Approximately 20% of all conceptions end in detectable spontaneous abortion. Recurrent abortion is a common and important clinical problem affecting approximately 1 in 300 pregnancies (14). The risks for recurrent abortion have been calculated by Warburton and Frazier (54) to be 24% after one abortion, 26% after two abortions, and 32% after three consecutive pregnancy losses before 20 weeks gestation. Many instances of recurrent spontaneous abortion have identifiable etiologies such as chromosomal (5), mullerian (38), endocrinological (26,55), and infectious (12,29) abnormalities. However, recurrent abortion was unexplained in as many as 40% of couples studied (52). An immunologic etiology is suspected in women with subclinical autoimmune disease such as systemic lupus erythematosus, who have an increased incidence of otherwise unexplained recurrent abortion (11,13,15,39). The transplacental passage of maternal immunoglobulins that are cytotoxic to trophoblastic or fetal tissue is presumed to be a pathologic mechanism for abortion in such cases (32). Recurrent abortion is also associated with immunity to allogenic (husband’s) lymphocytes, sperm, and trophoblast antigens (3,25,33). Our current evidence indicates that the mechanisms of immunologic abortion in women may not only be antibody mediated (humoral response) but could also be cellularly mediated (cellular response) due to cytotoxic effects of lymphokines and monokines released by reproductive antigen (sperm and/or trophoblast) or other foreign (i.e., microbial) antigen-sensitized lymphocytes and macrophages in reproductive tissues.

Our understanding of the interactions between the immune and reproductive systems is rudimentary. Accumulating evidence, however, suggests that the fetal-placental allograft is afforded protection by local immunomodulating factors (8), and that immunologic recurrent abortion may result from an imbalance or breakdown in the mechanisms responsible for immune homeostasis. Immunologic factors mediating abortion may operate at any stage of reproduction since spermatozoa, embryos, trophoblast, and reproductive tract tissues themselves are all capable of stimulating an immune response due to their paternally inherited gene products and tissue-specific differentiation antigens.

Rapid advances in immunoreproduction are occurring due to major advances in the field of immunology. It is now possible to perform in-depth studies of
immunoregulatory mechanisms. Numerous biochemical mediators of immunological responses (lymphokines and monokines) have been defined and mass produced in both culture purified and recombinant form for research use. These mediators enable the definition of cellular interactions within the immune system, and between the immune system and reproductive tissues. New monoclonal antibodies have also been produced that identify many of these mediators and leukocyte markers associated with reproductive/immune function. Until recently, immunologic studies have focused on the humoral immune response and the role of antibodies in recurrent abortion. It is now possible using these new immunological reagents to probe the cellular immune mechanisms and immunoregulatory events that also appear to affect reproductive failure both before and after implantation. In this chapter we will present evidence of cellular immune mechanisms that potentially underlie abortion.

Leukocyte Populations Residing in Reproductive Tissues

The human endometrium under hormonal stimulation, cyclically prepares to receive a fertilized ovum in a process known as the menstrual cycle (18). Since the classic histological description of Noyes, Hertig and Rock (40) on cyclic changes in the normal human endometrium, investigators have questioned the nature and activity of lymphoid, myeloid, and other antigen-presenting cells that migrate to the human endometrium and decidua (6,7,8,27,28,46). In the human female, the genital tract is well endowed with macrophages and other immunologically competent cells (46). These cells can process antigens for recognition by the host's immune system. Monoclonal antibodies have been used to identify T-lymphocyte subpopulations in nonpregnant normal and abnormal human endometrial biopsies (56). Both T-helper/inducer and T-suppressor/cytotoxic subpopulations were detected in histologically normal (in phase) biopsies and were present in significantly higher concentrations in proliferative than in secretory phase endometria. In normal biopsies, helper/inducer T cells outnumbered suppressor/cytotoxic T cells throughout the cycle except late in the secretory phase and during menstruation, when suppressor cells predominated. In abnormal (out of phase) biopsies, as revealed by histologic dating, there was a tendency for increased ratios of T-helper cell subpopulations as compared with normal biopsies. In abnormal biopsies from some women with a history of recurrent abortion there were extremely high helper:suppressor cell ratios suggesting that the uterus is indeed an immunologically dynamic tissue and that immunologic mechanisms may be operative in spontaneous abortion. Clark and McDermott (8) have also shown that a granular lymphocyte migrates to the endometrium during the mid to late secretory phase of the menstrual cycle and postulated that this cell type could play an immunoregulatory role in the maintenance of early pregnancy. Lymphoid cells of bone marrow origin are recruited to the uterine decidua at implantation and are shown to possess suppressor activity and are functionally hyporesponsive to paternal antigens (8,28,47). It is also known that human