Ray Peat's Newsletter

"Reason can answer questions, but imagination has to ask them." Ralph W. Gerard

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Autoimmunity

The thymus gland is important for growth and fertility, but it is now considered to be an important regulator of the immune system. As the gland shrinks with aging, the incidence of "autoimmune diseases" increases, possibly because the regulatory functions of the gland have been lost.

It has been shown that radiation, polyunsaturated fatty acids, estrogens, and heavy metals and other toxins including dioxins damage the thymus gland, and can produce immunodeficiency. These stressors also stimulate the "autoimmune" antibodies.

Estrogen shrinks the thymus and blocks NK cells, and blocks cell division in thymic cells. Thyroid stimulates regeneration of the thymus, even after age-related atrophy. Progesterone protects against the thymic atrophy produced by stress and cortisol, and promotes thyroid's effects, and protects against many of the conditions that are called "autoimmune." Estrogen creates both immunodeficiency and autoimmune degenerative conditions.

Hypothyroidism causes the thymus gland to atrophy (Abou-Rabia and Kendall, 1994), partly because the thyroid hormone itself is essential for the maintenance of the gland, and also because hypothyroidism is likely to be accompanied by excessive levels of estrogen and cortisol.

Polyunsaturated fatty acids interfere with the formation of the thyroid hormones, by preventing the coupling reaction, which converts iodotyrosine residues into iodothyronine residues in the thyroglobulin. The resulting abnormal thyroglobulin is antigenic.

Animals that are fed diets that completely lack the polyunsaturated fatty acids appear to be free of the autoimmune diseases: their tissues can even be transplanted into other animals with less antigenicity than is normal, so the dietary polyunsaturated fatty acids seem to be involved in the development of the abnormally increased antigenicity of the various autoimmune degenerative diseases.

Several years ago, I wrote about Metchnikov's theory of immunity, based on the role of the phagocyte in the organism's ordinary growth, and I also argued that inflammation was a pathological reaction, rather than being a healthy part of a defensive immune system. Since then, the role of inflammation has been recognized in heart and circulatory disease, Alzheimer's disease, and other diseases, and even in obesity, diabetes, depression, and osteoporosis, so that now it isn't a universal medical reflex to think of inflammation as a purely normal physiological response. However, the history of treating inflammation as part of "the immune system" has left a residue of medical ideology, in which a pathogenic organism must be invoked as the cause of any inflammation, even though the concept of "sterile inflammation" has a strong foundation of evidence.

Metchnikov's view, that the "immune system" is a constructive part of normal physiology, combined with the idea of inflammation as a pathological hindrance to normal functioning and development, forms the framework for a major reconsideration of the functions of antibodies, the thymus gland, lymphocytes, and other parts of "the immune system." A few people (Jamie Cunliffe and Polly Matzinger, for example) are working on this new paradigm of "immunity," challenging the "assumption that the immune system . . . has evolved to find, kill and eliminate foreign organisms." If they are right, then all of medical thinking about immunity since Metchnikov's ideas were discarded has been, effectively, an attack against a full and proper understanding of the nature of the organism, and specifically has led to a deep misunderstanding of growth, regeneration, aging, cancer, and the

functions of nerves, hormones, and tissue interactions.

A pathogen is usually defined as an organism or a substance that causes tissue damage. I think the definition should be "a substance or process that causes tissue damage," to include the pathogenic effects of malnutrition, stress, and radiation, for example. The consequences of tissue damage have to be distinguished from the causes of tissue damage. The failure to distinguish cause and effect has led to many foolish medical theories.

The new orientation toward the immune system is that its main function is to clean up the debris created by developmental processes (such as the elimination of red blood cells, or the regression of the tadpole's tail), or by injury, and to prepare the system for recovery or regeneration. This orientation brings together ideas from developmental biology and immunology in a very encouraging way. For example, a recent study shows that "autoimmune" antibodies are involved in brain repair after traumatic injury. (Hofstetter, et al., 2003.)

The example of the tadpole's tail provides a metaphor that might be useful in understanding the ways in which hormones and the immune system interact in mammals and people. Without the thyroid hormone, a tadpole keeps its tail, and fails to turn into a frog, though it keeps growing. The thyroid hormone causes the animal to progress to a higher stage of development, in which it has a higher metabolic rate and uses lungs rather than gills. The phagocytic cells rapidly consume the structures that were appropriate for the lower stage of development and metabolism.

I think we can see analogous processes in the functioning of our immune system. When cells in any part of the body aren't able to maintain an efficient energy metabolism, they tend to be replaced by new, more active cells, and the debris of the old cells is removed by phagocytosis, often without detectable inflammation. Stimulation and adaptation are always causing remodeling of our bodies, with bones growing along lines of stress, areas of the brain expanding with learning, and organs such as the intestine and liver modifying their metabolism according to diet and exposure to toxins.

Inflammation, atrophy, or tumefaction can occur when some part of the regenerative and developmental process is defective. A failure of energy metabolism can be seen in each of these types of problem. Usually, prolonged inflammation leads to atrophy and fibrosis, which in turn increases the likelihood that a tumor will develop.

Two organs that can change their mass greatly in a short period of time are the thyroid and the thymus.

The thyroid can be functionally suppressed, and, with stimulation, return to full activity within a few hours. If it is stimulated continuously, it can increase its mass greatly in a few days. The thymus can lose most of its mass in a few hours.

The remarkable ability of the thymus gland to shrink rapidly when it's exposed to estrogen or stress or cortisol is very probably related to the fact that "cleaning up messes" is a primary function of many of the cells that constitute it.

Most of the cells of the thymus are very dependent on sugar metabolism, and this is disturbed by stress, cortisol, estrogen, and some kinds of fat. Even under normal conditions, there is a rapid turnover of its cells. Many of the cells that make up the thymus, like leukocytes generally, are highly sensitive to anything that limits their energy.

These changes in the size and composition of the thyroid and thymus glands involve some of the biochemical processes that are involved in the developmental changes in tadpoles and frogs.

Inflammation occurs when the production of debris is too rapid for its quiet removal, as when energetic process fail, or when certain specialized organisms interact destructively with the tissues. The characteristic changes in metabolism, a shift toward the production of lactic acid and the breakdown of protein, are probably as much the cause of inflammation, as its effect.

Estrogen is an important regulator of energy metabolism, and it is therefore crucially involved in the diseases known as "autoimmune diseases."

Progesterone, thyroid, and various nutrients including vitamin E, oppose the actions of

estrogen, and so have a role in the prevention of the "autoimmune diseases."

These diseases include rheumatoid arthritis, multiple sclerosis, Sjogren's syndrome, Devic's optic neuritis, cystitis, and various types of hepatitis and nephritis and pancreatitis.

Aging and stress are estrogenic, and this estrogen effect leads to atrophy of the thymus, combined with inflammation. The associated cortisol excess decreases the inflammation, but aggravates the disregulation of the immune system. Serotonin is another stress-related factor that produces involution of the thymus (Bliznakov, 1980).

The thymus gland permits immune cells to mature and to become organized. It is a major factor in the regulation of the cells that produce antibodies, the B (bone marrow derived) lymphocytes, and when the thymus is chronically damaged, the production of antibodies tends to increase, but without the sensitive control the thymus provides. Thymus-type cells are produced not just in the thymus, but also in other organs, especially the liver.

In the young organism, the disruption of a tissue exposes a variety of antigens from the differentiated cells. Antibodies that are formed to these antigens have two very different functions. They stimulate the removal of the defective cells and debris, and they locally obscure the specifically differentiated tissue components, creating a sort of vacuum to be filled by the multiplication of undifferentiated "stem" cells, which repair the damaged region.

One line of research in developmental biology emphasizes the innate tendency of cells to grow and multiply, with differentiation and growth inhibition being the subsequent result of interactions with their environment.

For many years, researchers such as Szent-Gyorgyi searched for general or specific inhibitors of cellular multiplication. Szent-Gyorgyi gave the name "retin" to a molecule that he thought could restrain cancer growth. Leonell Strong studied liver extracts, and found several anticancer agents. W.S. Bullough extracted materials that were tissue specific, that he thought might synergize with adrenaline in restraining tissue growth.

About 50 years ago, an experiment with developing frogs' eggs encouraged this line of research. The experimenter found that when the juice extracted from a particular tissue was added to the water in an aquarium where frog eggs were starting to develop, the developing embryo had a deficiency of that particular tissue, and its development would stop when the absence or deficiency of that tissue became limiting. In rats, a similar organ-specific substance had been suggested by removing part of the liver of one rat of a pair that shared the same blood supply. The livers of both animals grew until the total mass was appropriate for two animals, but the operated liver stopped growing prematurely, apparently because a circulating growth inhibiting substance reached a certain level. Bullough's term "chalone" has been generally accepted as the name for such growth inhibiting substances.

I suspect that the immune system, and the "autoantibodies," can have a function complementary to that of the chalones, possibly by blocking the release of chalones.

In 1970, I. Hellstrom and K.E. Hellstrom showed that cancer growth is promoted by an antibody, and later they showed that antagonists to that antibody would allow the cancer to be suppressed. Their work is still progressing, and it is probably relevant to both the chalone theory, and to the processes of autoimmunity and tissue regeneration. Proper control in the immune system is very closely associated with the processes that maintain a proper balance between tissue growth and tissue atrophy. Too much of an anti-chalone agent would produce a tumor, but too little would lead to atrophy when stress-damaged tissues weren't replaced.

Recent work by M. Bissell and V. Weaver shows results parallel to the Hellstroms', but involving the interactions of cells, extracellular matrix, and antibodies.

The healthy thymus gland, which depends on a properly functioning thyroid gland, is essential for close regulation of the antibody-producing cells. With aging and the various stressors, the immune system tends to over-produce antibodies, as the cell-mediated process become weaker. This is similar to the changes produced by estrogen (for

example, see Ansar Ahmed, et al., 1989). It's generally accepted that the thymus is responsible for preventing the production of autoimmune antibodies. I suspect that its actions are more subtle, and that it is (or can be) involved in developmental and regenerative processes.

Animal studies of autoimmune degenerative diseases show that estrogen promotes autoimmunity, and that progesterone alleviates or prevents some of the typical autoimmune diseases. Their antagonistic effects on the mediators of inflammation are probably responsible, as well as their opposite effects on the activation of retroviruses and stress (or "heat shock") proteins.

Systemic lupus erythematosis, rheumatoid arthritis, and other autoimmune diseases are usually corrected by the combined use of progesterone and thyroid, both of which help to restore the thymus gland.

Although medical people have been taught to believe that aging isn't an estrogenic state, contrary to the clear evidence that estrogen production (by the aromatase enzyme) in many tissues increases with age, an experiment (Greenstein, et al., 1992) has demonstrated that giving an aromatase inhibitor to old rats causes their thymus to regenerate. Now that commercial aromatase-inhibiting drugs are coming onto the market, this experiment should be of considerable interest to people involved in cancer treatment, but its implications are so important that most researchers and therapists will prefer to forget it.

The estrogenic state of old age or of stress (with increased exposure to cortisol) is partly the result of the progressive decrease in thyroid and progesterone, which is closely associated with the decline in respiratory function and mitochondrial efficiency.

The declining energy functions increase the demand for an efficient immune system, especially when we see the immune system as a regulator of tissue repair and restoration.

The accumulation of polyunsaturated fats contributes to all phases of this process of holistic decline, from the decrease of the crucial respiratory enzyme cytochrome c oxidase, through decreased thyroid hormone activity and progesterone activity, to the activation of aromatase and estrogen and the production of tissue antigens by toxic products of lipid peroxidation.

A study in Hawaii found that men who ate tofu were more likely to have dementia and brain atrophy than men who ate a standard "western" diet. Soybeans contain estrogenic chemicals, such as genistein. In Alzheimer's disease brain metabolism is low. Genistein, like other estrogens, causes the thymus gland to atrophy (Yellayi, et al., 2002). Since Alzheimer's disease is now often considered to be an "autoimmune" disease (Grainger and Reckless, 2003; Kellet, et al., 1982; Lal and Forster, 1988; Bradford, et al., 1989), both preventive and curative approaches should probably concentrate on protecting and restoring the energy metabolism and the thymus gland.

Besides the systemic toxic effects of dietary polyunsaturated fats, those fats appear to be a major factor in making tissues susceptible to damage from immunological reactions, since the tissues of rats that are deficient in the "essential fatty acids" are not damaged by antibodies that would seriously injure or kill "normal" tissues. (Takahashi, et al., 1992; Schreiner, et al., 1988). These animals are also resistant to many toxins, including endotoxin.

The unsaturation of tissue lipids increases in aging animals, along with the increased production of estrogen and decreased production of pregnenolone, progesterone, and the T3 component of the thyroid hormone. Autoimmunity increases with aging, as the thymus gland atrophies. A program to prevent or correct autoimmunity should also help to reverse the very generalized inflammatory and atrophic processes of aging. Restoration of tissue lipids (especially cardiolipin, which activates the crucial respiratory enzyme) to the high-energy state of childhood would be a central part of such a program. (See for example Paradies & Ruggiero, 1991; Paradies, et al., 1997.)

Antibodies to cardiolipin are promoted by excess estrogen (Ahmed & Verthelyi, 1993), and this is probably related to estrogen's antirespiratory actions.

Rather than viewing autoimmune diseases as irreversible degenerative conditions, I think they should be viewed as problems of metabolic

energy, processes of self-repair that just need a little support from improved diet and other environmental conditions. (See Hofstetter, et al., 2003).

REFEREBCES

Cell Tissue Res 1994 Sep;277(3):447-55. **Involution of the rat thymus in experimentally induced hypothyroidism.** Abou-Rabia N, Kendall MD. The thymus, as part of the immune-neuroendocrine axis, is greatly influenced by factors from most endocrine glands, especially the thyroid. Antithyroid drugs (carbimazole and methimazole) were used to induce hypothyroidism in rats. Histological and ultrastructural examination of the thymus showed progressive thymic involution after 4 weeks of drug treatment to the end of observations (7 weeks). The involution was characterised by increased thymocyte apoptosis and thymocyte phagocytosis by macrophages. This resulted in thymocyte depopulation, increases in numbers of interdigitating cells, alterations to mainly subcapsular and medullary epithelial cells, an apparent increase of mast cells and collagen in the capsule and septa, and increased numbers of B cells and plasma cells. Lymphoid cells immuno-reactive with MRC OX12 (which detects B cells) were observed within blood vessel walls, suggesting that they may have been moving in and out of the thymus. The administration of drugs causing hypothyroidism, therefore, also caused marked involution of the thymus.

J Autoimmun 1993 Jun;6(3):265-79 **Antibodies to cardiolipin in normal C57BL/6J mice: induction by estrogen but not dihydrotestosterone.** Ahmed SA, Verthelyi D "Autoantibodies against cardiolipin, a phospholipid, have been demonstrated in a variety of pathological states including several autoimmune conditions in humans and in certain lupus-prone mice." "Similarly, estrogen treatment of female mice further augments the incidence and the levels of these autoantibodies. Estrogen-treated mice also have antibodies reactive against other membrane phospholipids including phosphatidylinositol (PI), phosphatidylserine (PS), phosphatidylcholine (PC) and phosphatidylethanolamine (PE)." "To our knowledge, this is the first report on the demonstration of antiphospholipid autoantibodies in normal mice and induction of these antibodies by estrogen."

J Autoimmun 1989 Aug;2(4):543-52. **Estrogen induces the development of autoantibodies and promotes salivary gland lymphoid infiltrates in normal mice.** Ahmed SA, Aufdemorte TB, Chen JR, Montoya AI, Olive D, Talal N "Sex hormones influence the immune system throughout life including postnatal and prenatal stages. For example, we find that administration of estrogen to normal mice markedly augments the ability of CD5+ B cells to express their autoimmune potential by producing increased numbers of plaque-forming cells (APFC) to bromelain-treated mouse erythrocytes (Br-ME)." "We hypothesize that an imbalance of the in utero sex hormone microenvironment critically influences the fetal immune system. **We have termed this influence immunological imprinting.** After birth this imprinting could contribute to immune-mediated disorders. To test this hypothesis, we developed a mouse model in which normal mice were prenatally exposed to estrogens. In preliminary experiments, these mice produced higher numbers of APFC to Br-ME, particularly in the peritoneal cavity cell exudates. Furthermore, mice prenatally exposed to estrogens had accelerated development of autoimmune salivary gland lesions indistinguishable from Sjogren's syndrome (SS) in humans. Further experiments are warranted to confirm these findings. The prenatal effects of estrogen may have relevance for familial and neonatal autoimmune syndromes."

J Immunol 1989 Apr 15;142(8):2647-53. **Estrogen induces normal murine CD5+ B cells to produce autoantibodies.** Ansar Ahmed S, Dauphinee MJ, Montoya AI, Talal N "Females have better humoral immune responses and are more susceptible to autoimmune diseases than males." "The increased autoantibody production in females can be attributed to the effect of estrogen on the immune response because this hormone markedly augments APFC to Br-ME in intact or orchidectomized males. Male hormone had little effect. Importantly, estrogen did not increase the numbers of B or CD5+ B cells but **augmented the ability of B cells to produce this response.** This was verified when a T cell-depleted B cell fraction or fluorescence-activated cell sorter purified CD5+ B cells from estrogen-treated mice proved more efficient in the production of APFC to Br-ME. These results suggest that the number of CD5+ B cells committed to produce autoantibodies to Br-ME is increased under the influence of estrogen. This is the first demonstration that estrogen can augment the production of natural autoantibodies in normal mice. The overall augmented humoral immune responses in females and the **B cell hyperactivity** in female predominant autoimmune diseases appears to be due to estrogen."

Cutis 1978 Mar;21(3):321-5. **Is vitamin E involved in the autoimmune mechanism?** Ayres S Jr, Mihan R

Free Radic Biol Med 2000 Jan 1;28(1):84-90. **Effect of exhaustive exercise on membrane estradiol concentration, intracellular calcium, and oxidative damage in mouse thymic lymphocytes.** Azenabor AA, Hoffman-Goetz L. "Intracellular Ca2+ levels were significantly higher in thymocytes of exercised compared with control mice ($p < .001$). There was a continuous flux of Ca2+ after exercise when cells were monitored in Ca2+ rich medium, with a significant influx between 160 and 200 sec ($p < .001$). Membrane bound estradiol was elevated in thymocytes of exercised compared to control mice ($p < .05$). Immediately after exercise there was a greater release of oxidative products by thymocytes in exhaustively exercised compared with control animals. There was also significant generation of lipid peroxide in thymus of exercised mice ($p < .001$). The findings suggest that exhaustive exercise may stimulate estradiol uptake by receptors on thymocytes, with a possible opening up of estradiol-receptor operated channels for Ca2+ entry into cells. This may have damaging effects on thymic lymphocytes by the triggering of oxidative reactions as determined by higher oxidative product release and greater generation of lipid peroxide."

Am J Pathol 1987 Jan;126(1):103-13 **Dietary fatty acid effects on T-cell-mediated immunity in mice infected with mycoplasma pulmonis or given carcinogens by injection.** Bennett M, Uauy R, Grundy SM. ". . . only mice on the POLY diet were significantly immunosuppressed, and only T-cell-mediated cutaneous sensitivity reactions were affected." "Deliberate infection with Mycoplasma pulmonis resulted in suppressed cutaneous T-cell responses in the POLY group of C3B6F1 mice, and aspirin partially reversed the immunosuppression." "It is tentatively concluded that diets rich in w-6 polyunsaturated diets, while not directly immunosuppressive, do predispose animals to suppression of certain T-cell-mediated immune responses. This immunosuppression can be "triggered" by infection and/or by exposure to carcinogens."

Trends Mol Med 2002 Oct;8(10):469-76. **Thymic regeneration: teaching an old immune system new tricks.** Berzins SP, Uldrich AP, Sutherland JS, Gill J, Miller JF, Godfrey DI, Boyd RL. **Recent studies in mice and humans show that the importance of the thymus extends well beyond the initial seeding of the peripheral T-cell pool.** Although peripheral homeostasis can maintain T-cell numbers, the thymus is the major,

if not the exclusive, source of new T-cell specificities. With age, thymus atrophy dramatically reduces the export of new T cells and predisposes an individual to impaired T-cell function, reduced T-cell immunity, and increased autoimmunity. Thymus atrophy is also the primary obstacle to restoration of the T-cell pool in the aftermath of HIV treatment or lymphoablative therapies. Here, we review thymus T-cell production, with particular attention to the factors that influence thymocyte export, and examine the impact that recent thymic emigrants have on the peripheral pool. In the future, thymic regeneration might become a feasible and potentially powerful approach to rejuvenating a depleted peripheral T-cell pool.

J Rheumatol 1990 Mar;17(3):311-7. **Sex hormone involvement in the induction of experimental systemic lupus erythematosus by a pathogenic anti-DNA idiotype in naive mice.** Blank M, Mendlovic S, Fricke H, Mozes E, Talal N, Shoenfeld Y "We found that injection of the pathogenic idiotype to BALB/c females and orchiectomized males treated with estrogen caused a rapid outburst of the disease 3 months after immunization, while nonestrogen treated mice developed the disease 5 months after immunization. The flare of SLE disease was characterized by raised levels of autoantibodies in the sera to dsDNA, histones, cardiolipin, Sm, RNP, SSA (Ro), SSB (La) and an emergence of high titers of mouse antibody carrying the 16/6 Id. These enhanced antibody levels were associated with an increase in erythrocyte sedimentation rate, proteinuria and leukopenia." "Our data demonstrate the importance of sex hormones on the induction of experimental SLE-like disease in mice with no genetic tendency to autoimmunity."

J Med 1980;11(2-3):81-105. **Serotonin and its precursors as modulators of the immunological responsiveness in mice.** Bliznakov EG. "The evidence of serotonergic-endocrine interrelations with regard to adrenal, thyroid, gonadal and prolactin functions is fast accumulating. Our study extends the importance of those interrelations to some functions of the immune system. **Multiple administration of 5-hydroxytryptamine(serotonin) or its precursor, 5-hydroxy-L-tryptophan(5-HTPH), produces marked depression of T cell dependent, humoral, hemolytic, primary immune response in mice. L-tryptophan, a more distant serotonin precursor, produces slight but significant depression of this immune response." "Administration of serotonin or 5-HTPH causes a marked reduction of the thymus weight. It is reasonable to postulate that the described effects result from the thymus involution which affects the T cell compartment of the immune system."** Since many clinically used drugs affect the serotonin metabolism, the clinical consequences of the resulting alteration of the immunological responsiveness should be considered."

J Steroid Biochem Mol Biol. 2002 Aug;81(4-5):309-17. **Differential activation of the IkappaBalpha and mouse mammary tumor virus promoters by progesterone and glucocorticoid receptors.** Deroo BJ, Archer TK. "To investigate how co-existing steroid receptors regulate gene transcription, we have compared two hormone-responsive promoters in T47D/A1-2 human breast cancer cells expressing both the GR and PR. The promoters chosen were those for the mouse mammary tumor virus (MMTV) and the gene for IkappaBalpha, the inhibitor of the ubiquitous transcription factor, nuclear factor kappa B (NFkappaB). Several differences between glucocorticoid and progestin activation of the IkappaBalpha and MMTV promoters were revealed. Both steroids activated the endogenous IkappaBalpha promoter, while only glucocorticoids activated a stably integrated MMTV promoter. In combination, progestins enhanced glucocorticoid activation of IkappaBalpha, but antagonized glucocorticoid activation of MMTV."

Fertil Steril 1991 Oct;56(4):718-24. **The relationship between in vitro fertilization and naturally occurring antibodies: evidence for increased production of antiphospholipid Autoantibodies.** Fisch B, Rikover Y, Shohat L, Zurgil N, Tadir Y, Ovadia J, Witz IP, Yron I OBJECTIVE: Assessment of possible effects of ovarian stimulation during in vitro fertilization (IVF) treatment cycles on circulating levels of antiphospholipid and antinuclear autoantibodies. DESIGN: The study was performed prospectively. Sera were obtained at three time points along IVF treatment cycle. Levels of autoantibodies directed against nuclear components, mitochondrial antigens, and phospholipids were determined using enzyme-linked immunosorbent assay. PATIENTS: Thirty-five patients, who underwent at least one previous IVF attempt, and 36 age- and sex-matched controls were analyzed. All participants were randomly selected. RESULTS: The mean levels of antiphospholipid (but not antinuclear) autoantibodies in sera from IVF-treated patients were found to be significantly higher than the corresponding values of the control group (for immunoglobulin [Ig]M isotype: anticardiolipin, antiphosphatidyl L-serine; for IgG isotype: anticardiolipin, antiphosphatidyl L-serine, and antiphosphatidylcholine; P less than 0.0001, assessed by Mann-Whitney test). The autoantibody levels remained more or less constant at different time points along the treatment cycle. No correlation with age and number of previous IVF cycles was demonstrated. CONCLUSIONS: Serum levels of antiphospholipid (but not antinuclear) autoantibodies increase after IVF treatment. Based on these preliminary data, it is not yet possible to estimate if the observed changes in autoantibody levels might have any future clinical influence on infertile patients undergoing IVF treatment. Comment in: Fertil Steril 1992 Oct;58(4):863-5.

Cell Mol Life Sci 1998 Oct;54(10):1076-82. **Regulation of B and T cell development by anterior pituitary hormones.** Foster M, Montecino-Rodriguez E, Clark R, Dorshkind K. Hormones produced by the anterior pituitary gland have been implicated in the regulation of primary lymphocyte development. In order to identify endocrine factors involved in that process, several strains of mice with genetic defects resulting in a selective impairment in the production of one or more anterior pituitary-derived hormones have been analysed. This study has resulted in the classification of endocrine hormones into the following four categories: (i) hormones such as prolactin with no apparent effects on primary lymphopoiesis; (ii) anabolic hormones such as growth hormone and insulin-like growth factor-I whose stimulatory effects on primary lymphopoiesis are non-lineage-specific and related to their actions as systemic mediators of growth and/or differentiation; (iii) hormones such as thyroid hormones that have an obligate role in primary B lymphopoiesis; and (iv) hormones such as oestrogens that act as negative regulators of lymphopoiesis.

J Clin Endocrinol Metab 1996 Mar;81(3):990-4. **Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy.** Giani C, Fierabracci P, Bonacci R, Gigliotti A, Campani D, De Negri F, Cecchetti D, Martino E, Pinchera A.

Schweiz Rundsch Med Prax 2001 Nov 1;90(44):1913-22. **[The environment and autoimmunity--from external causes to inner conflicts]** Gebbers JO. "Autoimmune disorders result from a breakdown of immunologic tolerance leading to an immune response against self-molecules. In most instances the events that initiate the immune response to self-molecules are unknown, but a number of studies suggest associations with environmental and genetic factors and certain types of infections. **The concordance of autoimmune diseases among identical twins is virtually always less than 50%, often in the 25-40% range.** This observation, as well as epidemic clustering of some autoimmune diseases following xenobiotic exposure, reinforces the thesis that autoimmune disease is secondary to both genetic and environmental

factors." "With these comments in mind it is important to note that there have been associations of a number of xenobiotics with human autoimmune disease, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, L-tryptophan, particulates, ultraviolet radiation, and ozone." "With the world-wide deterioration of the environment, this is a particular important subject for human health. This is best illustrated by the epidemics of eosinophilic myalgia syndrome with shared characteristics that occurred about 20 years ago. Another example is the toxic oil syndrome of Spain in 1981 involving cooking oil led to both acute and chronic disease as well as formation of auto-antibodies to collagen, DNA, and skeletal muscle. Currently the question is risen whether there is a link between environmental estrogens and autoimmune disorders, especially since these illnesses are reported possibly more frequent."

Biochem Pharmacol 2003 Apr 1;65(7):1027-34. **Broad-spectrum chemokine inhibitors (BSCIs) and their anti-inflammatory effects in vivo.** Grainger DJ, Reckless J.

Int J Immunopharmacol 1992 May;14(4):541-53. **Aromatase inhibitors regenerate the thymus in aging male rats.** Greenstein BD, de Bridges EF, Fitzpatrick FT.

Clin Exp Immunol 1993 Jun;92(3):432-6. **Pinealectomy ameliorates collagen II-induced arthritis in mice.** Hansson I, Holmdahl R, Mattsson R.

Physiol Behav 1999 Dec 1-15;68(1-2):169-74. **Effect of estradiol and exercise on lymphocyte proliferation responses in female Mice.** Hoffman-Goetz L. "This study investigated the effect of estradiol exposure and physical exercise on lymphocyte proliferation responses to T and B cell mitogens in female mice." **"In the thymus, there was a significant reduction of proliferation to ConA in the Ovx + E2 animals** relative to the other conditions at both concentrations of mitogen. At 1.0 microg/mL concentration, there was a significant interaction of hormone and exercise treatments. Sham (control) mice given exercise had a higher proliferation response relative to sedentary counterparts, whereas E2 mice did not differ in proliferation responses, irrespective of exercise condition. In the spleen, exposure to high concentrations of estradiol was associated with reduced proliferation responses to both mitogens; there were, however, no main or interaction effects of exercise. These results suggest that high levels of estradiol exposure following ovariectomy in mice significantly reduces lymphocyte blastogenesis responses, and that thymic immunomodulation after acute exercise is masked by the hormonal effect."

J Neuroimmunol 2003 Jan;134(1-2): 25-34. **Autoreactive T cells promote post-traumatic healing in the central nervous system.** Hofstetter HH, Sewell DL, Liu F, Sandor M, Forsthuber T, Lehmann PV, Fabry Z. In general, autoimmune responses are considered harmful to the host. In the best-defined model of autoimmune disease, murine experimental allergic encephalomyelitis (EAE), for example, brain-protein-specific autoimmune responses of both major classes, type-1 and type-2, have been implicated in causing brain pathology. We induced type-1 and type-2 autoimmunity to myelin oligodendrocyte protein (MOG) in C57.BL/6 mice. Instead of using pertussis toxin (PTX) to open the blood-brain barrier (BBB), which is the classic procedure, we set an aseptic cerebral injury (ACI) to see what the consequences of pre-primed, autoreactive type-1 and type-2 memory T cells gaining access to the brain in the course of sterile tissue injury would be. **Neither of these autoimmune response types induced pathology; on the contrary, both accelerated re-vascularization and post-traumatic healing.** The data suggest that induction of either type-1 or type-2 autoimmune responses is not inherently noxious to the host, but can have beneficial effects on tissue repair. Autoimmune pathology may develop only if molecules of microbial origin such as pertussis toxin additionally induce the "infectious nonself/danger" reaction in the antigen-presenting cells (APC) of the target organ itself.

Arch Histol Cytol 1997 Mar;60(1):65-78. **Glucocorticoid-induced thymocyte death in the murine thymus: the effect at later stages.** Ishii T, Nakamura M, Yagi H, Soga H, Kayaba S, Gotoh T, Satomi S, Itoh T. "We report here on kinetics of glucocorticoid-induced murine thymocyte death in vivo by the TUNEL method. TUNEL-positive cells were observed as early as at 2 h after intraperitoneal injection of glucocorticoid." "At 6 to 8 h after the injection, the number of phagocytosed thymocytes per individual macrophage had reached its maximum, and at 8 to 12 h many ruptured macrophages ingesting too many dying thymocytes became noticeable. During the process, no additional macrophages appeared to be mobilized to the thymus. At 6 to 8 h after the injection, however, coincidentally with the fact that macrophages had become unable to further ingest dying lymphocytes, dead cells were left unphagocytosed, and ultimately became "free" positive cells, probably due to some proteolytic process ongoing within the thymus. As late as at 12 h, morphological examination revealed that epithelial cells seemed to begin engulfing thymocytes, almost simultaneously with the start of rupture of the macrophages due to the ingestion of too many thymocytes." "Altogether, these results suggest that: 1) even though thymocytes were exposed to glucocorticoid in vivo, most of them were not TUNEL-positive unless they were phagocytosed; 2) even after most macrophages had ingested too many cells at later stages, macrophages in other locations did not migrate to the thymus; and finally, 3) deletion of damaged thymocytes was also carried out by thymic epithelial cells, though not frequently, at around 12 h and later."

Rinsho Shinkeigaku 1993 Sep;33(9):995-7. **[A case of Hashimoto's encephalopathy with a relapsing course related to menstrual cycle]** Ishii K, Hayashi A, Tamaoka A, Mizusawa H, Shoji S. A case of 43-year-old woman with Hashimoto's encephalopathy who experienced three relapses closely associated with the menstrual cycle is reported. In April 1992, she began to experience occasional tremors in her arms. Three months later, she experienced a generalized seizure and was transferred to our hospital. Hashimoto's thyroiditis was diagnosed on the basis of high thyroid microsomal titer and mild hypothyroidism. Neurological findings in admission included action tremor in both hands, myoclonus in all extremities, cerebellar ataxia, confusion, and hyperreflexia. Cerebrospinal fluid showed elevated protein level without pleocytosis. Electroencephalogram showed diffuse slowing and magnetic resonance imaging of brain was normal. Hashimoto's encephalopathy was diagnosed from these findings. **These episodes of remission and exacerbation were observed during the admission. Her symptoms started at ovulation, worsened during the luteal phase, and improved when menstruation started. After the third relapse, she was treated with oral thyroxine for hypothyroidism and with an estrogen and progesterone combination to regulate the menstrual cycle. Her thyroid function gradually became euthyroid and she did not experience any subsequent relapses. The relation between the relapsing course and menstrual cycle suggests that the periodic alteration of gonadotrophic and/or gonadal hormones or the menstrual regulating center itself in the brain may be an important factor of pathogenetic mechanism of the disorder.**

Transplantation 1989 Jul;48(1):98-102. **Enhancement of immunosuppression by substitution of fish oil for olive oil as a vehicle for cyclosporine.** Kelley VE, Kirkman RL, Bastos M, Barrett LV, Strom, T.B.

Berl Munch Tierarztl Wochenschr 1992 Mar 1;105(3):81-85. **[Modification of lymphoblastic transformation by estradiol, progesterone and corticosterone in vitro].** Kuhn V, Hardegg W "In conclusion, corticosterone, E2 and progesterone showed a dose-dependent influence on lymphoblast transformation of thymocytes and splenocytes and progesterone had opposite effects on corticosterone-induced suppression of blastogenesis in rat lymphocytes, especially in thymocytes."

J Immunol 1990 Mar 15;144(6):2147-51. **The nonobese diabetic mouse model. Independent expression of humoral and cell-mediated autoimmune features.** Lehuen A, Bendelac A, Bach JF, Carnaud C. "Altogether, these results suggest that NOD mice, like other autoimmune strains, **suffer from a genetically inherited defect of B cell regulation resulting in the hyperproduction of natural autoantibodies."**

Int J Immunopharmacol 1984;6(4):287-97. **Mechanisms of estrogen-induced myelotoxicity: evidence of thymic regulation.** Luster MI, Boorman GA, Korach KS, Dieter MP, Hong L. "Mice exposed to pharmacological levels of steroidal and nonsteroidal estrogens including alpha-dienestrol, 17 beta-estradiol, and diethylstilbestrol **demonstrate bone marrow hypocellularity, and decreased numbers of pluipotent hemopoietic stem cells.** Hormones with little estrogenic activity including testosterone and progesterone failed to induce myelotoxicity as did nonestrogenic metabolites of DES." "One of these mechanisms is mediated through the thymus since surgical thymectomy abolished the ability of estrogens to suppress CFU proliferation." "That the initial events in estrogen-induced myelotoxicity may be mediated through a receptor

mechanism was suggested by the ability of antiestrogens to induce antagonism when administered prior to estradiol and the presence of estrogen binding components in lymphoreticular tissues including the thymus and bone marrow. These studies suggest that reduced CFU kinetics observed following estrogen exposure is, in part, due to alterations in regulatory factors produced by thymic epithelial cells in response to a specific estrogen stimulus."

Fertil Steril 1983 Apr;39(4):485-489. **The effect of aqueous progesterone on operative adhesion Formation.** Maurer JH, Bonaventura LM "Progesterone (P) has been shown to have antiinflammatory and immunosuppressive properties. This study was designed to evaluate these effects on operative adhesion formation." Forty guinea pigs received standardized injuries to their uterine horns. Four groups were examined. Normal saline was used as an irrigant in the first, or control, group. Aqueous P (50 mg or 1 ml) was dripped over the injured site and instilled intraperitoneally in the second group. The third group received intramuscular aqueous P (3.3 mg/kg body weight) 1 day postoperatively, the day of surgery, and either 6 or 13 days postoperatively until reexploration. In the fourth group 1 ml of 32% dextran 70 (Hyskon) was administered in the same manner as aqueous P in the second group. The animals in all groups were reexplored 1 or 2 weeks after the initial surgical procedure, and the adhesions were scored. Adhesion formation was significantly reduced (P less than 0.001) in all treatment groups when compared with the control group."

Int J Immunopharmacol 2000 Nov;22(11):955-65. **Progesterone inhibits glucocorticoid-induced murine thymocyte apoptosis.** McMurray RW, Wilson JG, Bigler L, Xiang L, Lagoo A. "Sex and sex hormones modulate immune development and responses. A primary target of their effects is the structure and cellularity of the thymus; therefore, we examined the effects of sex and sex steroids on thymocyte apoptosis." **"Both estrogen and testosterone increased in vitro thymocyte apoptosis. In contrast, progesterone not only inhibited spontaneous in vitro thymocyte apoptosis, but also prevented in vitro glucocorticoid-induced apoptosis. Progesterone administration also suppressed glucocorticoid-induced in vivo thymocyte apoptosis. These results suggest that anti-apoptotic effects of progesterone may influence T cell development and subsequent immune responses."**

J Neuroimmunol 1997 May;75(1-2):1-8. **Inhibitory effect of pregnancy on stress-induced immunosuppression through corticotropin releasing hormone (CRH) and dopaminergic systems.** Nakamura H, Seto T, Nagase H, Yoshida M, Dan S, Ogino K "Decreases in splenic NKCA, corticotropin releasing hormone (CRH) in the hypothalamus, and increases in progesterone (P), beta-endorphin (beta EP), and dopamine (DA) metabolic ratios in the frontal cortex and nucleus accumbens produced by stress were recognized in the virgin rats, but not in the pregnant rats. Pregnancy reduced splenic NKCA in rats without stress, but elevated it in the rats exposed to stress with a duration of 180 min. These findings suggest inhibitory Effects of pregnancy on stress-induced immunosuppression and neuroendocrine changes, thereby promoting homeostasis in the neuroendocrine-immune system against stress. Such enhanced homeostasis associated with pregnancy seemed to be mediated by the activation of placental P and placental or pituitary beta EP in cooperation with mesocortical and mesolimbic DA systems and hypothalamic CRH."

Toxicology 2001 May 28;163(1):49-62. **Evidence for estradiol-induced apoptosis and dysregulated T cell maturation in the thymus.** Okasha SA, Ryu S, Do Y, McKallip RJ, Nagarkatti M, Nagarkatti PS. "The thymocytes from E2-treated mice when cultured in vitro for 24h, showed increased levels of apoptosis when compared to controls." "However, the total cellularity of all T cell subsets in the thymus was decreased following E2 treatment." "These data therefore confirmed that the thymocytes were indeed undergoing apoptosis following E2 treatment. Together, our studies suggest for the first time that estrogen may induce thymic atrophy by triggering apoptosis."

Am J Physiol Endocrinol Metab 2002 Nov;283(5):E909-16. **Endotoxemia reduces skeletal muscle protein synthesis in neonates.** Orellana RA, O'Connor PM, Nguyen HV, Bush JA, Suryawan A, Thivierge MC, Fiorotto ML, Davis TA. **"Protein synthesis in skeletal muscle is reduced by as much as 50% as early as 4 h after a septic challenge in adults."** "These findings suggest that, when substrate supply is maintained, skeletal muscle protein synthesis in neonates compared with adults is relatively resistant to the catabolic effects of sepsis."

Exp Neurol 1987 Mar;95(3):639-51. **Immunocomplexes in rat and rabbit spinal cord after injury.** Palladini G, Grossi M, Maleci A, Lauro GM, Guidetti B. "The possibility that, following a major lesion of the central nervous system, a humoral immune response could be evoked with formation of immune complexes "in situ" was investigated. For this purpose, an immunohistochemical study on rabbit and rat spinal cord at different times after surgical transection was carried out." "The results showed in the rabbit the absence of antibodies to neural antigens before surgical injury and its appearance within a few days after surgery. On the other hand, in the rat, even before the injury, we found antibodies to neural tissue which decreased in the first few hours after injury, and returned to control values during successive days." "The possible role of this immune response in the failure of axonal regeneration in mammalian spinal cord is briefly discussed."

FEBS Lett 1997 Apr 7;406(1-2):136-8. **Age-dependent decline in the cytochrome c oxidase activity in rat heart mitochondria: role of cardiolipin.** Paradies G, Ruggiero FM, Petrosillo G, Quagliariello E. "Cardiolipin is a major mitochondrial membrane lipid and plays a pivotal role in mitochondrial function. We have recently suggested a possible involvement of this phospholipid in the age-linked decline of cytochrome c oxidase activity in rat heart mitochondria [G. Paradies et al. (1993) Arch. Gerontol. Geriatr. 16, 263-272]." "We demonstrate that the lower cytochrome c oxidase activity in heart mitochondria from aged rats can be fully restored to the level of young control rats by exogenously added cardiolipin. No restoration was obtained with other phospholipids or with peroxidized cardiolipin. Our data support a key role for cardiolipin in the age-linked decline of rat heart mitochondrial cytochrome c oxidase activity."

Arch Biochem Biophys 1991 Feb 1;284(2):332-7. **Effect of aging on the activity of the phosphate carrier and on the lipid composition in rat liver mitochondria.** Paradies G, Ruggiero FM. "The effect of aging on the activity of the phosphate carrier and on the lipid composition in rat liver mitochondria has been investigated. It was found that the rate of phosphate transport in mitochondria from aged rats (28 months old) is significantly reduced (around 40%) compared to that obtained in mitochondria from young control rats (5 months old)." "The hepatic mitochondrial lipid composition is altered significantly in aged rats: the total cholesterol increases (31%), the phospholipids decrease (12%), and the cholesterol/phospholipid molar ratio increases (44%). Among the phospholipids cardiolipin shows the greatest alteration (30% decrease with age). Alterations were also found in the pattern of fatty acids. The age-related decrement in the activity of the phosphate carrier appears to be dependent on changes in the lipid domain surrounding the carrier protein molecule in the mitochondrial membrane."

J Exp Med 1978 Jun 1;147(6):1568-83. **Effect of castration and sex hormone treatment on survival, anti-nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice.** Roubinian JR, Talal N, Greenspan JS, Goodman JR, Siiteri PK."Mice receiving androgen showed improved survival, reduced anti-nucleic acid antibodies, or less evidence of glomerulonephritis as determined by light, immunofluorescent, and electron microscopy. By contrast, opposite effects were observed in castrated mice receiving estrogen. Intact male NZB/NZW F1 mice received androgen implants at 8 mo, an age when they develop an accelerated autoimmune disease associated with a decline in serum testosterone concentration. Such treated mice had improved survival and reduced concentrations of antibodies to DNA and to polyadenylic acid (Poly A)."

J Clin Invest 1977 Jun;59(6):1066-70. **Androgenic hormones modulate autoantibody responses and improve survival in murine lupus.** Roubinian JR, Papoian R, Talal N

Int J Immunopharmacol 1999 Dec;21(12):861-8. **Inhibitory effect of natural and environmental estrogens on thymic hormone production in thymus epithelial cell culture.** Sakabe K, Okuma M, Karaki S, Matsuura S, Yoshida T, Aikawa H, Izumi S, Kayama F. "The production of thymosin-alpha 1 by TECs was significantly inhibited by increasing concentrations of 17beta-estradiol (natural estrogen) over 3 x 10(-11) M, genistein (phytoestrogen) over 3 x 10(-9) M, coumestrol (phytoestrogen) over 3 x 10(-9) M, alpha-zearalanol (livestock anabolic) over 3 x 10(-7) and bisphenol-A (plastic) over 3 x 10(-6) M." "The above results clearly indicate that natural and environmental estrogens directly modulate TECs to produce thymic hormone probably through an estrogen receptor mechanism."

J Immunol 1994 Mar 1;152(5):2586-95. **Ionizing radiation and autoimmunity. Induction of autoimmune disease in mice by high dose fractionated total lymphoid irradiation and its prevention by inoculating normal T cells.** Sakaguchi N, Miyai K, Sakaguchi S. "Ionizing radiation can functionally alter the immune system and break self-tolerance."

Immunol Invest 1992 Feb;21(1):1-10. **Studies on the immunosuppressive role of steroid hormones during Pregnancy.** Saleem MA, Jha P, Buckshee K, Farooq A

Science 1988 May 20;240(4855):1032-3. **Essential fatty acid depletion of renal allografts and prevention of rejection.** Schreiner GF, Flye W, Brunt E, Korber K, Lefkowith JB "Kidneys subjected to EFAD and thus depleted of resident Ia-positive macrophages survived and functioned when transplanted across a major histocompatibility antigen barrier in the absence of immunosuppression of the recipient. Control allografts were rejected promptly. Allografts from donors subjected to EFAD normalized their lipid composition and were repopulated with host macrophages by 5 days. Administration of Ia-positive cells at the time of transplantation established that the resident leukocyte depletion induced by EFAD was responsible for the protective effect."

Microsc Res Tech 1997 Aug 1;38(3):216-26. **Thymic microenvironment at the light microscopic level.** Schuurman HJ, Kuper CF, Kendall MD. "The thymus is a primary lymphoid organ that serves the immune system by providing an optimal microenvironment for developing T cells to rearrange the genes encoding the T-cell receptor and to undergo positive and negative selection in shaping the peripheral T-cell repertoire." "Bone marrow-derived interdigitating cells and macrophages are the main accessory cell populations. The epithelium, interdigitating cells, and macrophages each contribute to the T-cell selection process."

J Immunol 1979 Jun;122(6):2541-7. **Natural killer cells, bone, and the bone marrow: studies in estrogen-treated mice and in congenitally osteopetrotic (mi/mi) mice.** Seaman WE, Gindhart TD, Greenspan JS, Blackman MA, Talal N **"Mice lose natural killer cells after 6 weeks of treatment with 17 beta-estradiol."** "From these observations, we conclude that estrogens do not reduce natural killer cells simply by reducing the volume of bone marrow. Estrogens may instead have an effect on bone marrow cells that leads both to osteoproliferation and to a deficiency of marrow-dependent cells."

J Immunol 1978 Dec;121(6):2193-8. beta-**Estradiol reduces natural killer cells in mice.** Seaman WE, Blackman MA, Gindhart TD, Roubinian JR, Loeb JM, Talal N. "Four to 6 weeks of estrogen administration caused a substantial reduction in natural killer cell activity in the spleens from mice of either sex. Androgen (5alpha-dihydrotestosterone) did not." "The effects of estradiol were not dependent on the thymus, since estradiol reduced natural killing in mice that had been neonatally thymectomized. After removal of the estrogen implant, natural killing recovered over a period of 8 weeks. The loss of natural killing may reflect a loss of bone marrow secondary to estrogen-induced osteosclerosis."

Lupus. 2004;13(4):217-22. **Possible mechanisms of gender bias in SLE: a new hypothesis involving a comparison of SLE with atopy.** Sekigawa I, Naito T, Hira K, Mitsuishi K, Ogasawara H, Hashimoto H, Ogawa H. **"Estrogens seem to play an important role in the overexpression of endogenous autoantigens, such as human endogenous retroviruses (HERV),** and this may be related to the existence of a gender bias in the incidence of SLE but not atopy."

Ann N Y Acad Sci 1999 Jun 22;876:159-63. **Association between anticardiolipin antibody positivity and increased 17-beta-estradiol levels in premenopausal women with rheumatoid arthritis.** Seriolo B, Accardo S, Garnero A, Fasciolo D, Cutolo M

Clin Immunol Immunopathol 1983 Mar;26(3):361-9. **Effects of castration and sex hormones on immune clearance and autoimmune disease in MRL/Mp-lpr/lpr and MRL/Mp-+/+ mice.** Shear HL, Wofsy D, Talal N. "The clearance of erythrocytes sensitized with IgG was studied in MRL/Mp-lpr/lpr (MRL-lpr) and MRL/Mp-+/+ (MRL-+/+) mice, which spontaneously develop autoimmune disease." "Androgen treatment improved clearance in MRL-+/+ mice but not in MRL-lpr mice, even though autoantibody levels, renal function, and survival were improved. These results suggest that the beneficial effects of androgen on autoimmune disease are not due solely to improved clearance of immune complexes."

Kidney Int 1992 May;41(5):1245-53. **Essential fatty acid deficiency normalizes function and histology in rat nephrotoxic nephritis.** Takahashi K, Kato T, Schreiner GF, Ebert J, Badr KF "The central lipid abnormality in essential fatty acid deficiency (EFAD) is the lack of availability of arachidonic acid. To examine the role of total eicosanoid's biosyntheses in the pathology and pathophysiology of glomerulonephritis, EFAD was induced in weanling rats, which were then subjected to antiglomerular basement membrane antibody (NTS)-induced injury in adulthood." "Two hours post-NTS, and despite the occurrence of proteinuria in both EFAD and STD animals, glomerular dynamics were essentially normal in EFAD rats, whereas STD animals had reduced values for glomerular filtration rate (GFR) and renal plasma flow rate (RPF). At two weeks, severe histologic changes were observed in STD animals including mesangial and stalk hypercellularity, moderate sclerosis, and interstitial nephritis, coupled with heavy proteinuria and reduced GFR and RPF. In dramatic contrast, EFAD rats displayed totally normal glomerular structures and functions. In parallel, glomerular generation rates of prostaglandin E2 and thromboxane A2 were suppressed markedly in EFAD rats. **Thus, EFAD confers complete protection against the histopathologic and functional sequelae of immune-initiated injury in the glomerulus.** The data suggest that the initial wave of complement-induced neutrophil infiltration (with resultant proteinuria) is not sufficient to perpetuate injury into the more destructive chronic phases."

The New England Journal of Medicine Volume 326:513-518 February 20, 1992 Number 8. **Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis.** N Takasu, T Yamada, M Takasu, I Komiya, Y Nagasawa, T Asawa, T Shinoda, T Aizawa, and Y Koizumi. "Hypothyroidism may result from the production of antibodies that block the actions of thyrotropin." "Thyrotropin-blocking antibodies were detected in 9 percent of the patients with goitrous autoimmune thyroiditis and in 25 percent of those with atrophic autoimmune thyroiditis. Among the 21 patients studied serially while receiving levothyroxine, thyrotropin-blocking antibodies disappeared in 15 (group 1), 7 of whom had goiter initially, and persisted in 6 (group 2), none of whom had goiter initially. Levothyroxine therapy was subsequently discontinued in these 21 patients. Six of those in group 1 (four with goiter) remained euthyroid (mean follow-up after discontinuation of therapy, 2.1 years), and nine became hypothyroid again within 3 months. All six patients in group 2 remained hypothyroid." "Hypothyroidism in some patients with autoimmune thyroiditis may be due to thyrotropin-blocking antibodies. The production of thyrotropin-blocking antibodies may subside, producing remissions of hypothyroidism. Chronic autoimmune thyroiditis may therefore cause transient as well as permanent hypothyroidism."

J Rheumatol 1987 Jun;14 Suppl 13:21-5 **"Interleukin 2, T cell receptor and sex hormone studies in autoimmune mice."** Talal N, Dang H, Ahmed SA, Kraig E, Fischbach M. "Systemic lupus erythematosus (SLE) is a disease of immune dysregulation in which B cell hyperactivity and T cell deficiency are important characteristics. Sex factors also play a major role in the pathogenesis based on the physiologic effects of estrogen in promoting immunologic hyperactivity." "This aberrant T cell receptor might be explained by a defect in glycosylation. The administration of estrogen to pregnant mice late in gestation results in offspring with a permanently altered immune system. These mice develop features of autoimmunity similar to those that occur spontaneously in genetically susceptible autoimmune mice. This phenomenon may have etiopathological significance for familial SLE.

Isr J Med Sci 1988 Dec;24(12):725-8. **Sex hormones, CD5+ (Lyl+) B-cells, and autoimmune diseases.** Talal N, Ahmed SA

Ann N Y Acad Sci 1986;475:320-8 **Hormonal approaches to immunotherapy of autoimmune disease.** Talal N, Ahmed SA, Dauphinee M

Clin Rheum Dis 1982 Apr;8(1):23-8. **Sex hormones and modulation of immune response in SLE.** Talal N. Clearance of sensitized erythrocytes in NZB/NZW mice. Effects of castration and sex hormone treatment. Shear HL, Roubinian JR, Gil P, Talal N. The clearance of particulate immune complexes consisting of erythrocytes sensitized with IgG or complement was investigated in (NZB x NZW)F1 (B/W) mice. Treatment of castrated B/W mice with androgen or estrogen was able to modulate this clearance. Young (3-month-old) male and female B/W mice cleared IgG-sensitized mouse erythrocytes rapidly, whereas older males (13 months) and females (7 months) showed a marked impairment in their ability to clear these cells. In addition, erythrocytes sensitized **with complement in the absence of antibody were cleared within 5 min in**

young B/W mice. Older mice showed a greater and more rapid clearance rate of these cells. Castrated female B/W mice treated with androgen implants from three weeks of age showed improved clearance of IgG-sensitized erythrocytes at 7 months, whereas **estrogen-treated male mice showed delayed clearance. These results suggest an age-dependent defect** in the clearance of IgG-sensitized particles, perhaps due to diminished levels of serum complement and/or saturation of Fc receptors. In addition, there is an alteration in the clearance of complement-sensitized erythrocytes which may be related to changes in macrophage activity or enzyme inactivators of C3 and C4. The possible mechanisms responsible for the hormonal modulation of clearance are discussed in relation to the known ability of these hormones to influence autoimmune diseases.

Arthritis Rheum 1981 Aug; 24(8):1054-6 **Sex steroid hormones and systemic lupus erythematosus.** Talal N.

Med Cutan Ibero Lat Am 1980;8(1-3):15-21. **[Postovulation dermatitis (dermatitis caused by progesterone)]** Torras H, Ferrando J, Mallolas J. Postovulation Dermatitis is a frequent clinical picture although it is not well known. Clinically a polymorphous eruption appears between than 8 or 10 day before menses. The Authors report three cases in which an complete immunological investigation was performed. They conclude that there is no objective evidence of the autoimmune pathogeny of this picture in spite of the clinical relationship between the dermatitis and the ovulation. Therefore they suggest that diseases should be described as "Postovulation Dermatitis" instead "Autoimmune Progesterone Dermatitis".

J Endocrinol Invest 1993 Sep;16(8):619-24. **Hormonal pattern in women affected by rheumatoid arthritis.** Valentino R, Savastano S, Tommaselli AP, Riccio A, Mariniello P, Pronesti G, De Divitiis PM, Lombardi G. **"We have previously reported the presence of progesterone (P) deficiency in female patients with thyroid and ovarian autoimmune disease."** "In this context, the hormonal profile in 9 women with rheumatoid arthritis (RA) and in 9 age-matched ealthy women, were evaluated to verify the presence of a steroid hormone secretion impairment in a systemic autoimmune disease, further supporting our hypothesis of P deficiency involvement. P and androgen plasma levels, in the luteal phase, were significantly lower ($p < 0.05$ and 0.005, respectively) in RA patients than in the control group...." "Moreover, despite normal cortisol values, corticosterone (B) plasma levels were significantly higher in the RA patients ($p < 0.01$ and 0.05 in follicular and luteal phase, respectively). Therefore, our present data confirm the androgen deficiency in patients with a systemic autoimmune disease, such as RA and support the immunomodulator effect of P." "In conclusion, in addition to androgens, the immunomodulator role of P should also be taken into account in the pathogenesis of the systemic autoimmune disease."

Endocrinology 1994 Dec; 135(6): 2615-22. **"17 beta-estradiol, but not 5 alpha-dihydrotestosterone, augments antibodies to double-stranded deoxyribo- nucleic acid in nonautoimmune C57BL/6J mice."** Verthelyi D, Ahmed SA "In this study, we investigated the influence of gender and sex hormones on the development of antibodies to double-stranded DNA in nonautoimmune C57BL/6J mice." "In summary, our findings suggest that estrogen, but not dihydrotestosterone, promotes anti-dsDNA antibodies in normal mice."

Int Immunopharmacol 2001 Jun;1(6):983-93. **Sex hormones as immunomodulators in health and disease.** Verthelyi D. **"Studies in normal mice show that estrogen treatment induces polyclonal B cell activation with increased expression of autoantibodies characteristic of autoimmune diseases.** Several mechanisms appear to contribute to the break in tolerance and the increase in plasma cell activity including a reduction of the mass of the bone marrow and the thymus, the emergence of sites of extramedullary hematopoiesis and altered susceptibility of B cells to cell death. In addition, sex hormone levels in both humans and experimental models correlated with the activity of their cytokine-secreting cells indicating that sex hormones influence the cytokine milieu and suggesting that altered sex hormonal levels in autoimmune patients contribute to the skewed cytokine milieu characteristic of systemic lupus erythematosus (SLE)."

Cell Immunol 1998 Nov 1;189(2):125-34. **"Estrogen increases the number of plasma cells and enhances their autoantibody production in nonautoimmune C57BL/6 mice."** Verthelyi DI, Ahmed SA "In this study, by employing ELIspot, image cytometry, flow cytometry, cytology, and ELISA, we show that long-term exposure of normal mice to estrogen activates B cells to produce higher numbers of not only immunoglobulin-producing cells, but also autoantibody-producing cells. **Estrogen promoted a decrease in B220(+) splenic lymphocytes, but resulted in a 10-fold increase in plasma cells.** Further, the output of immunoglobulins including autoantibodies from individual plasma cells from estrogen-exposed mice was markedly increased, suggesting B cell hyperactivity. Importantly, our findings show that treatment of normal mice, solely with estrogen, can override B cell tolerance and promote autoreactive B cells in normal individuals."

Immunol Rev 1989 Aug;110:173-85. **Peripheral T cells select the B-cell repertoire in old mice.** Weksler ME, Russo C, Siskind GW. "These studies have shown that the alterations in the repertoire of antibody produced by old mice is not due to an intrinsic defect in the bone marrow or in the B-lymphocyte population arising from the bone marrow but rather to a selective downregulation by auto-anti-idiotypic antibody and idiotype-anti-idiotype interactions, shifting the idiotype distribution in the peripheral B-cell population." "The overall shift may be described as a decreased reactivity to foreign antigens and a complementary increase in reactivity with self antigens."

Proc Natl Acad Sci U S A 2002 May 28;99(11):7616-21. **The phytoestrogen genistein induces thymic and immune changes: a human health concern?** Yellayi S, Naaz A, Szewczykowski MA, Sato T, Woods JA, Chang J, Segre M, Allred CD, Helferich WG, Cooke PS. "Use of soy-based infant formulas and soy/isoflavone supplements has aroused concern because of potential estrogenic effects of the soy isoflavones genistein and daidzein. Here we show that s.c. genistein injections in ovariectomized adult mice produced **dose-responsive decreases in thymic weight of up to 80%.** Genistein's thymic effects occurred through both estrogen receptor (ER) and non-ER-mediated mechanisms, as the genistein effects on thymus were only partially blocked by the ER antagonist ICI 182,780. **Genistein decreased thymocyte numbers up to 86% and doubled apoptosis, indicating that the mechanism of the genistein effect on loss of thymocytes is caused in part by increased apoptosis." "Critically, dietary genistein at concentrations that produced serum genistein levels substantially less than those in soy-fed infants produced marked thymic atrophy.** These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants."

Life Sci 2000 Mar 3;66(15):1451-9. **Supraphysiological level of estrogen exposure in vivo increases lymphoid cell death in mice.** Zajchowski S, Hoffman-Goetz L. "These results suggest that supraphysiological levels of estrogen in vivo induce damage in lymphoid cells; however, the impact of estrogen associated lymphoid tissue damage on specific immune functions remains to be determined."

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