INTRODUCTION
The principal aim of this work was to gain significant insights into immunogenetic influences on immune responses to the GnRH vaccine and into optimal and rational designing of this vaccine. An important consideration in the development of any vaccine is the immunogenetics of responses to the immunogen. An ideal vaccine should elicit a response high enough to carry out the expected function in all individuals immunized, irrespective of the genetic background of the individual. Anti-fertility vaccines principally aim at counteracting a self protein or hormone critical to the success of reproduction. One such vaccine developed at the N.I.I. and initially explored as a candidate uses a highly conserved decapeptide hormone, the gonadotropin releasing hormone (GnRH) as the immunogen. Since GnRH is a hapten, it has to be linked to carrier proteins in order to render it immunogenic. Immunization of rats and monkeys with GnRH linked to carriers such as diphtheria toxoid (DT) or tetanus toxoid (TT) results in a marked atrophy of the prostate. This vaccine is now being explored for its potential in non-surgical immunotherapy of prostatic hypertrophy in men and is currently undergoing Phase I/II clinical trials.

The first part of the work described in this thesis deals with investigating the influence of the genetic background of immunized mice on the antibody response
to GnRH conjugated to DT (GnRH-DT). Mice of different strains were injected with GnRH-DT, and the antibody levels against GnRH and DT quantitated. All immunized animals produced antibodies to DT. Anti-GnRH antibodies were generated by all strains of mice except 129. The low anti-GnRH response in the "129" mice did not appear to be MHC-linked because C57BL/6 as well as B10 mice, both of which bear the same MHC haplotype as 129 mice, were able to generate a strong anti-GnRH response. The hyporesponsiveness to the hapten (GnRH) in 129 mice was overcome by the use of an "alternate" carrier approach. Immunization of GnRH-DT-immunized 129 mice with GnRH linked to an alternate carrier, TT, (GnRH-TT) resulted in the production of high levels of anti-GnRH antibodies. This showed that 129 mice are not deficient in GnRH-specific B cells and that the lack of response to GnRH in 129 mice is possibly due to (i) the lack of appropriate helper T cells, or (ii) the presence of suppressor cells. Further experiments provided evidence to support the existence of suppressor cells in GnRH-DT-immunized 129 mice by adoptive transfer experiments.

The second aspect of this study involved the assessment of carrier-induced suppression of immune responses to GnRH in the GnRH-DT/TT hapten-carrier system. We observed that pre-existing immunity to the carrier molecule had an inhibitory effect on the antibody
response to GnRH linked to the same carrier molecule. We show that preimmunization with carriers DT and TT results in a strain-dependent inhibition of anti-GnRH responses in mice. Results of adoptive transfer experiments indicate that T cells from carrier-presensitized mice are responsible for anti-haptenic suppression and that T cells from conjugate immunized mice, on the other hand, can actually help overcome hyporesponsiveness.

Epitope-specific regulatory effects have been attributed by some workers to suppressor T cells, and by others to antigenic competition or clonal dominance of carrier-specific B cells. Whatever be the case, we speculated that epitope-specific suppression could be bypassed or circumvented by the use of a synthetic T helper epitope from DT, as carrier. We therefore focussed attention on the development of a strategy to circumvent the inhibitory effect brought about by the pre-existing immunity to the carrier. Furthermore, because this vaccine is eventually intended for humans where one aims for a universal response, the use of a "universal" T cell epitope as a carrier would be ideal. We identified a helper T cell epitope from DT which induces a proliferative response in three out of three strains of mice tested. When this peptide was conjugated to GnRH and injected into DT presensitized mice, it was found that DT-induced suppression can indeed be circumvented.
The conventional dogma that carrier molecules have to necessarily be "large" molecules is being disproved by several laboratories; in this context, the final part of this thesis discusses the use of short synthetic peptides from tetanus toxin and malarial circumsporozoite protein as carriers for the GnRH hapten.

In summary, the studies described in this thesis contribute to optimizing and improving on hapten-carrier conjugate vaccines. These studies also pave the way for totally synthetic B cell determinant-plus-T cell epitope vaccines.