh McLaren I owe almost everything. A man who led by example and no one ever treated his trainees with more concern and decency. To Hugh Phillpott whose ability to pass on his knowledge, skills and commitment to our specialty was quite simply unforgettable. And to Bob Greenblatt's innovative work in so many fields who delighted his many friends and confounded his many critics by being right when the herd was off in the wrong direction. They are all men with the courage and integrity to take unpopular medical, social or political positions. Perhaps the minority is usually right after all! Certainly our profession needs this sort of iconoclastic teacher to question conventional wisdom and keep debate on the boil.

No publisher works fast enough for an unreasonable author or editor. It is

only by more experience and comparisons in the publishing world that I can now appreciate the professionalism of Churchill Livingstone's handling of the Progress series. After 5 years I wish publicly to thank Sylvia Hull for her efforts and particularly Mary Lindsay for her prompt and efficient editing.



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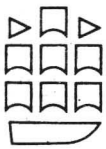

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Gordon M. Stirrat

Immunology of pregnancy

To be asked to write about the immunology of pregnancy is akin to a request to discuss the biochemistry of pregnancy. The scope of both is vast. Why then is it impossible to contemplate a comprehensive summary of the latter within the confines of 4–5000 words? The reason is that our knowledge of biochemistry in general and in pregnancy in particular is so much greater than our understanding of immunology. There is, however, no doubt that more progress has been made in general immunology over the past 20 years than in the 100 years from the time of the original discoveries by Jenner and Pasteur which created the new discipline. The immunological implications of pregnancy have only been perceived since Medawar & Sparrow (1956) made their observations in mice. In reproductive immunology it is only within the last decade that a significant body of knowledge has begun to accumulate which can be described as hard scientific fact.

What follows is a distillation of the current understanding of the immunobiology of the feto-maternal relationship as a guide for the bemused clinician. All the data discussed are either referenced specifically or mentioned within referenced overviews.

BASIC IMMUNOLOGY

The presence of a gene system located within a circumscribed chromosomal region which controlled graft rejection was first described 40 years ago. The genes involved were subsequently called the *major histocompatibility complex* (MHC). It was predicted that a similar genetic system would be present in all mammalian species including man. Since no 'in-bred' strains of humans exist, the research into the MHC in man was carried out using the sera from a large number of multiparous women tested against an even greater number of leucocytes taken from unrelated donors. The multiparous sera contained antibodies which had been induced by paternally derived tissue in the fetus. Under appropriate experimental conditions, the extent to which these sera destroyed the donor leucocytes was directly proportional to the genetic differences between them. From statistical analyses of these results, subsequently confirmed by extensive family studies, the presence of an MHC

in man was confirmed. Because it was first defined on leucocytes this system was called the human leucocyte system A or HLA. From what has been learned subsequently, we now know that:

1. The MHC is located on chromosome 6.
2. It consists of at least four major subregions or loci now named HLA-A, -B, -C and -D. The D subregion probably contains several loci of which 3 (DR, DC and SB) have so far been recognised.
3. The HLA gene combination on one parental chromosome (called a *haplotype*) is usually passed on as a complete unit. We therefore inherit one haplotype from our mother and one from our father as shown in Fig. 1.1. In general, only four combinations can be passed on from any two parents.

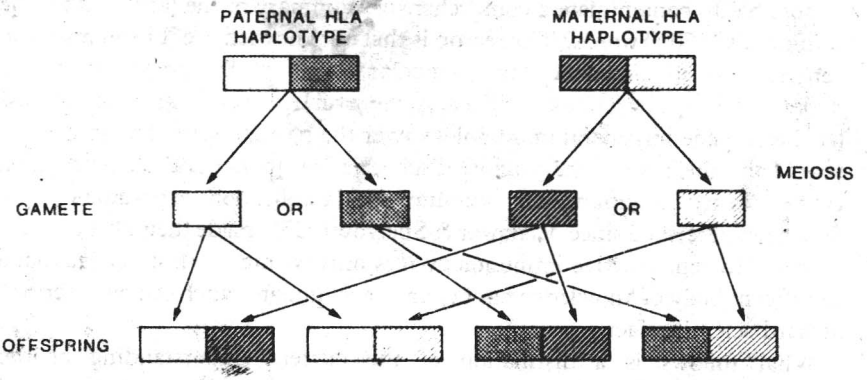

Fig. 1.1 The inheritance of HLA gene combinations (haplotypes)

4. Each haplotype contains genetic contributions from the four main loci. During human development the polypeptide structure of the genes has diversified to the extent that in any one individual each locus contains two of a large number of alternative genes (*alleles*), more of which are constantly being discovered. The end result of this diversity or *polymorphism* is that the number of possible haplotypes is over 1700 with close to 10^6 genotypes. The likelihood of any one unrelated individual being HLA identical to another is, therefore, remote.
5. Each genetic locus codes for the production of glycoproteins which have important functions in the initiation and control of immune mechanisms which are discussed below. The glycoproteins produced by the HLA-A, -B and -C loci are called Class I major histocompatibility antigens: those produced by HLA-D are Class II major histocompatibility antigens. Class I antigens are expressed on the surface of most cells. Class II antigens are only found on certain immunologically active cells. The importance of this difference will become apparent later.

The biochemical structure of these gene products has only begun to become apparent (Peterson et al 1983) and a stylised version of current understanding is shown in Fig. 1.2.

It is becoming increasingly clear that the structure of these antigens is integral to their function which is basic to immunological reactions. It is through the balance of similarities and differences between them that these MHC gene products exert influences which initiate, control, amplify and suppress the immune response at a cellular level.

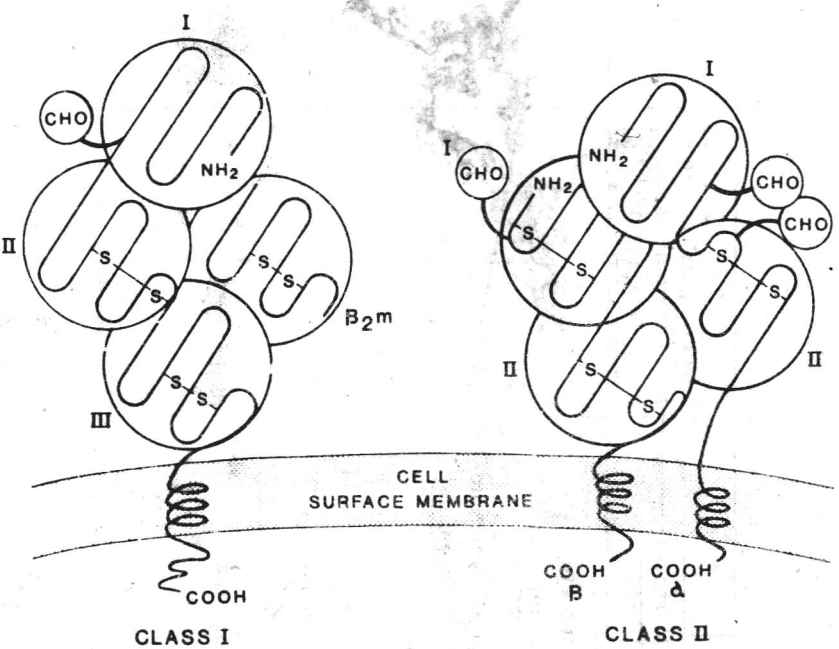

Fig. 1.2 Structure of Class I and II MHC antigens. Class I antigens consist of three convoluted protein chains (or domains), a transmembrane region and a cytoplasmic tail. Another protein β_2 microglobulin is always bound to domain III. Class III antigens have two close but unbound chains (α & β), each of which has two extracellular domains, transmembrane segments and short cytoplasmic tail. The second domain of Class II, and one third domain of Class I are biochemically similar to one another and do become part of the immunoglobulin molecule

Cells of the immune response (Fig. 1.3)

The most important cells of the immune response are *lymphocytes*. Although lymphocytes look similar, they divide functionally into several different populations. The two major types are:

1. B cells, precursors of the plasma cells which secrete specific antibodies
2. T cells, the orchestrators and drivers of the immune response. Among the most important sub-populations of T cells are those which help B

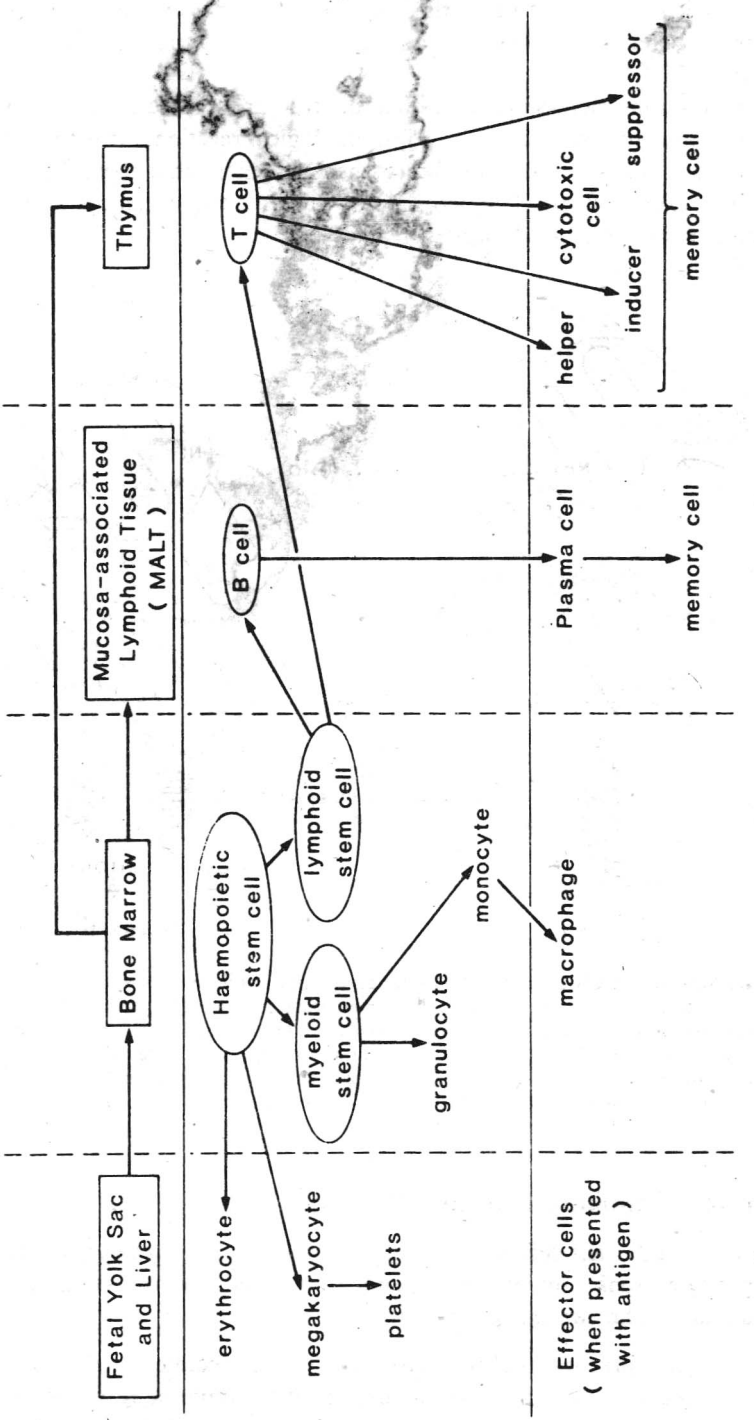

Fig. 1.3 Cells of the immune response

cells to produce antibody (helper T cells), those which kill foreign cells (cytotoxic T cells), those which keep immune reaction within reasonable bounds (suppressor T cells), and those which induce the appropriate reaction in other T cells (inducer T cells).

Macrophages are also important immunologically because they both process antigens for presentation to lymphocytes and act as phagocytes once the battle is over.

Other lymphocyte-like mononuclear cells exist which are also relevant and to these has been given such names as K (for killer) and NK (for natural killer) cells.

Origins of immunologically active cells

Stem cells from which immunologically active cells will arise can be found within the fetal yolk sac within 4 weeks of fertilisation. As can be seen from Fig. 1.3, the bone marrow plays an important part in the maturation of these cells and is their most important source in later life.

A significant proportion of the bone marrow derived stem cells migrate to the thymus where they appear initially in the sub-capsular cortex. Most die within the cortex but about 15% migrate successfully to the medulla where they mature into functionally active T-cells. The amazing thymus is only active during growth and atrophies, with consequent loss of function, when adult stature is achieved. Indeed lymphoid cells processed by the thymus during embryonic and early developmental life may well make up the total T-cell population of the adult. It is while they are within the thymus that the lymphocytes are programmed to discriminate between self and non-self. The exact mechanism by which this is achieved is unknown but the fact that the supporting cells of the cortex and medulla express Class I and II MHC antigens respectively in high-density is probably highly relevant.

About 1% of the total lymphocyte population enters and leaves the thymus daily, moving on to populate the peripheral lymphoid tissue and the lymph-nodes in particular. Mature T-cells probably live as long as the host.

While maturing in the thymic medulla the T-cells develop a receptor for antigens. In those T-cells which are destined to have a cytotoxic or suppressor function, the antigen receptor bears a striking resemblance to Class I MHC antigen. Inducer and helper T-cells carry a receptor resembling Class II MHC antigens. This is integral to the way in which these cells recognise foreign antigens for they can only do so when the antigens are in a cell surface membrane which also contains a MHC molecule which they can recognise. Thus for a T-cell to induce an immune response either by acting on other T-cell populations or by helping B cells produce antibody, it must be able to recognise part of its own Class II MHC antigen make-up in the surface membrane of the foreign antigen. Likewise for an effector response by cytotoxic or suppressor T-cells, part of their own Class I MHC antigen composition must also be present