A striking common feature of many autoimmune diseases in humans and experimental animals, despite differences in pathology, is that females are highly susceptible to autoimmune conditions compared to males. In several animal models, estrogens promote, whereas androgens abrogate, B-cell-mediated autoimmune diseases. To understand mechanisms by which estrogens regulate autoimmunity, it is first necessary to decipher estrogen effects on the normal immune system. Estrogen treatment of nonautoimmune mice diminished lymphocyte numbers in both developmental and mature lymphoid organs. Estrogen dysregulated T- and B-cell balance by inducing selective T-cell hyporeactivity and B-cell hyperactivity. Even though estrogen did not alter the relative percentages of splenic T-cell subsets, splenic lymphocytes had a reduced proliferative response to T-cell stimulants and were refractory to rescue from activation-induced apoptosis compared to cells from placebo-treated mice. In contrast, estrogen induced B-cell hyperactivity (promoted autoantibodies to double-stranded DNA and phospholipids, increased numbers of plasma cells, and increased autoantibody yield per B cell). Note that treatment of normal mice with estrogen can alter T- and B-cell regulation and overcome B-cell tolerance to result in autoimmunity in normal individuals. Could environmental estrogens promote some human autoimmune disorders? Is there a link between environmental estrogens and autoimmune disorders, especially since these disorders are reported possibly more frequently? These provocative questions warrant investigation. Our findings on immunomodulatory effects may serve as a benchmark to examine whether endocrine-disrupting chemicals will have similar immunologic effects. Key words: autoantibodies, autoimmune diseases, autoreactive cells, B cells, diethylstilbestrol, endocrine-disrupting chemicals, estrogens, T cells. — Environ Health Perspect 107(suppl 5):681–686 (1999). http://ehpnet1.niehs.nih.gov/docs/1999/suppl5/681-686ahmed/abstract.html

It is evident that there are marked or subtle gender differences in the functioning of several nonreproductive tissues. There are thousands of research manuscripts that have pointed out gender differences in various tissues and systems, including the immune system. The immune system serves as an archetypal example of gender differences in nonreproductive sites (see "Gender Differences in Immune Responses"). Given the marked impact of gender on tissue physiology, it is imperative to include gender as a variable in clinical and experimental studies. Nevertheless, many research protocols do not include study subjects of both genders nor do they strictly control for gender (unlike a gender-related variable given to age or strain), an aspect that warrants attention.

Females as a gender group have heightened immune responses not only to foreign antigens but also to self-antigens [reviewed in (1-6)]. Thus, there is a greater preponderance of autoimmune disorders in women than in men [see "Gender Differences in Immune Responses"; also reviewed in (1-5,7)]. It is important to recognize that autoimmune diseases can afflict almost any tissue, akin to cancer. Conceivably, the initiating and pathogenic mechanisms are most likely to be different in various types of autoimmune diseases. Yet, in general, women are more susceptible than men to autoimmune diseases. Therefore, gender is a common thread that stitches together the disparate autoimmune conditions.

**Gender Differences in Immune Responses**

In general, females as a gender group have better B-cell–mediated immunity (often, perhaps incorrectly, referred to as humoral immunity) than age-matched male counterparts [reviewed in (1-6)]. They have higher immunoglobulin levels, stronger antibody responses to various foreign antigens, and increased resistance to certain infections [reviewed in (1-6)]. Gender differences in T-cell–mediated immunity also exist, although the gender influences appear to be complex [reviewed in (1-6,8)]. Females have greater resistance to induced tolerance, increased ability to reject grafts, and increased CD4 to CD8 ratios. Also, females tend to secrete higher levels of interleukin (IL)-4, interleukin-10 (IL-10), and IL-1. Sex hormonal action on the immune system is thought to account for gender differences in immune capability, dispelling the notion that sex steroid hormones exclusively affect sex-related endocrinologic functions.

**Sources of Exposure to Estrogens: Natural, Synthetic, and Environmental Estrogens**

In addition to natural estrogens, human and animals are exposed to estrogens in different forms. The exposure to synthetic and environmental estrogens is believed to have increased over the years. Diethylstilbestrol (DES), a potent synthetic estrogen, has been used as a therapeutic agent in a variety of clinical situations including threatened abortions, preeclampsia, prior premature labor, prosthetic and breast cancer, pregnancy complications in diabetic women, and whenever estrogen-replacement therapy was indicated (9-11). Although DES is no longer used during pregnancy, it is estimated that 2-4.8 million human offspring were exposed to DES from the 1940s through 1971 (12). Human exposure to DES is suspected to have also occurred through consumption of meat and milk products of livestock that were fed DES as a food additive. Moreover, there was an occupational exposure to farmers handling DES (13). Estrogens are now increasingly prescribed for postmenopausal women for prevention of bone loss and cardiac myocardial infarctions. Further, a greater number of women worldwide are on prolonged estrogen-based oral contraceptives. Finally, an increasing number of people are unintentionally exposed to a wide range of synthetic chemicals such as pesticides, industrial byproducts, insecticides, fungicides, and herbicides that have estrogenic or antiestrogenic effects (13-15). Food animals are likely to have been exposed to estrogenic zearealenol and/or zearalenone, an estrogenic Fusarium-derived mycotoxin in contaminated diet. It is likely that a subset of...
the population that may be exquisitely sensitive to estrogenic compounds may be at risk for the development of autoimmune diseases.

**Gender Difference in Autoimmune Diseases: The Role of Estrogenic Compounds**

**Human Studies**

Genetic, viral, stress, and sex hormonal factors all play a complex role in the etiology of autoimmune diseases. For the first three of these factors, despite intense research activity and exciting new data, their precise contribution to autoimmune disease is not yet clear. For sex hormones, however, the clinical observations that autoimmune diseases occur more frequently in females compared to males offers exciting new avenues of research to better understand the promotion, progression, and possible treatment of autoimmune diseases. We and others have extensively documented gender differences in the expression of autoimmune diseases in previous reviews (1–5, 7). A partial list of female predominance of autoimmune diseases is shown in Table 1. [See Ansar Ahmed et al. (1) for a more detailed list of gender differences.] A recent epidemiologic study on the prevalence of 24 autoimmune diseases estimated that 1 in 31 Americans (almost 9 million), mostly women, are affected with some type of autoimmune disease (16). Of the autoimmune diseases studied, thyroid autoimmune disorders, rheumatoid arthritis, insulin-dependent diabetes, and pernicious anemia were common autoimmune disorders. Most of these disorders predominantly afflict women. Although individual autoimmune disease may be relatively uncommon, collectively they constitute a significant concern to internal medicine. Autoimmune diseases are believed to be more frequently reported, which may be due to better recognition of these diseases by physicians and patients, coupled with more sensitive diagnostic procedures. Nevertheless, the possibility that there is a true increase in autoimmune disease cannot be completely discounted. Could the possible increase in the incidence of autoimmune diseases be due to exposure to environmental estrogens? This provocative question needs to be answered in future studies, especially with regard to the impact of endocrine-disrupting chemicals on disease initiation or progression.

The influence of sex hormones on human autoimmune diseases is evidenced by the observation that the course of many of these disorders is modulated during the periods of sex hormonal alterations (e.g., pregnancy, administration of oral contraceptives, or menopause) [reviewed in (1–5, 7)]. Limited data in humans have shown that dehydroepiandrosterone therapy in systemic lupus erythematosus (SLE) patients (17) or androgen replacement therapy in a Klinefelter syndrome patient with SLE (18) had apparent beneficial effects.

Women prenatally exposed to DES are susceptible to the development of adenocarcinomas of the cervix and vagina (9–12, 19) and reproductive abnormalities [vaginal adenosarcoma and infertility (9, 12)]. Further, a link between prenatal DES exposure and autoimmune disease has been suggested (20, 21). Women prenatally exposed to DES appear to have a higher incidence of autoimmune diseases but only when various autoimmune disorders are grouped (20, 21). Women with vaginal epithelial changes had nearly 50% more autoimmune diseases than DES-exposed women lacking these pathologic changes (20). The DES–adenosarcoma report (20) stated

The information presented in this preliminary communication also supports the concept that human exposure before birth to DES may subsequently affect the adult immune system. Additional studies should be undertaken to thoroughly investigate the function of the immune system in DES-exposed women by means of appropriate serologic testing.

An epidemiologic questionnaire-based study involving 1,700 respondents (including mothers, daughters, sons) revealed that respiratory infections (flu, colds), asthma, arthritides, and lupus were reported more frequently (21). This suggests that prenatal DES exposure contributed to immune impairment. Another recent but smaller preliminary study involving self-reported cases of allergy, infections, and autoimmune diseases did not find an association of these disorders with prenatal DES exposure (22). Nevertheless, these authors felt further studies are needed to conclusively establish the link between prenatal DES exposure and autoimmune diseases. Large double-blind human studies are needed to address this aspect.

**Animal Studies**

Akin to the human situation, gender differences in autoimmune diseases and/or sex hormonal influences on the expression of these disorders are evident in many animal models of autoimmune diseases [Table 1; (1–5)]. Space restrictions do not permit comprehensive discussion of literature and therefore only selected recent information is included here. A relatively new murine model for SLE has been described in female (SWR × SJL)F₁ mice. These mice have increased hypergammaglobulinemia, a 2-fold increase in spleen cell numbers, and make anti-Sm/U1snRNP antibodies (which react with autogenic peptides), compared to males. IgG antibodies react with PPGMRPP, an octapeptide thought to be a strong immunoreactive linear epitope in SLE patients with anti-Sm/U1snRNP antibodies (23). The increased susceptibility of female (SWR × SJL)F₁ mice to lupus resembles the differential sex susceptibility in (NZB × NZW)F₁, or B/W, and (NZB × SJR)F₁, or SNF₁, mice. In B/W mice, depletion of male hormones (by administration of estrogens or antiandrogens to orchietomized males) accelerates the manifestation of the disease (1–5, 24, 25). Conversely, female B/W mice can be made resistant to the disease by administration of androgens or antiestrogens (1–5, 24). In SNF₁ mice, resistant males were rendered susceptible by estradiol or 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (26). Estrogen-induced exacerbation of

| Table 1. A partial list of gender differences in human and experimental autoimmune disease. |
| --- |
| **Human** | **Female to male ratio** | **Animal models** | **Female to male ratio** |
| **Autoimmune disease** | **Autoimmune disease** | **Autoimmune disease** | **Autoimmune disease** |
| Hashimoto thyroiditis | Spontaneous (BUF rats) | 3:1 | Autoimmune thyroiditis |
| Graves-Basedow disease | Induced | 4 to 6:1 | Thymectomy-irradiation |
| | | | Neonatal thymectomy |
| | | | Chemical and antiandrogen |
| SLE | Rheumatoid arthritis and/or | 2:1 | Earlier expression of autoimmune disease |
| Sjogren syndrome | Sjogren syndrome | 9:1 | autoimmune disease or autoantibodies in |
| | | | females, e.g., |
| | | | (NZB × NZW)F₁, SNF₁, |
| | | | (NZB × DBA/2F₁, |
| | | | MRL/prpr/pr |
| Rheumatoid arthritis | Polyarthritis (LEW rats) | 3 to 4:1 | |
| Juvenile onset of myasthenia gravis | 2:1 | 6:1 |
| (White patients) | | | |
| (Black patients) | 2 to 14:1 | | |
| | 1:1 (approx) | | |

SLE, systemic lupus erythematosus. Modified from Ansar Ahmed et al. (1).
autoimmune disease is thought to be mediated through alterations in T cells (increased CD4+ cells in the thymus and CD4- memory T cells in the spleen and kidneys) (26). Estrogen promotion of autoimmune disease has also been shown in MRL/lpr/lpr mice, which develop an aggressive disease with lymphadenopathy (27), and in an immunized model for SLE (166 idiotype bearing anti-DNA antibodies) (28). In the nonobese diabetic strain of mouse, the incidence of spontaneous diabetes is increased in females compared to males. The susceptibility of males is augmented by orchietomy (29). Orchietomy combined with thymectomy considerably enhances the incidence of the disease, suggesting that male hormones may act via the gonadal–thymic axis. In a mouse model of arthritis, female mice have a greater ability to degrade implanted cartilage than males (30). Granulomata from female mice had higher levels of IL-1, implying that sex hormone modulation of cartilage destruction may be mediated by cytokines. In experimental autoimmune encephalomyelitis in SJL mice injected with myelin basic protein-specific T cells, dihydrotestosterone was effective in diminishing the severity of the disease (31). The protective effects appear are related to enhanced production of IL-10 by antigen-specific T lymphocytes.

Mice given DES during the perinatal (neonatal) period have an impaired immune system (particularly T cells), including atrophy of the thymus, reduced proliferative response to T-cell mitogens, diminished antigen-specific delayed-type hypersensitivity response and graft versus host reaction, decreased cytotoxic response to mammary tumor virus, and decreased natural killer cell function (32–36). Therefore, concerns have been raised that the exposure of fetuses to estrogenic compounds during the highly critical stage of immune development may alter the immune system. We are currently investigating the immune consequences of prenatal exposure to DES in a murine model. These studies may also be relevant to other endocrine-disrupting chemicals (e.g., octylphenol or genistein).

The following section describes studies from our laboratory as well as others on the immune effects of estrogen in normal animals. Extensive studies in our laboratory have identified immune cells that are modulated by estrogen.

Immune Biomarkers for Estrogenic Compounds

Effects on Thymus and T Cells

To better understand how sex hormones regulate autoimmune responses and to identify the target organs and cells, it is essential to first decipher their effects on normal immune systems, an aspect thus far not well understood. Toward this aim, we gave estrogen (17β-estradiol in silastic capsules) to prepubertal orchietomized normal C57BL/6 mice and examined their splenic and thymic tissues after 3–6 months (37–40). Extensive studies from our laboratory as well as others have established immune biomarkers for estrogen [Table 2; (37–41)]. These parameters may be useful in ascertaining the immunologic consequences of exposure to endocrine disruptors. Chronic estrogen treatment diminished lymphocyte numbers in both developmental (thymus, bone marrow) and mature (spleen, lymph nodes) lymphoid organs. Estrogens (presumably including DES) induced atrophy of the thymus. Estrogen also altered intrathymic T-cell subsets (e.g., loss of CD4+8+ thymocytes) (Figure 1). To address whether estrogenic compound-induced atrophy of the thymus is due to direct induction of apoptosis of thymocytes, normal thymocytes were cultured with various doses of DES and the kinetics of apoptosis was determined. Parallel cultures of thymocytes were exposed to a known thymic atrophy- and thymocyte apoptosis-inducing hormone, dexamethasone (DEX). Apoptosis was evaluated by flow cytometric examination of cells stained with propidium iodide (PI), 7-aminoactinomycin D (7-AAD), or fluorescein isothiocyanate–annexin V; by forward/side scatter analysis, cell-size analyzer, and cytopathologic examination. In our extensive studies, apoptosis could only be detected in thymocyte cultures exposed to DEX but not in those exposed to DES (41). These studies imply that these two synthetic hormones induce atrophy of the thymus by dissimilar mechanisms in vivo. A recent study using transgenic mice overexpressing antiapoptotic oncogene bel-2 has shown that administration of 17β-estradiol, but not DEX, can induce thymic atrophy, thereby suggesting that these two hormones have different modes of action (42). Alternatively, thymic injury mediated by estrogen or DES may be due to diminished immigration of prothymocytes from the bone marrow or hormonal effects on thymic stromal cells (possibly by altering their secretion of crucial cytokines such as IL-1, IL-6, or IL-7, or by inducing apoptosis of these cells). Sex steroid receptors have been demonstrated on thymic epithelial/stromal cells, possibly on thymocytes, and on peripheral T-cell subsets in a number of species [reviewed in (1–6)]. A putative model suggests that sex steroid hormones bind to intracellular receptors (nuclear or possibly in the cytosol) in lymphocytes; this complex binds to sex steroid hormone-responsive elements in the DNA to modify cellular activity. Sex hormones induce the thymus to release immunoregulatory thymic factors that can also act on the hypothalamus–pituitary axis to release other immunoregulatory peptides [reviewed in (1–6)]. Studies also suggest that developing thymus and T cells are direct or indirect targets for estrogenic compounds. Induction of a hyperestrogenic state induced by estrogen treatment of pregnant guinea pigs or DES injections of pregnant mice resulted in reduction in the number of large cortical cells of the fetal guinea pig thymus (43) and lowered response to T-cell mitogens (27). Our ongoing studies show that nonautoimmune mice prenatally exposed to DES have altered thymocyte numbers or functions (44). Thus, it is conceivable that exposure to estrogenic compounds during fetal life could be a potential immunologic

| Table 2. Immune biomarkers for estrogen. |
|-----------------------------------------|
| **Hyperactivity of B cells** |
| ↑ Immunoglobulins and autoantibodies |
| ↑ Number of plasma cells |
| ↑ Output of autoantibodies per B cell |
| ↑ Number of cells in the S phase of cell cycle |
| ↑ Survival of activation-induced apoptosis |
| **Impairment of T-cell function** |
| ↓ Proliferative response to T-cell stimulants |
| Unresponsive to activation signals for rescue from apoptosis |
| ↓ CD69 expression after T-cell stimulation |
| ↓ IFN-γ at protein and mRNA levels |
| **Dampened NK cell activity** |
| Increased granulocytes |
| ↑ Ly6G* (Gr-1) |

Abbreviations: IFN-γ, interferon-γ; NK, natural killer.
hazard. Concanavalin A (ConA)-stimulated T cells from estrogen-treated mice have an early defect, as they have decreased expression of CD69 and have decreased ornithine decarboxylase activity (an early enzyme in polyamine biosynthesis) compared to that in controls.

Sex hormones can affect autoimmune diseases by modulating the activity of CD4+ helper cells. The effects of estrogen on CD4+ cells are best depicted in studies on β2-microglobulin–deficient mice infected with lymphocytic choriomeningitis virus. Females were more susceptible to fatal CD4-mediated meningitis compared to males (45). Estrogen treatment of orchitectomized mice rendered these males susceptible to meningitis. In vivo studies confirmed that CD4-mediated cytotoxicity was dependent upon estrogen.

Sex hormones could affect the type or levels of T-cell–derived cytokines. In our studies on estrogen-treated normal C57BL/6 mice, splenic lymphocytes stimulated with T-cell stimulants had increased IFN-γ mRNA as well as IFN-γ protein (46). Addition of estrogen to CD4+ T-cell lines from multiple sclerosis patients resulted in increased production of IL-10 and IFN-γ (47). Sex hormones could have differential effects on lymphocytes from autoimmune patients compared to those of controls, as was noticed in IL-1 and IL-6 production in lymphocytes from healthy and rheumatoid arthritis patients, which were cultured with estrogen (48). Similarly, it is plausible that endocrine disruptors could have differential effects on normal and autoimmune individuals, an aspect currently investigated in our laboratory. Further evidence for sex hormonal effects on T-cell–derived cytokines is evident in studies where culturing of antigen-specific CD4+ T-cell lines in the presence of progesterone resulted in a shift from Th1 to Th2 cytokine profiles (49).

Further, when known Th1 cells were cultured in the presence of progesterone, there was a transient synthesis of IL-4 and transient expression of CD30, which are characteristics of Th2 cells (49). Receptors for progesterone in lymphocytes appear to be selectively increased during pregnancy or mitogenic stimulation (50). Other studies have shown that lymphocytes cultured in the presence of progesterone produce an immunomodulatory protein that selectively induces IL-10, IL-4, and IL-3 production by ConA-stimulated lymphocytes (51). Th2-type cytokines secreted by placental tissues are thought to play an important role in maintenance of pregnancy. Is the pregnancy loss noticed in SLE patients (who manifest altered levels or metabolism of sex hormones) due to shifts in the hormone-induced cytokine balance (possibly to Th1 type)? This challenging question warrants further studies.

Estrogenic Compounds, B-Cell Hyperactivity, and Autoantibodies

Since estrogen drastically reduces the size of the bone marrow cavity and the bone marrow cellularity (and thymus), organs where deletion of autoreactive cells occurs, it is likely that lymphocytes such as B cells may develop in alternative sites where there is less stringent selection (Figure 2). We thus envisioned the possible appearance of autoreactive cells in the peripheral tissues (e.g., spleen) and expression of autoantibodies in the serum of estrogen-treated mice. We observed that estrogen-treated mice have extensive hematopoietic centers in the liver and spleen (40). Estrogen treatment of MRL/lpr/lpr mice resulted in the appearance of forbidden clones in the liver (52). These cells include αβTCRIntermediate, VB3+, or VB8+ T cells that are often deleted in the thymus. Our studies show, by EL1spot and image cytometry, that estrogen activates B cells to produce higher numbers of not only immunoglobulin–producing cells but also autoantibody-producing cells in the spleen which were directed against double-stranded DNA (dsDNA), cardiolipin, phosphatidylserine, and actin (53). The number of plasma cells was significantly increased in the spleens of estrogen-treated mice, suggesting B-cell hyperactivity. Further, sera of estrogen-treated normal C57BL/6 mice had IgM and IgG (predominantly IgG2b) autoantibodies against dsDNA (39), cardiolipin, phosphatidylserine, and phosphatidylinositol (37–39). Although the pathogenic significance of these estrogen-induced autoantibodies is not yet determined, these studies may be important, as anti-dsDNA antibodies are often seen in patients with SLE and antiphospholipid antibodies are present in antiphospholipid syndrome and a subset of SLE patients. Our findings show that treatment of normal mice solely with estrogen can override B-cell tolerance and promote autoimmunity. It is likely that endocrine-disrupting chemicals can also similarly promote B-cell hyperactivity. Our recent preliminary data on mice prenatally exposed to DES also suggest that B cells are modulated by these estrogenic compounds. It is not clear how estrogens (and, by analogy, environmental estrogens) promote B-cell hyperactivity. Conjectural possibilities include a direct effect on the immune system or an indirect effect via the hypothalamic–pituitary axis. It is likely that estrogen may act on T cells to elaborate cytokines (e.g., Th2 cytokines), which in turn promote the function of B cells. Estrogen may downregulate natural killer cells or T-suppressor cells that regulate B-cell functions. B cells from estrogen-treated mice may be readily activated by autoantigens (which may be available following increased hormone-promoted cell death).

Although not conclusively proven, infectious agents in the environment have long been suspected to play a role in the onset or progression of autoimmune diseases. It is thus conceivable that estrogen and possibly environmental estrogens could activate a latent infection that in turn could influence the onset or course of autoimmune diseases.

Estrogenic Chemicals and Apoptosis

Estrogenic compounds can conceivably affect the immune and autoimmune responses by directly or indirectly regulating the apoptotic patterns of lymphocytes. This should not be surprising considering that related steroid hormones such as glucocorticoids directly affect apoptosis of thymocytes. Further, estrogenic hormones affect apoptosis of nonlymphoid cells. For example, depletion of estrogen can
induce apoptosis in the uterine epithelium (54). In breast tissue, however, estrogen is thought to contribute to the pathology by promoting the survival of estrogen-responsive cancer cells, which is related to bcl-2 mRNA and protein expression (55). Recent studies in our laboratory suggest estrogen also modulates the apoptosis of lymphocytes (40,56). By several methods, including flow cytometric analysis of cells stained with PI, 7-AAD, and Annexin, we find that spleens from estrogen-treated mice have increased numbers of apoptotic splenic lymphocytes. We are currently investigating whether lymphocytes from estrogen-treated mice have an altered expression of Bcl-2 or fas proto-oncogenes. Splenic lymphocytes from placebo-treated but not from estrogen-treated mice, when activated with T-cell stimulants (e.g., anti-CD3 antibodies) were rescued from apoptosis. Lymphocytes exposed to B-cell stimulants were resistant to cell death (57). We also find that lymphocytes from mice prenatally exposed to DES have altered apoptosis in response to certain stimulators (58). There is evidence of apoptosis and autoimmune diseases in patients with Sjögren syndrome. There is an excessive and inappropriate apoptosis of glandular epithelial cells and inhibition of apoptosis in infiltrating lymphocytes (59). bcl-2 is a potent downregulator of apoptosis in many systems, including peripheral blood of patients with lupus. The sex hormonal modulation of apoptosis through effects on bcl-2 is a fertile field for future research uniting the three important fields of hormones, oncogenes, and apoptosis.

Conclusions
The fact that various types of organ and nonorgan-specific autoimmune diseases in both humans and experimental animals occur predominantly in females strongly implies that gender plays a major role in the initiation or progression of these disorders. Studies from a number of laboratories have clearly shown that sex steroid hormones markedly modulate many of these disorders. There is a paucity of information, however, that links environmental estrogens (endocrine-disrupting chemicals) with autoimmune diseases. It is conceivable that a subset of the human population may be more susceptible to autoimmune diseases (as opposed to the general population). It is possible that susceptibility to environmental chemical-induced autoimmunity may vary with the genetic background, gender, previous immune status, age and duration of exposure, and immune status at the time of contact with these agents. Chronic exposure (e.g., sustained low dose) may have more adverse effects than acute exposures. Although valuable data to ascertain the linkage of environmental agents with autoimmune diseases in humans can be obtained (e.g., performing sequential immunological studies in occupational or accidentally exposed populations, or populations living near contaminated sites), there are inherent limitations in performing detailed mechanistic studies in humans. Animal models can be advantageously employed to study a number of these aspects. For example, the availability of several strains of genetic-prone autoimmune and nonautoimmune mice will elucidate the response of normal and autoimmune individuals to a given chemical. Animal models will also permit the performance of studies involving chronic or acute exposure of chemicals during fetal to adult stages of life. Certain ages of life (e.g., fetal, neonatal, or senescent stages of life) may be more susceptible to environmental chemical-induced autoimmunity.

Our studies and those of others show that estrogens induce imbalances in T and B cells. In general, estrogens bring about hypoactivity of T cell subsets and hyperactivity of B cells (3–5,32). This may form the underlying basis for induction of autoimmunity by estrogen. Although estrogen induces hypoactivity of T cells (as in the above experimental systems), it is nevertheless likely that selected subsets of T cells may be errant in functioning (e.g., overproducing certain cytokines or responding aberrantly to T-cell activation signals). Regulatory cells that hold in check auto-reactive cells may be affected by hormones. This could promote immune dysregulation including autoimmunity.

It is important to recognize that the effects of sex hormones on the immune system should not be generalized. To illustrate this point, Sullivan (60) has shown that androgens have a stimulatory effect on mucosal immunity in the eye, no effect on the uterus, and an inhibitory effect in the mammary gland. The outcome of immune responses is dependent upon highly complex interactions of sex hormones with several tissues. Estrogen could have either a stimulatory or suppressive effect on the immune system, depending on dose and duration, the age of the individual, local site, activation status of the cells, availability of costimulatory signals, or the expression of receptors. It should therefore not be surprising that environmental estrogens may have the same or varied effects on various autoimmune diseases. It is anticipated that much human and animal data will become available in the near future to address the precise association of environmental agents and autoimmune diseases. Mechanistic studies in animal models (or in humans) may then prove to be very useful in understanding the induction or advancement of disease, and exploring new avenues to correct these conditions therapeutically.

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