INTRODUCTION
In a genetically outbred population such as humans, there exists considerable histoincompatibility between mating partners. This results in the fetus being semi-allogeneic to the mother. The survival of the semi-allogeneic fetus in a potentially hostile maternal environment appears to contradict the laws of transplantation since as a rule, only syngeneic grafts survive while allogeneic grafts are rejected. The manner in which the fetal allograft survives, and in fact thrives, in the mother during gestation has been a subject of intense investigation. After nearly three decades of research, the precise nature and extent of the various immunological mechanisms responsible for the paradoxical success of the feto-placental unit are still far from clear. However, a large body of evidence suggests that a complex set of immunoregulatory mechanisms at the vicinity of the feto-placental unit beneficially regulate maternal immunity to aid fetal survival. In 1953, Medawar [1] for the first time proposed some ingenious explanations for the success of the fetal allograft. Some of these theories have been disproved by experimentation but they have provided an excellent framework for elucidating the mechanisms of fetal survival.

It has been definitively demonstrated that the uterus is capable of eliciting a normal immune response against allografts and is not a classical immunologically privileged site [2]. What then protects the fetus in utero from maternal immune effectors? The success of pregnancy has been attributed primarily to the physical and immunological capabilities of the placental tissue. The placenta comprises of two components: fetal trophoblastic tissue and maternal decidual tissue. The trophoblast rather than the fetus per se is the intrauterine allograft in pregnancy since it is the foreign tissue in direct and continuous contact with maternal tissues. The ability of the trophoblast to survive conditions of allograft rejection was initially attributed to its non-
antigenic status. However, it has been shown that the trophoblast expresses paternally-derived MHC antigens, tissue specific antigens and oncofetal antigens [3-8]. Furthermore, these potentially foreign antigens are readily accessible to the maternal immune system and can lead to alloantibody formation during normal pregnancy [9-11]. The question then arises: Can fetal anti-paternal antibodies traverse the placenta to harm the fetus?

It is known that beneficial maternal antibodies are transported across the placenta and are essential for conferring immunity to the fetus against a variety of infections [12]. How then are potentially harmful antibodies prevented from harming the fetus? Paternal alloantigens on the placenta confer on it an immunoabsorbent capability, by virtue of which the placenta functions as an immunological filter, obstructing the passage of potentially deleterious antibodies to the fetus [4,13-15]. Thus, the placenta acts as an immunological barrier shielding the fetus from deleterious maternal reactions.

A particularly important point to be noted is that while maternal recognition of the conceptus results in a variety of antibody responses, deleterious cell-mediated immunity is generally not generated. There is only occasional, if any, induction of specific maternal antipaternal cytotoxic effectors at the fetomaternal interface in normal pregnancy [16]. This suggests that active immunosuppression operative in the vicinity of the feto-placental unit may prevent sensitization of the maternal immune system by fetal alloantigens and the development of subsequent effector functions. Evidence suggests that both the decidual and trophoblastic components of the placenta may elaborate a range of soluble suppressor factors and cells that effectively
block effector and/or effector limbs of anti-fetal immune reactions \textit{in utero} [17-20].

Interestingly, even deliberate induction of maternal anti-paternal cytotoxic T lymphocytes by alloimmunization does not adversely affect the survival of the feto-placental unit [21,22]. Furthermore, in mice, litter size in allogeneic matings far exceeds those in syngeneic matings [23]. This suggests that maternal recognition of fetally derived antigens may actually be beneficial to fetal survival. The immunotrophism model suggests that maternal immune recognition of fetally-derived antigens leads to the activation of maternal T cells and subsequent release of cytokines promoting the growth of placental tissue, which in turn provides an efficient barrier for the fetus from harmful maternal immune reactions [24,25].

However, immunosuppression and immunotrophism may not be mutually exclusive but appear to act synergistically to allow fetal survival. Thus, successful pregnancy appears to be a delicate balance between over- and under-responsiveness of the maternal immune system.

Given this scenario, this study was undertaken to elucidate immunosuppressive activities mediated by placental suppressor factors. While human trophoblast cultures constitute the ideal test system for the study of placental function, working with human placental tissue is often cumbersome. Human choriocarcinoma cell lines which are of trophoblastic origin are convenient experimental model systems for the analysis of immunological capabilities of the placenta. Choriocarcinoma cell lines are used as models of normal human trophoblast because they have retained several characteristics of the placenta: (i) they are homogeneous trophoblast...
cell lines uncontaminated by other cellular constituents, (ii) their invasive capabilities and cell surface antigen profiles are similar to those of early normal human trophoblast and (iii) they secrete several placental proteins and hormones [26].

While the capabilities of supernatants from human choriocarcinoma cell lines (HCS) to inhibit mitogen-induced proliferation of lymphocytes has been reported earlier [27,28], the effects of HCS on other in vitro and in vivo proliferative responses of lymphocytes have not been reported. Little is also known about the nature and mechanism(s) of action of the HCS-derived immunosuppressive factor(s).

The first part of this thesis, describes the effects of HCS on proliferative responses of lymphocytes in vitro and in vivo. HCS mediates profound inhibition of mitogen-induced lymphocyte proliferation, mixed lymphocyte reactions and antigen-induced proliferation in the human and murine systems. In this study, we have demonstrated for the first time the suppressive capability of HCS in vivo. HCS administered in vivo effectively blocks allogeneic responses in mice. The in vivo efficacy of HCS is further emphasized since it effectively blocks both local as well as systemic graft versus host reactions in mice. However, the constitutive proliferation of, and antibody secretion by B cell hybridomas and in vivo antibody production in mice primed to antigens remain unaffected in the presence of HCS.

The possibility that the inhibitory effects of HCS are due to its toxic effects on cells has been clearly ruled out. That HCS is not merely cytolytic but truly immunosuppressive is further emphasized by the observation that the
constitutive proliferation of murine and human lymphoma cell lines is
unaffected by HCS.

The second part of this thesis focuses on elucidating the plausible
mechanism(s) of HCS-mediated immunosuppression. HCS injected
intraperitoneally into mice appears to induce suppressor cells which in
tum prevent the mounting of an allogeneic response in other mice.

While the phenomenology of trophoblast-mediated suppression has been
documented even earlier, little is known about the nature of the
immunosuppressive molecules involved. The major thrust of this work has
been to characterize the HCS-derived immunosuppressive factor (HCSf).
Purification of HCSf has been accomplished by HPLC and FPLC.
Fractionation of HCS on anion-exchange column followed by gel
filtration suggested that the immunosuppressive capability of HCS is associated with
a peak eluting at 70-74 kDa. However, further purification by reverse phase
chromatography under acidic conditions revealed HCSf to be a highly
hydrophilic low molecular weight compound which in tissue culture medium
containing fetal calf serum appears bound to the 67 kDa bovine serum
albumin. Data on biochemical characterization of HCSf is presented in the
last part of this thesis. Correlations between HCSf, placentally-derived
immunosuppressive factors and other immunosuppressive factors at the
vicinity of the feto-placental unit are discussed.

In summary, this study demonstrates the in vivo capabilities of placental
suppressor factors and has led to the characterization of one such factor.
Local immunosuppression may play key roles in pregnancy. While the
ultimate evidence for actual physiological roles for such factors will have to
await direct studies on their indispensability in pregnancy, studies such as this shed light on the interaction of immunosuppressive factors with maternal lymphocytes at the feto-maternal interface and their role in supporting the fetal allograft.