INTRODUCTION
In outbred species, the fetus is semiallogeneic to the mother; indeed the antigenic composition is different for each conceptus. Yet, the fetus manages not only to survive, but to thrive quite well in the face of a potentially hostile maternal immune system. After four decades of research, the precise nature of immunoregulatory events responsible for the success of the fetal allograft are far from clear. However, much evidence has been gathered to show that immunological mechanisms play key roles in the success or failure of pregnancy. In 1953, Medawar [1] proposed a paradigm to explain the survival of the fetal allograft. Many of the theories of this paradigm are not valid now as evinced by experimentation; but they do provide us an excellent framework for exploring, by observation and experimentation, the mechanisms preventing fetal rejection.

It has been convincingly demonstrated that the uterus is not a immunologically privileged site; it is capable of eliciting normal immune responses against allografts, although the presence of the decidua and/or gestational hormones may retard the process. What then protects the fetus from maternal immune effectors in the uterus? The crucial anatomic positioning of the trophoblast at the maternal-fetal interface together with the fact that it is the only fetal tissue which is in direct and continuous contact with maternal blood makes it a potential target for graft rejection. The ability of the trophoblast to survive the conditions of allograft rejection was initially attributed to a supposed lack of antigenicity. However, direct investigations into the antigenicity of the trophoblast have resulted in the firm consensus that the trophoblast expresses paternally-derived MHC antigens, oncofetal antigens and tissue specific antigens [2,3]. Furthermore, it has been demonstrated that these antigens are accessible to maternal circulation and
can induce alloantibody formation during normal pregnancy [4,5]. This then poses the question of whether these maternal anti-paternal antibodies can traverse the placenta and harm the fetus.

Swinburne [6] first proposed the idea that the placenta could act as a specific antibody-binding "sponge", expressing target antigens which bind circulating maternal antibody. Empirical evidence for the existence of a barrier was obtained when the offspring of multiparous, transfused, or grafted females with circulating antibodies developed no abnormalities during subsequent pregnancies [7,8]. Paternal antigens on the placenta confer on it an immunoabsorbent capability, obstructing the passage of potentially deleterious antibodies to the fetus [9]. Thus, the placenta acts as an immunologic barrier shielding the fetus from deleterious maternal reactions.

It is interesting to note that while maternal recognition of the conceptus results in a variety of antibody responses, deleterious cell-mediated immunity is generally not generated. There is occasional induction of maternal anti-paternal cytotoxic effectors at the feto-maternal interface in normal pregnancy. This suggests that active immunosuppression in the vicinity of the feto-placental unit may prevent sensitisation of the maternal immune system by fetal alloantigens and the development of subsequent effector functions. Systemic suppression is not a common feature of pregnancy, but local active, cell-mediated suppression seems to be an essential concomitant of successful pregnancy. In this context, it has been reported that both decidual and trophoblastic components of the placenta secrete or contain immunosuppressive substances [10,11]. Moreover the existence of decidual suppressor cells capable of impairing lytic effector functions have
been demonstrated [12].

Interestingly, it has been observed that induction of maternal anti-paternal cytotoxic T lymphocytes by allovaccination does not affect the survival of the fetus [13]. Furthermore, not only is the fetus unharmed but, in fact in such a preimmunized mother, the mean litter size and placental weight were higher than in unimmunised ones. Moreover, in mice, the litter size in allogeneic matings far exceeds those in syngeneic matings. This suggests that maternal recognition of fetally-derived antigens may actually be beneficial to fetal survival. The immunotrophism model [14] suggests that maternal recognition of fetally-derived antigens leads to the activation of maternal T cells and the subsequent release of cytokines promoting the growth and functioning of the placenta and in turn the survival and growth of the fetus.

It appears that local immunosuppressive and immunostimulatory events cooperate beneficially in fetomaternal co-existence, a failure of this equilibrium may result in embryonic demise and abortion. Thus, successful pregnancy appears to be a delicate balance between over- and under-responsiveness of the maternal immune system.

Given this background, this study was undertaken with the objective of elucidating the plausible role of immunotrophism in pregnancy. Working on the human system poses inherent problems, therefore the use of animal models to study the effect of immune manipulations or immunostimulation has become of increasing significance. The availability of murine models of immunologically-mediated spontaneous resorptions has provided scope for investigating interactions between the maternal immune system, lymphoid
cells and cytokines on the one hand and the feto-placental unit on the other. The conclusion that the increased rate of resorption in these mice is immunologically-mediated comes from findings that a) there is infiltration of leukocytes into the decidua before the onset of fetal resorptions. b) immunisation of resorption-prone mice with third party lymphocytes prior to mating reduces the resorption rate and c) this protective effect can be adoptively transferred to virgin mice by sensitised T-cells.

Even though these models have been available for a few years, the mechanistic basis of the immunological damage and the puzzling question of why these particular strain combinations are susceptible to immunologically-mediated resorptions remains unanswered.

The first part of this thesis, deals with elucidating the roles of immunostimulation within the context of the immunotrophism model in these models of immunologically-mediated resorptions. Our work demonstrates that mixed lymphocyte reactions (MLR), were substantially higher when maternal strain cells were stimulated with lymphocytes from the male partner of the normal combination than when stimulated with lymphocytes taken from the male partner of the abortion-prone combination. We also conducted mixed lymphocyte-placenta reactions (MLPR) between maternal strain lymph node cells and irradiated placental cells; placental cells of the "normal" combinations stimulated maternal strain lymph node cells to a significantly higher extent than did placentas from the abortion-prone strain combinations.

The key mediators in the immunotrophism model being cytokines, we undertook the analyses of cytokine profiles of the MLPR supernatants. The
results indicate that the levels of the cytokines TNFα, IFNγ and IL-2 were significantly higher in MLPR supernatants from the abortion-prone combinations than in the MLPR supernatants from normal combinations.

We also establish that MLPR-stimulated cells have relevance to the outcome of pregnancy. We find that the injection of MLPR-activated cells from abortion-prone combinations results in an increase in the resorption rate significantly, whereas the injection of MLPR-activated cells from normal combinations do not have any effect.

The second part of this thesis, deals with establishing whether cytokines (IL-2, TNFα, IFNγ) exist at the materno-fetal interface. Our studies using hybridisation techniques indicate that the expression of IL-2, TNFα and IFNγ is higher on the placentas from the abortion-prone mating combination as compared to their levels on placenta obtained from normal mating combinations.

In summary, this study was aimed at providing important clues into the mechanistic basis of spontaneous abortions in the CBAxDBA/2 murine model of immunologically-mediated spontaneous abortion.