PROGRESS IN OBSTETRICS AND GYNAECOLOGY

Volume Seven

EDITED BY

JOHN STUDD

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Preface

I write this Preface to Volume 7 during the 40th anniversary of one of this country's great achievements, the National Health Service, at a time when its defects are being emphasized from all directions. Certainly there are problems. One that should concern all in training is the question of future career prospects. It is hard to understand the co-existence of long waiting lists and middle-aged trainees waiting for jobs. Although this career bottleneck is worse in surgery and medicine than in our own specialty, our record is no cause for congratulation and our failure to promote married women is a waste of great talent. This enigma of unemployed doctors and untreated patients is even more incomprehensible because the UK has fewer doctors per unit population than any European country except Turkey. The response to this are plans to reduce the number of medical students and also limit the number of specialists in training!

There are many deficiencies, such as nurses' pay and equipment expenditure, in the National Health Service but the fundamental cause of these manpower anomalies is the fact that overwhelming health demands are supported by too few consultants. The promise of consultant expansion over the years has been a cruel political deception and simply has not happened. A 1986 report from the Royal College of Surgeons quantified this deficiency in terms of numbers of consultant surgeons. The 12 per hundred thousand population of West Germany, 11 in Belgium and the USA, 6 in Holland compare well to the miserable 2 in the United Kingdom. It is difficult to obtain comparable figures for obstetrics and gynaecology but it would appear to me that the 3000 ACOG Fellows in New York State and the 850 in rural North Carolina are examples of how the 900 consultants in England and Wales is a hopelessly inadequate number to do the job. This deficiency is the result of medicine being poorly funded by a monopoly employer.

The prolonged, even excessive, training for consultants in the United Kingdom creates highly trained and competent individuals but the result of the financial restrictions is that too few consultants chase around doing too many things. They have to cope with a busy NHS practice embracing all areas of our specialty from oncology to endocrinology. They will also have extensive undergraduate and postgraduate teaching commitments, occasionally a research interest and frequently a large private practice. The disheartened 'juniors' wait in the wings for a consultant post to appear at the average age of 38—sometimes 42 in many surgical specialties. All this is bad for the quality of patient care and for the recruitment of talented graduates into hospital medicine. It is my belief that greater use of the private sector can ease many of these problems.

Funding for health care in this country is believed to be inadequate because it compares unfavourably with the total health care budget of other Western countries. Comparable OECD figures for 1985 (Table 1) which are the latest available show

Table 1. Health expenditure in 1985 as a percentage of GNP (Gross National Product)

	Public %	Private %	Total %
Canada	6.5	2.1	8.6
Denmark	5.2	1.0	6.2
France	6.7	2.7	9.4
Germany	6.3	1.8	8.1
Greece	4.1	0.1	4.2
Italy	6.2	1.2	7.4
Netherlands	6.6	1.7	8.3
Spain	4.3	1.7	6.0
Sweden	8.4	0.9	9.3
United Kingdom	5.2	0.7	5.9
United States	4.4	6.4	10.8
OECD average	5.7	1.7	7.4

that the 5.9% of gross national product spent in the UK is almost the lowest with the USA, spending 10.8% of GNP, being the highest. However, the deficit is nearly all explained by the size of the contributions from the private sector (Table 1). The UK private health care expenditure is 12% of total health care expenditure compared to 20% for the Netherlands, 22% for Germany, 29% for France and 59% for the United States. The OECD average is 22%. If we can make this up we can have a properly funded health service.

The private sector is at last expanding with new hospitals being built and staffed. All this is for the good, but it must not become the privileged layer of a two-tier medical system. The challenge of the times is to use the revenue and skills from the private sector to increase the number of consultants by producing more posts for trainees, more choice for the patients and thus maintain high medical standards. We must recognize that this can only happen with little extra cost to the exchequer as no government of whatever hue has ever chosen to adequately fund the NHS or create the number of consultant posts necessary.

I have previously written (*Progress in Obstetrics & Gynaecology*, Volume 7) of the way in which excellent clinical research occurs using private funds. The private sector can also be used to support the NHS if consultants with busy private practice commitments give up sessions in order to create new consultant posts. This is already happening and one can only hope that the trend accelerates allowing many new and virtually cost-free five to eight session consultant posts to be created. The income will be made up by research sessions or from the greater amount of private work that will be available.

Would not our major hospital departments be better off without the senior registrar logjam but with 10 committed half-time consultants rather than five nearly whole-time consultants? At the same time it will remove the brutalizing effect of a perceived professional failure on the families of decent, able senior registrars. Such a formula will not work for all specialties, in all parts of the country but it is an option that could be offered to a London surgeon even if not to a Tyneside perinatal paediatrician.

There is no doubt that British medical standards are under siege and being eroded by crude financial controls. Fortunately alternative resources are available to correct this. We must forget our prejudices and allow the vast clinical, research and employment potential of private funding to be exploited for the general benefit of the nation's health care.

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1989

J.S.

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PART TWO: GYNAECOLOGY

Human fetal allograft survival

INTRODUCTION

The question of human fetal allograft survival and growth in a potentially hostile immunological environment constitutes the greatest paradox of all the laws of tissue transplantation. Rejection of foreign tissue by a host is known to be an immunological phenomenon, yet the human fetal allograft has the unique opportunity (under normal circumstances) to grow and develop for a limited period of time, prior to delivery. This perfect symbiotic relationship between mother and fetus has been alluded to as 'Nature's allograft' and an understanding of this phenomenon would be of prime importance to our understanding about cancer and transplantation immunology in general. One of the first pioneers in this field—Medawar (1953)—proposed some interesting explanations as to the success of Nature's allograft, some of which are shown in Table 1.1.

Table 1.1 Theories for the survival of the fetal allograft

Antigenic immaturity of the conceptus
Immunologically privileged uterine site
Placental barrier theory
Blocking antibodies
Altered maternal cellular immunity

Before discussing some of these theories further, a brief description of the components and function of the immune system is necessary.

IMMUNE SYSTEM

In recent years, important advances have been made due to new sophisticated methodology. Most of these discoveries have been carried out on inbred strains of mice and the results have been applied to humans. Care must be exercised in extrapolating results obtained in mice to humans.

The function of the immune system is to recognize and inactivate pathogenic organisms and their products. This relies upon the ability of the immune system to discriminate between 'self' and 'non-self' by detecting the presence of antigens on cell surfaces. Individual cells display self antigens which are genetically predetermined and unique to that individual. Hence, when cells are transferred from one genetically dissimilar individual into another, a rejection reaction occurs. Tissues transferred between individuals from the same species are referred to as 'allografts'. Genetically identical individuals, such as inbred strains of mice or uniovular twins, can thus accept grafts between each other freely. In man, the genes controlling antigens which provoke strong rejection reactions are situated on the short arm of chromosome 6 and are located within a region called the major histocompatibility complex (MHC). Within this complex are at least four major subregions or subloci called HLA-A, -B, -C and -D (also DR). Since these antigens were first isolated on leucocytes, they are also referred to as human leucocyte antigens (HLAs).

The products encoded by the HLA-A, -B, -C loci are known as class I MHC antigens, and the -D antigens are class II MHC antigens. At each locus there are many different alternative genes or alleles, which results in considerable genetic diversity or polymorphism. The HLA genotype of an individual consists of two haplotypes. A haplotype is a set of genes which occupy a given chromosome and which are inherited en bloc, one set from each parent.

The class I genes determine strong transplantation antigens by eliciting the development of cytotoxic T lymphocytes and then by serving as targets for T cell mediated cytolysis in allogeneic immune responses. Class I antigens are found on practically all cells of the body, especially on lymphoid organs. They are not detectable on erythrocytes. The normal physiological role of class I antigens may be in protection against viral infection.

Class II antigens have a restricted tissue distribution, being found on macrophages, activated T cells and B cells. T cells are apparently unable to recognize free conventional antigen and instead recognize antigen in the context of self MHC molecule, which is usually HLA-DR. Thus, if a tissue lacked class II MHC antigens, it would not be directly immunogenic to T lymphocytes, although it would act as a target for cytotoxic T cells, assuming class I antigens were expressed.

SOLUBLE FACTORS

Interleukin-1

Interleukin-1 (IL-1) is a macrophage-derived hormone-like factor having a molecular weight of 12–16 000. It is a genetically unrestricted and immunologically non-specific factor that is active at low concentrations. Resting monocytes or macrophages produce little IL-1, but when activated can be made to do so. IL-1 acts as an augmenting second signal.

Interleukin-2

Interleukin-2 (IL-2) is produced in response to IL-1 stimulating lymphocyte activation (Smith 1980). IL-2 is a lymphokine with a molecular weight of 15 000, and like IL-1 is genetically unrestricted and active at low concentration. IL-2 plays a key role in cellular and humoral T cell dependent immune responses by stimulating the clonal expansion of T cells by binding to specific receptors on their cell surface (Watson & Moschizuki 1980). It is thought that the IL-2 producing cell is a helper cell with the OKT4+ phenotype and that the responding cell bearing the IL-2 receptor is from a different group of cells, namely cytotoxic and suppressor cells having the OKT8+ phenotype.

Interferon-gamma (IFN-γ)

IFN-γ appears to play a key role in the cascade of lymphokines produced during an immune response. IFN-γ is produced during an immune response by antigen-specific T cells and probably also by natural killer (NK) cells recruited by IL-2. IFN-γ is a 20–25 KDa glycoprotein often seen as a 50 KDa dimer, and is coded for by a single gene on the long arm of chromosome 12 in man. IFN-γ enhances the expression of class II antigens on various cell types such as macrophages, Langerhans' cells, endothelial cells and tumour cells. The position of IFN-γ in the immunoregulatory pathway is different to that of IL-1 or IL-2. As an inducer of HLA-DR expression on antigen-presenting cells, it forms part of a positive feedback loop whereby activated T cells produce IFN-γ, thus inducing more HLA-DR and an augmented capacity to present antigen.

Little is known about the role of interferons in pregnancy, although they are thought to have immunoregulatory effects. Suppression of antibody activity and enhanced suppressor cell activity have been noted (Johnson et al 1977a,b). From both animal (Djeu et al 1979) and human studies (Santoli et al 1978) it now appears that NK cell function is promoted by interferons. Bizhan et al (1978) studied the production of endogenous interferons by T cells and found that in the first trimester there were elevated plasma levels and increased leucocyte interferon production, and that in the second trimester these levels dropped but rose again in the third trimester.

Clinical correlations between interferon production and disease susceptibility, such as cytomegalovirus (CMV) infection are only speculative. Stagno et al (1975) were able to show decreased susceptibility to CMV during the first part of pregnancy when interferon levels are greatest.

T cell activation and regulation

It appears that T cell proliferation occurs following a cascade of carefully orchestrated events. The resting T cell encounters a foreign antigen which it recognizes by its specific receptor structure in association with histocompati-

bility antigens on the antigen-presenting cell, i.e. the macrophage. In order to recognize both antigens, it is suggested that either the T lymphocyte has two receptors, one for foreign antigen and one for MHC-encoded self antigen (dual recognition theory), or that there is only one receptor on the T cell recognizing foreign antigen complexed to self antigen (modified self theory). Either model is difficult to prove or disprove. Within 6–12 hours the IL-2 receptor is expressed and has a high binding affinity to IL-2. In the second stage of the T cell response the same antigen stimulates the production of IL-2 predominantly by the T helper cell population. Since highly purified T lymphocytes free of macrophage contamination will respond to a T cell mitogen by expressing IL-2 receptors, but do not produce IL-2, it is generally assumed that macrophages or IL-1 are necessary for IL-2 production. Once IL-2 is produced it binds to the IL-2 receptor and DNA and cell mitosis occurs. In the absence of continued antigenic stimulation, there is re-expression of the surface T cell receptor and a reciprocal reduction of IL-2 receptors. This model of T cell proliferation was initially proposed by Meuer et al (1984). It does not necessarily follow that all T cells produce and respond to their own IL-2 (Fig. 1.1). In fact, failure of certain cells to proliferate to antigen

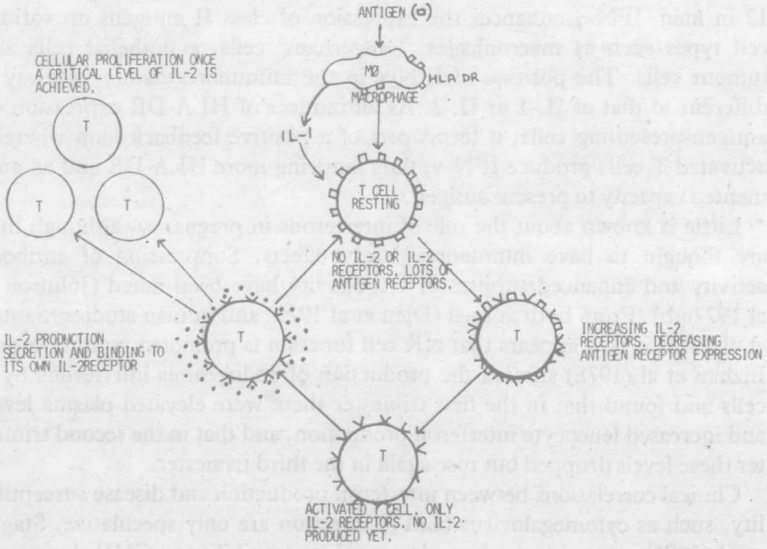

Fig. 1.1 Schematic representation of cellular activation

may occur as a result of their inability to produce sufficient IL-2, even though they may be triggered to express IL-2 receptors. The question of whether IL-2 receptor expression occurs on other cells, i.e. B and NK cells, has yet to be clearly answered. Certainly B cells taken from individuals with

hairy cell leukaemias have been reported to express the receptor for IL-2 as defined by Tac antigen (Korsmeyer et al 1983).

FETAL ANTIGENICITY

The human conceptus is not antigenically immature for several reasons. The fertilized ovum is known to express both minor and major transplantation antigens very early on in embryogenesis (Seigler & Metzgar 1970). There is also strong evidence that the fetus plays an active role in its own protection by developing suppressor cells with functional activity by the eighth week of gestation (Unander & Olding 1981). Strong suppressor activity is one way that fetal lymphocytes are able to respond to the transplacental passage of maternal lymphocytes (Olding 1979). In vitro studies have shown that fetal lymphocytes can release soluble factors that inhibit both mixed lymphocyte reactivity and phytohaemagglutinin (PHA) response to adult lymphocytes (Olding et al 1977). Furthermore, as reported by Jacoby et al (1984), the identity of these factors is thought to be prostaglandins of the E series (namely PGE_1 and PGE_2 (Johnsen and Olding, unpublished observations).

PRIVILEGED UTERINE SITE

There are specialized sites in the body, such as the brain and anterior chamber of the eye, which display immunological privilege to transplanted tissues. The explanation is said to be due to the relative lack of lymphatic drainage in that region, thus delaying recognition of foreign antigen and subsequent attack (Billingham 1964). Current evidence indicates that the uterus is not immunologically privileged because it is adequately drained by pelvic and para-aortic lymph nodes (Park 1971). Tumour allograft transplanted into the uterine horn of pregnant, non-pregnant and pseudo-pregnant female rats are quickly rejected (Schlesinger 1962). Beer and Billingham (1974a) also demonstrated that allogeneic skin grafts, leucocytes or lymph node cells placed into the uterine lumen sensitized the host into rejecting a subsequent skin graft. There is evidence that decidualized tissue in the uterus may confer a weak protective effect on the efferent arc of the immune response, since skin allografts placed in the decidualized uterine bed survive for longer (Beer & Billingham 1974b), but the decidua alone are not sufficient to prevent rejection of intra-uterine grafts in presensitized hosts. Thus the uterus does not seem to be protected from participation in immune reactions.

PLACENTAL BARRIER THEORY

Since the placenta represents the interface between mother and fetus, the question of whether HLA antigen is expressed on the outermost layer, i.e. the syncytiotrophoblast, is very important. Numerous research groups claim

that class I and II antigenic expression is normal (Loke et al 1971, Lawler et al 1974, Doughty & Gelsthorpe 1976), whilst others have not been able to demonstrate any MHC expression (Faulk et al 1977, Sundqvist et al 1977). Inevitably there are some (Goodfellow et al 1976), who have taken a middle-of-the-road view by demonstrating low levels of antigens on the placental surface. The overall evidence seems to suggest that HLA antigen expression is probably absent or sparse on the human syncytiotrophoblast. Therefore, the conceptus is not analogous to an allograft in the context of MHC expression across this barrier. There is evidence that class II MHC antigen expression by antigen-presenting cells is inhibited by factors in human retroplacental serum. The mechanism is thought to be mediated by a sugar–sugar interaction between the carbohydrate moiety of the DR antigen and the serum inhibitory factor, causing masking of DR antigen presentation and thus immune non-reactivity (Nicholas et al 1986). Although HLA expression is absent, the trophoblast does express other allo-antigenic systems. There are at least 50 proteins on the trophoblast surface, which makes the answer to the question as to which of these is immunologically relevant very difficult (Faulk & Johnston 1977). Faulk et al (1978) have used serologically defined antigens raised in rabbits to identify trophoblast-specific minor histocompatibility antigens named TA_1 and TA_2 from trophoblast cell cultures, which are collectively called the TLX system (trophoblast lymphocyte cross-reacting antigens). TA_1 antigens are shared by trophoblasts and human cultured cell lines (HeLa and human amnion cells), whilst TA_2 antigens are shared by placental blood vessel endothelium and peripheral monocytes. It is suggested that the gene(s) responsible for the production of TLX antigens is (are) situated on chromosome 1.

The hypothesis is that during normal human pregnancy the maternal immune system recognizes the TA_2 antigen by producing anti-TA_2 antibodies, and thus there is non-recognition of TA_1. If TA_2 is not recognized, this may lead to recognition of TA_1 and subsequent termination of pregnancy, or it may lead to abnormal pregnancy. In vitro studies by Faulk have shown that TA_2 and anti-TA_2 antibodies are able to inhibit the MLR (mixed lymphocyte reaction) of maternal lymphocytes and allogeneic stimulator cells. In addition, these antibodies are both trophoblast- and species-specific (Faulk et al 1978). Faulk and McIntyre (1985) further suggest that sharing of TLX antigens between couples may lead to failed pregnancy, thus having similar functions to the transplantation antigens. Natural selection would favour HLA–TLX incompatible mating, thus perpetuating genetic diversity among the species.

SERUM BLOCKING FACTORS

Hellstrom et al (1969) described a shielding role for blocking antibodies in protecting antigenic tumour cells from sensitized lymphoid cells of the host. Similarly, anti-paternal antibodies may serve as blocking factors by binding

to the placental trophoblast, thereby protecting the fetus from maternal cellular attack.

Chaouat et al (1979) have been able to elute these antibodies that could enhance the growth of tumour allografts of the paternal strain from the placenta (Fig. 1.2). These antibodies have been characterized as IgG, based on

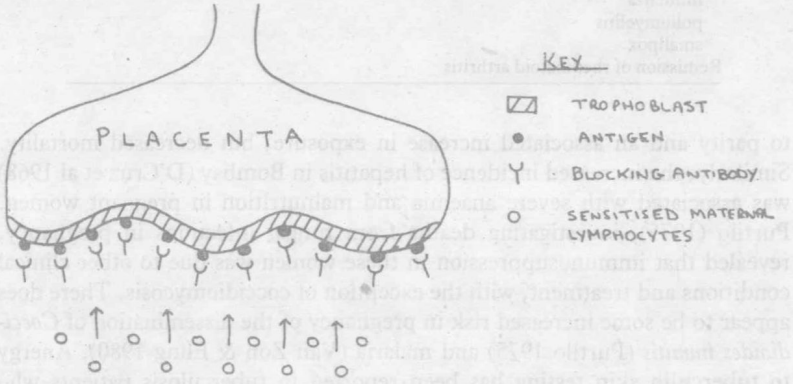

Fig. 1.2 Possible mechanisms of trophoblast (fetal) survival

their electrophoretic mobility and their removal of inhibitory activity after passage of maternal sera over an anti-IgG affinity column (Rocklin et al 1976). Furthermore, absorption of these antibodies in maternal sera by paternal cells, and not pooled human platelets, suggests that they are directed mainly against class II MHC products of fetal tissues (Rocklin et al 1979). Women who recurrently abort have been shown to share HLA identity with their partners more commonly than would be expected (Rocklin et al 1976, Taylor & Faulk 1981). As a result of this tissue compatibility between mother and fetus, these women do not produce blocking antibodies (Stimson et al 1979). There is, however, evidence against this hypothesis, namely (1) anti-HLA-DR antibodies are not detectable in all normal pregnancies, and when they are found they occur late in pregnancy (Terasaki et al 1970), (2) it is difficult to reconcile how anti-HLA-DR antibodies can have such influence in early pregnancy when HLA-DR antigens are not expressed on placental tissues at that time (Faulk & Temple 1976), and (3) agammaglobulinaemic females have been reported to have normal pregnancies (Holland & Holland 1966).

MATERNAL IMMUNOCOMPETENCE

The in vivo evidence for depressed maternal cell-mediated immunity is by no means accepted (Table 1.2). It has been suggested that the incidence of certain bacterial and viral infections is increased during pregnancy. The balance of evidence suggests, however, that this is not the case. Siegel and Greenberg (1955) showed an increased incidence of poliomyelitis attributable