The studies reported in this thesis were designed to assess the ability of mycobacterium and leishmania infected macrophages to provide help to CD4+T cells. These studies have revealed some very interesting findings regarding the pathogenesis of these organisms.

The following facts have emerged from the studies :

The most important immunopathological consequence of mycobacterial and leishmanial infection is the suppression of T cell-mediated immune response to both mitogens and related antigens. It was registered that there was decreased Con A induced spleen cell proliferation in infected susceptible BALB/c mice as compared to the normal mice. In resistant mice, infection with these pathogens did not induce any suppression in the mitogen induced lymphoproliferation. Likewise, delayed-type hypersensitivity (DTH) response, to limpet hemocyanin (KLH) and crude soluble antigens (CSA) was suppressed in infected BALB/c mice but not in resistant mice to these pathogens. The observed depression in the function of T helper cells may either be due to (I) defective T cell receptor occupancy by antigen-Ia complex or (II) inability of infected cells to provide optimum level of co-stimulatory signals. In past, considerable efforts have been made to understand antigen processing and presentation by infected macrophages. However, no literature was available regarding the status of co-stimulatory molecules expressed on the infected macrophages. Therefore, the status of certain co-stimulatory molecules was investigated on the tuberculosis and leishmania infected macrophages derived from both susceptible and resistant mice. The results demonstrated that upon mycobacterial and leishmanial infections, the macrophages were rendered incapable of delivering the co-stimulatory signals to T helper cells, possibly due to the involvement of prostaglandin, as inhibition of its biosynthesis by indomethacin reversed the defect. Furthermore, the selective regulation was pathogen induced as killing of the bacteria and parasites by refampicin and stibogluconate abrogated the derangements in the expression of co-stimulatory molecules on the infected macrophages. The observations described in this thesis revealed that upon infection with *Mycobacterium tuberculosis* and *Leishmania donovani*. B7-1 was down regulated while the expression of ICAM-1 increased only in BALB/c but not in the resistant strains of these pathogens. Expression of VCAM-1 did not change during the infection in either

strains of mice. It was found that these changes in ICAM-1 and B7-1 expression on the surface of infected macrophages resulted in inhibition of DTH-mediating functions of T helper cells from infected BALB/c mice. The result obtained in this study describe not only a novel immune evasion strategy adopted by *Mycobacterium* and *Leishmania*, but also open up the possibility of immunotherapy of these infections by selective manipulation of co-stimulatory molecules.

Optimum activation of T cells require not only TcR occupancy but also a second set of signals called as co-stimulatory signals. Moreover, cross linking of TcR in absence of second signals, leads to anergy and apoptosis in T cells. Therefore, experiments were also designed to understand whether loss of T cells by apoptosis and activation induced cell death could be a possible cause for the observed suppression of cell mediated host immune response during infection of these pathogens.
These results demonstrated that unlike T cells derived from resistant mice, T cells from susceptible BALB/c mice showed unresponsiveness and apoptosis. Further, these T cells failed to respond to Con A and also to cross linking of TcR alongwith second signal in the form of PMA, rather they go for inactivation and apoptosis. In contrast, T cells response from resistant strains of tuberculosis and leishmania infected mice responded to these signals was similar to the normal mice.

It may be mentioned here that successful elimination of both *Mycobacterium* and *Leishmania* requires the generation of Th1 like response. Activated Th1 cells, secrete IFN-γ and IL-2 which inturn activate macrophages and cytotoxic T cells, necessary for the elimination of the pathogens.

While considering findings and also earlier observations, that in susceptible host, these pathogens engineer massive apoptosis of both : the antigen specific and also irrelevant cells, a question may arise whether apoptosis is restricted to all the type of Th cells or to a particular subtype of T cells. On examination, it was found that in contrast to the T cells derived from uninfected normal BALB/c, T cells from infected susceptible mice produce very little IL-2 and IFN-γ on activation. However, there was no marked change in the levels of IL-4 suggesting thereby that consequence of mycobacterial and leishmanial infection leads to the selective inactivation to the Th1 like response.

How, at mechanistic level these infections cause inactivation of IL-2 and IFN-γ secreting cells but not of IL-4 producing cells? To answer this question precisely, one probably needs to look for the regulation of co-stimulatory molecules which are concerned with either generation of Th1 or Th2 type of responses. In this regard, it may be mentioned here that my lab has recently identified a macrophage membrane associated co-stimulatory molecule which signals antigen specific Th cells to secrete lymphokines representing the Th1 type of response. In the last chapters, evidences have been provided that both these pathogens manipulate the expression of a Th1 specific co-stimulatory molecule M150. It has also been demonstrated that these pathogens induce anergy and apoptosis in T cells, with a bias towards Th1 cells, which can be corrected *in vitro* by allowing T cells to be signaled by infected macrophages and exogenous M150. In a nutshell, the data presented in this thesis for the first time demonstrate the existence of parasite engineered down regulation of co-stimulatory molecules on the infected host cells. By doing so, the pathogen ensures that interaction between infected macrophages and T cells, instead of resulting in clonal amplification, leads to anergy and apoptosis of protective T cells.