Ray Peat's Newsletter

Copyright 2005 Raymond Peat P.O. Box 5764 Eugene OR 97405 March 2006

To the wicked, everything serves as pretext. – Voltaire

Inflammation, endotoxin, estrogen, and other problems

Over the last few decades, the meaning of inflammation has changed a little, from being thought of simply as an essential part of the immune reaction, to being recognized as something that can interfere with the immune system, and that contributes to chronic disease and degeneration.

Many components of the inflammatory reaction have been identified lately, but the way those fit into the context of the whole organism still isn't clear.

Many of the "evolutionary interpretations" of particular biological features are just words, empty speculations that can't be tested. (Selective breeding experiments and comparative physiology can provide some basis for arguments about the evolution of the immune system, but the people who created the "big picture" weren't burdened by a need for detailed evidence.)

Developmental processes, however, have been studied in great detail, and as information accumulates, it is becoming clear that the traditional view of inflammation has little to do with reality. When inflammation is "explained" as something that evolved to protect the organism against infection, people will be taught that theory, and will feel no need to think about the subject again.

With the newer realization that inflammation can lead to cancer, heart disease, diabetes, dementia, and other degenerative processes, the logical seeming course of action for people taught the traditional "evolutionary" view of inflammation has been to look for the infectious organism causing the problem.

But if we put inflammation into the developmental context, it is immediately clear that infectious agents are just one of the many factors that we interact with and that can be involved in the inflammatory and degenerative processes. Nutrition, toxins, environmental stresses, and biological cycles influence the way we react to infectious organisms, and even in the absence of virulent organisms, can cause inflammation and degeneration. In the uterus and ovary, for example, inflammatory and degenerative changes are part of normal functioning.

In those organs, the cyclic changes in structure are orchestrated to a monthly rhythm that makes them very obvious. But in other organs, such as the adrenal cortex, the intestinal epithelium, the liver, and the skin, there is a continuous process of renewal (and degeneration) of cells that is fairly well known, despite the dogmatists who want to cling to the "Hayflick limit," that denies the existence of a flowing renewal of cells in every organ, or that insists that no renewal is possible after 50 divisions of a cell line. Cell renewal occurs even in the brain and the heart. The Hayflick doctrine was plausible to people who were committed to a Weismannist view of genetics and development, a view that radically denied the role of organismic and environmental interactions in development.

Cells that are well insulated from the environment can live for a very long time, but cells that directly contact the environment, i.e., the skin and the intestinal epithelium, divide rapidly, and are shed.

When stimulation is great, and energy supply is weak, a cell will either adapt to the conditions, sometimes increasing its rate of division, or die. Nerve cells can protect themselves by becoming insensitive to stimulation; in some cases, the

stress-induced loss of its axon can probably turn a nerve cell into a resting, or stem, cell.

The dissolution of a cell releases its materials in different ways, according to the conditions that caused it to die. Sometimes it releases histamine and other substances that can increase blood flow in nearby capillaries, but under other conditions it can liquefy without causing much change in its environment. When a significant amount of cellular debris accumulates in an area, wandering cells sense it, and depending on the nature of the injury, they may simply remove the debris, or stay and adapt, forming part of a repair structure.

Proteolytic enzymes and nucleases can decompose most of the structural proteins and nucleic acids, but the lipases that act on the dead cell's structural lipids release a variety of modified phospholipids, fatty acids, and cholesterol, with considerable biological activity or significance. These substances appear with regularity when cells are being damaged, and they are the most important class of signals acting on the immune system. Oxidized phospholipids can cause other cells to form a variety of substances that amplify the alarm signal (e.g., Kadl, et al., 2002). Their importance justifies the view of J. Cunliffe and P. Matzinger, that the immune system is actually a system of structural development and maintenance, and that its role in killing alien organisms is triggered when tissue damage releases our intrinsic signal substances.

Polyunsaturated fatty acids, derived from foods, have a special role in the immune system, intensifying the effects of stress (cholesterol newsletter, September, 2005) in killing lymphocytes, and blocking the proliferative response of thymic cells (Rotondo, et al., 1994). They tend to shift immune functions from cellular immunity to humoral (antibody) immunity, and this pattern predisposes to autoimmunity. They are probably directly toxic to the liver (Ritskes-Hoitinga, 1998). DHA increases the leakiness of the bowel, allowing more endotoxin to enter the circulation (Roig-Perez, et al., 2004).

When cells have enough glucose, oxygen, and thyroid hormone, and aren't being over-stimulated, energy consumption can be uncoupled from the formation of ATP. This allows the mitochondria to devote more energy to the production of the material needed for synthesizing cholesterol and its derivatives, pregnenolone, progesterone, and DHEA, and to form carbon dioxide at a high rate. Uncoupling helps to lower the formation of inflammatory cytokines (Horvath, et al., 2003). A chronically "uncoupled" metabolic state has been associated with longevity (Speakman, et al., 2004). The rate of cholesterol production, and the amount in circulation, tend to be inversely related to systemic inflammation. All of the types of lipoprotein absorb, bind, and help to eliminate endotoxin, for example. Carbon dioxide and the major steroids stabilize cells against excessive stimulation, and protect the cell structure.

Bacteria and plants produce a variety of lipids that serve some purposes analogous to our cholesterol and phospholipids. Some of the common intestinal bacteria produce a molecule containing amino sugars and fatty acids (lipopolysaccharide, LPS), that's called endotoxin. The "endo" root distinguishes it from the "exotoxins" secreted by some bacteria, because the endotoxin is a structural part of the bacterium, that protects the bacterium against some of the exotoxins produced by other microorganisms. Normally, our intestine and liver destroy most of the LPS endotoxin before it reaches the general circulation. The bile acids, a major end product of cholesterol, have a detergent action in the intestine that usually keeps endotoxin in solution, away from the absorptive surfaces of the intestine. If the flow of bile is obstructed, endotoxin is allowed to enter the system (Bertok, 2004). Estrogen can inhibit the flow of bile (Stieger, et al., 2000). A mucus lining is part of the protective barrier, but the microscopic integrity of the intestinal cells themselves finally regulates the passage of materials into the blood and lymphatic vessels.

The barrier function of the intestine is weakened by poisons, malnutrition, and the reduced circulation that can result from stress. Estrogens, such as oral contraceptives or Premarin, can cause colitis by shutting off the blood supply (Gurbuz, et al., 1994; Deana and Dean, 1995).

When our cells are exposed to LPS, they produce many of the same reactions that they

would produce in response to our endogenous phospholipids. The major proteins that interact with cholesterol contain lipophilic regions called beta sheets, in which a relatively flat surface is formed by parallel strands of the protein. LPS contains a group of fatty acids bound together by the polysaccharide, that strongly binds to these proteins.

The alarm reaction produced either by damage of some of our own tissue or by the entrance of LPS into the circulation can, under ideal circumstances, lead to a series of protective and defensive reactions, that resolve the problem. The production of steroids is increased, and, early in life, the liberation of fatty acids itself can contribute to the antiinflammatory processes that restore the barrier function and energy production. But when the endogenous omega-9 fatty acids have been thoroughly displaced by dietary omega-6 and omega-3 fatty acids, the systemic release of fatty acids becomes an amplifier of the stress state initiated by injury or other stress. The liver, for example, decreases its detoxification of estrogen in the presence of polyunsaturated fatty acids.

In the ovary and uterus, the healthy alternation of excitation and quiescence usually continues for many years, and in rodents it often ends in a state of "persistent estrus," in which the excitatory state can't be terminated in the usual way, by the production of progesterone. In humans, menopause is analogous, because the excitatory FSH hormone from the pituitary becomes excessive, with the ovary continuing to produce estrogen but failing to produce progesterone, sometimes with the pituitary failing to shift from FSH to LH. In rodents, it's recognized that persistent estrus is caused by chronically elevated estrogen, but in humans there has been tremendous resistance to the recognition of estrogen's central role in menopause and senescence. An excess of the basic promoter of inflammation, serotonin, which is closely associated with estrogen's influence, can have similar effects on the reproductive cycle (Cooper, et al., 1986). The industry has devoted the necessary funding to making the easily manipulated medical culture, and the public, believe the opposite, i.e., that reproductive aging is mainly caused by estrogen deficiency.

The liver, besides its important role in keeping endotoxin from reaching the circulation, normally "destroys" all of the estrogen that reaches it, that is, it makes it water soluble so that it will be excreted in the urine or bile, rather than being retained by cells. But in malnutrition, hypothyroidism, or stress, the liver allows estrogen to pass through without being completely inactivated. M.S. Biskind and G.R. Biskind (1941, 1946) showed that the B vitamins were crucial for estrogen elimination, and others around the same time demonstrated that toxins, protein deficiency, hypothyroidism, and even hyperestrogenism itself tended to reduce the liver's ability to detoxify estrogen. Endotoxin's inhibition of this detoxifying system (Banhegyi, et al., 1995) is just one of the ways that it increases estrogen systemically.

Estrogen, which was named for a gadfly, is excitatory in all of its biological actions (including nervous excitation and cellular proliferation), and in most tissues this excitatory action has been shown to cause oxidation damage. Many different toxic changes have been produced in the liver by estrogen, but lipid peroxidation can be clearly demonstrated in the liver as an early reaction to subcutaneous estrogen injection (Genc, et al., 1999).

Endotoxin and estrogen interact in many interesting and potentially deadly ways. Both of them activate many of the same alarm systems, including phospholipases, nitric oxide synthase, tumor necrosis factor (TNF), interleukins (including IL-6, according to Bengtsson, et al., 2004), and the enzymes that form prostaglandins from polyunsaturated fatty acids. Estrogen makes the toxic-mediator-producing cells in the liver (Kupffer cells) hypersensitive to LPS--15 times more sensitive than normal (Ikejima, et al., 1998). One way estrogen increases the toxicity of endotoxin is probably by making the intestine more permeable (Enomoto, et al., 1999). The acute phase reaction, a process in which the liver decreases its production of albumin and increases the production of serum amyloids, lipoproteins, and fibrinogen, is promoted by both estrogen and endotoxin. Estrogen (like endotoxin) activates nuclear factor kappa-B (Shyamala and Guiot, 1992; Hamilton, et al., 2003), which activates

cells to produce TNF, nitric oxide, prostaglandins, and interleukins. A long series of observations have indicated that estrogen's main effects begin with redox changes in the mitochondria, and recent evidence (Felty and Roy, 2005) shows that oxidative free radicals produced in the mitochondria by estrogen induce NF kappa-B. Old age is associated with increased activity of NF kappa-B.

Aspirin, increased levels of carbon dioxide (Ni Chonghaile, et al., 2005), and progesterone (Deroo and Archer, 2002; Kelly, et al., 2001; Allport, et al., 2001; van der Burg and van der Saag, 1996; Caldenhoven, et al., 1995) inhibit NF kappa-B, and NF kappa-B inhibits the synthesis of both testosterone (Hong, et al., 2004) and progesterone (Allport, et al., 2001).

The amount of injury needed to increase the endotoxin in the blood can be fairly minor. Two thirds of people having a colonoscopy had a significant increase in endotoxin in their blood, and intense exercise or anxiety will increase it. Endotoxin activates the enzyme that synthesizes estrogen while it decreases the formation of androgen (Christeff, et al., 1992), and this undoubtedly is partly responsible for the large increases in estrogen in both men and women caused by trauma, sickness or excessive fatigue.

The positive interactions among estrogen and endotoxin and NF kappa-B, and their negative interactions with progesterone and testosterone, tend to "stabilize" the inflammatory condition. In a young person, good food, sunlight, and a high altitude can often overcome severe and progressive inflammatory conditions. In an older person, whose tissues contain larger amounts of polyunsaturated fats and their breakdown products, it takes more environmental support to get out of the inflammatory pattern.

Glycine (the main amino acid in gelatin) is an important nutrient with powerful antiinflammatory actions (Zhong, et al., 1999; Wang, et al., 2004). Saturated fatty acids can help to reduce chronic inflammatory states, but it's essential to eliminate as far as possible the unstable polyunsaturated fatty acids, which suppress normal immune functions, besides contributing to the free radical-lipid peroxidation burden. Cholesterol and ATP have been used therapeutically, but ordinarily their synthesis can be increased safely by using a diet that contains a significant amount of ordinary sugar (sucrose, from fruits) when the thyroid function is adequate.

Since vascular leakiness is involved in the inflammatory syndromes, as well as in shock, I think it's reasonable to treat them similarly, keeping in mind the importance of normal blood volume and viscosity. Sodium and sugar help to lower adrenaline, and so they can make a contribution to preventing high blood pressure, while maintaining normal hydration of the blood. Estradiol and cholera toxin, which both increase vascular leakiness, probably exert some of their influence by lowering the osmotic tension of the extracellular fluid (Webster, et al., 1984; Witten and Bradbury, 1951). The enzyme activated by cholera toxin, estrogen, and hypotonic medium in the study by Webster, et al., was ornithine decarboxylase, which produces the polyamines. The polyamines promote cellular proliferation, and promote the actions of the excitotoxic amino acids. Histamine also activates excitotoxicity, and magnesium opposes it.

The inflammatory states that produce the age-related degenerative diseases have many things in common with "pre-eclampsia" or pregnancy toxemia, and the same simple things can usually alleviate both kinds of problem. With aging, intracellular water tends to decrease, as the extracellular water increases (Lesser and Markovsky, 1979), probably because of reduced cellular energy, and increased vascular permeability. When albumin production is adequate, it "binds" sodium, and the combination osmotically increases the ability of the blood to retain water.

Sodium bicarbonate can provide a little extra carbon dioxide, along with the sodium, and its diuretic action is well established, but it works by improving perfusion of the tissues, reducing any abnormal water retention, rather than by causing the kidneys to lose water in unphysiological ways. One of progesterone's important functions is the maintenance of blood volume, and adequate thyroid is essential for preventing hyponatremia (insufficient sodium in the blood, which often occurs in combination with decreased formation of albumin).

Stress, trauma, and shock start an inflammatory process, that can cause progressive damage to the organs, including the liver. Giving progesterone following the injury protects against the increase of TNF, IL-6, and leakage of liver enzymes (Kuebler, et al., 2003). It has similar protective effects in the brain, lungs, and other organs. During the normal menstrual cycle, IL-6 is inversely related to the level of progesterone (Angstwurm, et al., 1997).

The liver's important role in regulating endotoxin and estrogen, and the cascade of inflammatory mediators that can be released as a result of a depression of the liver's function, makes it important to keep the liver in mind, even when the immediate problem seems to be in the brain, the lungs, kidneys, pancreas, blood vessels, heart, eyes, prostate, ovaries, muscles, or any other organ.

Estrogen is obviously part of a primitive repair system, more fundamental or general than its role in reproduction. When a tissue is injured, it forms large amounts of an enzyme, beta-glucuronidase, that removes the water soluble sugar acid, glucuronic acid, from the estrogen glucuronide which circulates harmlessly in the blood after its formation in the liver, and before its elimination in the urine. The injured tissue reverses the inactivation of the estrogen that has occurred in the liver, causing the fat soluble estrogen to remain in the damaged tissue, where it changes the metabolism, activating enzymes that stimulate proliferation and accelerate collagen formation and other processes involved in repair. (Other enzymes, sulfatases and aromatase, contribute to the increase in estrogen in stressed tissues, but beta-glucuronidase has been studied most, because it is very easy to identify.)

These local processes don't depend on liver failure to become active, but in the systemic effects of liver failure they probably play a very important role in amplifying the effects of endotoxin and unprocessed estrogen.

The effects of endotoxin and estrogen on cells are additive, for example in causing vascular leakiness (e.g., Tollan, et al., 1992), even in the brain (Oztas and Kaya, 1998). Dementia, respiratory distress/shock lung, and all of the classical inflammatory conditions, are promoted by the simple process of making capillaries excessively permeable. But the cellular changes that make capillaries leaky, also affect other cells, changing their antigenicity, leading to "autoimmune" processes (Sekigawa, et al., 2004).

Protein deficiency creates an inflammatory state, and since stress causes tissue proteins to be destroyed and converted into sugars and fats, it's common to underestimate the amount of protein needed. One of the functions of sucrose in the diet is to reduce the production of cortisol, and so to spare protein.

Milk has a variety of antiinflammatory functions. Its saturated fats help to prevent oxidation of lipids, including cholesterol. Several of its vitamins, especially vitamins D and K, have antiinflammatory and even antiestrogenic actions. Since the parathyroid hormone (like some of the other pituitary hormones) is pro-inflammatory, a generous supply of calcium is important because it inhibits the secretion of the parathyroid hormone.

Stress activates the endorphin system (partly by increased histamine, according to Kjaer, et al., 1993), and these intrinsic hormones, like morphine and the other opiates, are pro-inflammatory. Both estrogen and endotoxin activate the endorphin system. Excessive exposure to estrogen destroys many of the beta-endorphin nerves in the hypothalamus, resulting in an adaptive hypersensitivity, that maintains a chronic activation of the endorphin sensitive tissues, suppressing progesterone production (Desjardins, 1995).

There are drugs (e.g., naloxone) that can help to block the actions of the endorphins, and since the endorphins inhibit the luteinizing hormone (LH) which promotes the production of progesterone and testosterone, a little naloxone can often restore normal menstrual cycles that have stopped because of stress and excessive exposure to estrogen. Endorphins are probably involved in menopausal flushing, and drugs of the naloxone type have been used to relieve it. But a combination of other antistress factors can do the same.

Salicylic acid, which occurs naturally in many fruits, as well as in aspirin, is unlike the other antiinflammatory drugs so vaguely classified with

it as "nonsteroidal," in having a broad spectrum of antiinflammatory effects, inhibiting the prostaglandins and NF kappa-B, TNF, and IL-6, besides contributing to the inhibition of estrogen synthesis and actions.

Magnesium is lost during stress, and that can lead to destabilization of the mast cells, with increased release of histamine and other promoters of inflammation and excitation. Thyroid hormone helps cells to assimilate and retain magnesium. Estrogen's effect on magnesium seems to be antagonistic (e.g., Muneyyirci-Delale, et al., 1999). Fruits and meats are good sources of magnesium, but coffee and chocolate are among the best sources of it, and the caffeine they contain adds to their antiinflammatory and liver-protective effect (see Sakamoto, et al., 1999).

The saturated fatty acids found in coconut oil inhibit the formation of histamine (Mimura, et al., 1980), as does glucose (Kaneko, et al., 1997), and prevent leakiness of the intestine, protecting the liver from endotoxin (Kono, et al., 2003). Progesterone and testosterone protect against histamine, while estrogen increases its formation and actions. Benadryl (diphenhydramine) protects the liver and other organs from various toxins, and from the toxic effects of histamine.

Thyroid's antiinflammatory function in arthritis and rheumatic conditions has been known for about a century, but there aren't many contemporary publications on its roles in inflammation and degeneration (see Bartalena, et al., 1994; Rittenhouse and Redei, 1997).

TSH, the thyroid stimulating hormone secreted by the pituitary, stimulates some of the inflammatory mediators, and although the definition of the "normal range" has been decreasing, the people I see whose TSH is "normal" aren't as healthy as those whose TSH is well "below normal." Other indicators of adequate thyroid function are needed.

Expired carbon dioxide ("end tidal") is a good indicator, but it's rarely measured. Lactic acid tends to rise in hypothyroidism, so measuring its level in the blood can be helpful. Oxygen consumption, serum cholesterol, daily cycle of temperature and pulse rate, and calorie consumption are good indicators of thyroid function. The inflammatory cytokines can activate the glycolytic enzymes that produce lactic acid (Bauer, et al., 2004), and the thyroid hormone accelerates the oxidation of lactic acid, so I think it's reasonable to think of a higher metabolic rate as a corrective compensation for inflammation, as well as the most important factor in preventing it.

Anyone can measure their calorie consumption with enough accuracy to be useful. Considering that the Criles' measurements of oxygen consumption in the 1930s showed that Americans as a group were extremely hypothyroid, and that other studies done around the same time suggested that nearly half of the population benefitted from supplemental thyroid, we should probably ignore the present "official" recommendations regarding caloric require- ments.

Besides keeping track of the caloric value of the food we eat, it's possible to estimate our metabolic rate fairly closely by measuring our daily fluid intake, and subtracting the amount of urine produced during 24 hours. The missing water was evaporated, and with moderate atmospheric humidity, we evaporate about a liter of water for every 1000 calories we burn.

One of the roles of fat in the food is to stimulate the secretion of bile by the gall bladder. Besides that important function, saturated fats have a variety of protective, antiinflammatory effects, including the reduction of endotoxemia and lipid peroxidation (Nanji, et al., 1997). "Coconut oil completely abolished the responses to endotoxin" (Wan and Grimble, 1987).

Appetizing foods stimulate the digestive secretions, but it's important to avoid foods that directly trigger an inflammatory reaction, or that are indigestible and as a result support harmful bacterial growth. Cellulose can accelerate transit through the intestine and lower estrogen systemically (partly by simply preventing the reabsorption of estrogen that has been secreted by the bile), but the lignans found in many seeds and grains tend to promote inflammation. Raw carrots, for example, lower estrogen, while flax meal can increase it.

Constipation or diarrhea, or their alternation, usually develops when there is inflammation in the bowel. A laxative can sometimes reduce the inflammation, but it's important to identify the

foods that contribute to the problem. A salad of shredded carrot, with oil and vinegar dressing, has a germicidal action, and is stimulating to the digestive processes. Most salad vegetables, though, are likely to produce intestinal irritation, directly or as a result of bacterial decomposition.

One or a few of the antiinflammatory measures can often make a tremendous difference, but for serious chronic problems, it's best to use as many safe techniques as possible, including periodic breathing in a paper bag to increase carbon dioxide retention, and taking niacinamide to inhibit lipolysis, until the signs of inflammation begin to subside. Eventually, the goal should be to become "deficient" in the "essential fatty acids," since experiments have shown that such animals are extremely resistant to endotoxin poisoning (Li, et al., 1990).

REFERENCES

Mol Hum Reprod. 2001 Jun;7(6):581-6. **Human labour is associated with nuclear factor-kappaB activity which mediates cyclo-oxygenase-2 expression and is involved with the 'functional progesterone withdrawal'.** Allport VC, Pieber D, Slater DM, Newton R, White JO, Bennett PR.

Cytokine. 1997 May;9(5):370-4. **Cyclic plasma IL-6 levels during normal menstrual cycle.** Angstwurm MW, Gartner R, Ziegler-Heitbrock HW. **"Interleukin 6 (IL-6) in plasma changed periodically during 12 of 13 cycles in five women. The IL-6 levels were lowest in the luteal phase when progesterone levels were elevated and highest preovulatory when progesterone levels were low...."**

J Steroid Biochem Mol Biol 1997 Apr;61(3-6):323-39. **Steroid control and sexual differentiation of brain aromatase.** Balthazart J. "Together, these data indicate that the removal of estrogens caused by steroidal inhibitors decreases the synthesis of ARO, presumably at the transcriptional level."

Biochem Pharmacol. 1995 Jan 6;49(1):65-8. **Endotoxin inhibits glucuronidation in the liver. An effect mediated by intercellular communication.** Banhegyi G, Mucha I, Garzo T, Antoni F, Mandl J.

Eur J Endocrinol. 1994 Sep;131(3):302-6. **Interleukin 6 effects on the pituitary-thyroid axis in the rat.** Bartalena L, Grasso L, Brogioni S, Martino E.

FASEB J. 2004 Aug;18(11):1303-5. Epub 2004 Jun 04. **Cytokine stimulation of aerobic glycolysis in hematopoietic cells exceeds proliferative demand.** Bauer DE, Harris MH, Plas DR, Lum JJ, Hammerman PS, Rathmell JC, Riley JL, Thompson CB.

Blood. 2004 Sep 1;104(5):1404-10. Epub 2004 May 13. **17beta-estradiol (E2) modulates cytokine and chemokine expression in human monocyte-derived dendritic cells.** Bengtsson AK, Ryan EJ, Giordano D, Magaletti DM, Clark EA. "In summary, E(2) may affect DC regulation of T-cell and B-cell responses, as well as help to sustain inflammatory responses. This may explain, in part, the reason serum levels of estrogen correlate with the severity of certain autoimmune diseases."

Pathophysiology. 2004 Dec;11(3):139-145. **Bile acids in physico-chemical host defence.** Bertok L.

Int J Sport Nutr Exerc Metab. 2002 Jun;12(2):145-56. **Influence of carbohydrate supplementation on plasma cytokine and neutrophil degranulation responses to high intensity intermittent exercise.** Bishop NC, Gleeson M, Nicholas CW, Ali A.

Science, Vol. 94, No. 2446 (Nov. 1941), p. 462. **Diminution in Ability of the Liver to Inactivate Estrone in Vitamin B Complex Deficiency,** Biskind, M.S., and G. R. Biskind.

Am. Jour. Clin. Path., Vol. 16 (1946), No. 12, pages 737-45. **The Nutritional Aspects of Certain Endocrine Disturbances,** Biskind, G. R., and M. S. Biskind.

Biol Reprod, 1993 Oct, 49:4, 647-52. **Pathologic effect of estradiol on the hypothalamus.** Brawer JR; Beaudet A; Desjardins GC; Schipper HM.

Mol Endocrinol. 1995 Apr;9(4):401-12. **Negative cross-talk between RelA and the glucocorticoid receptor: a possible mechanism for the antiinflammatory action of glucocorticoids.** Caldenhoven E, Liden J, Wissink S, Van de Stolpe A, Raaijmakers J, Koenderman L, Okret S, Gustafsson JA, Van der Saag PT.

Life Sci, 1992, 50:19, 1459-68. **Effect of the aromatase inhibitor, 4 hydroxyandrostenedione, on the endotoxin-induced changes in steroid hormones in male rats.** Christeff N; Auclair MC; Dehennin L; Thobie N; Benassayag C; Carli A; Nunez EA.

Liver. 1998 Oct;18(5):343-51. **Estrogen-induced hepatic toxicity and hepatic cancer: differences between two closely related hamster species.** Coe JE, Ishak KG, Ross MJ.

Neurobiol Aging. 1986 Jan-Feb;7(1):9-15. **Catecholaminergic-serotonergic balance in the CNS and reproductive cycling in aging rats.** Cooper RL, McNamara MC, Linnoila M.

Prostate. 1981;2(4):337-58. Fluid **imbibition as a factor in estrogen-induced increase of prostatic weight in castrated rats.** Corrales JJ, Kadohama N, Chai LS, Hoisaeter PA, Hampton MT, Murphy GP, Sandberg AA.

Gynecol Oncol. 2004 Aug;94(2):463-70. **Identification of a novel mechanism of NF-kappaB inactivation by progesterone through progesterone receptors in Hec50co poorly differentiated endometrial cancer cells: induction of A20 and ABIN-2.** Davies S, Dai D, Feldman I, Pickett G, Leslie KK

Am J Surg Pathol. 1995 Apr;19(4):454-62. **Reversible ischemic colitis in young women. Association with oral contraceptive use.** Deana DG, Dean PJ.

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. "The promoters chosen were those for the mouse mammary tumor virus (MMTV) and the gene for Ikappa-Balpha, the inhibitor of the ubiquitous transcription factor, nuclear factor kappa B (NFkappaB). Several differences between glucocorticoid and progestin activation of the IkappaBalpha and MMTVpromoters 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."

Endocrinology, 1992 Nov, 131:5, 2482-4. **Vitamin E protects hypothalamic beta-endorphin neurons from estradiol neurotoxicity.** Desjardins GC; Beaudet A; Schipper HM; Brawer JR.

Exp Gerontol, 1995 May-Aug, 30:3-4, 253-67. **Estrogen-induced hypothalamic beta-endorphin neuron loss: a possible model of hypothalamic aging.** Desjardins GC; Beaudet A; Meaney MJ; Brawer JR.

Am J Physiol. 1999 Sep;277(3 Pt 1):G671-7. **Estriol sensitizes rat Kupffer cells via gut-derived endotoxin.** Enomoto N, Yamashina S, Schemmer P, Rivera CA, Bradford BU, Enomoto A, Brenner DA, Thurman RG.

Alcohol Clin Exp Res. 2002 Aug;26(8 Suppl):66S-69S. **Estriol enhances lipopoly- saccharide-induced increases in nitric oxide production by Kupffer cells via mechanisms dependent on endotoxin.** Enomoto N, Takei Y, Kitamura T, Hirose M, Ikejima K, Sato N.

Am J Obstet Gynecol. 1994 Jul;171(1):158-64. **A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in** pregnant rats. Faas MM, Schuiling GA, Baller JF, Visscher CA, Bakker WW.

Med Hypotheses. 2005;64(1):133-41. **Mitochondrial signals to nucleus regulate estrogen-induced cell growth.** Felty Q, Roy D.

Psychoneuroendocrinology. 2003 Jul;28(5):657-73. **Olanzapine's effects to reduce fear and anxiety and enhance social interactions coincide with increased progestin concentrations of ovariectomized rats.** Frye CA, Seliga AM.

Gut. 1995 Oct;37(4):530-5. **Colitis and colonic mucosal barrier dysfunction.** Gardiner KR, Anderson NH, Rowlands BJ, Barbul A. "Trauma, infection, neoplasia, and inflammation can all disrupt the intact intestinal mucosal barrier to intraluminal bacteria and bacterial antigens."

Neuroendocrinology. 1990 Sep;52(3):221-4. **Estrogens modulate the circadian rhythm of hypothalamic beta-endorphin contents in female rats.** Genazzani AR, Trentini GP, Petraglia F, De Gaetani CF, Criscuolo M, Ficarra G, De Ramundo BM, Cleva M.

Res Commun Mol Pathol Pharmacol. 1999;105(3):253-61. **Acute effects of estradiol and of diethylstilbestrol: pro- or antioxidant potential?** Genc S, Gurdol F, Oner-Iyidogan Y, Suzme R.

J Clin Gastroenterol. 1994 Sep;19(2):108-11. **Premarin-induced ischemic colitis.** Gurbuz AK, Gurbuz B, Salas L, Rosenshein NB, Donowitz M, Giardiello FM.

J Mol Cell Cardiol. 2004 Apr;36(4):577-84. **Estrogen and regulation of heat shock protein expression in female cardiomyocytes: cross-talk with NF kappa B signaling.** Hamilton KL, Gupta S, Knowlton AA. "Western blot analyses revealed that treatment with 17 beta-estradiol (10 or 50 microM), tamoxifen (25 microM), and geldanamycin (all doses) resulted in significant increases in HSP72." "HSP72 induction via HSF1 activation was confirmed using transcription factor decoys containing the heat shock element, which prevented the estrogen-related HSP72 induction." "NF kappa B activation is necessary for the increase in HSP72, suggesting that estrogen treatment activates NF kappa B, with subsequent HSF1 activation. NF kappa B activation is critical for estrogen-associated HSP induction...."

Mol Cell Biol. 2004 Apr;24(7):2593-604. **Molecular mechanism of suppression of testicular steroidogenesis by proinflammatory cytokine tumor necrosis factor alpha.** Hong CY, Park JH, Ahn RS, Im SY, Choi HS, Soh J, Mellon SH, Lee K.

Int J Obes Relat Metab Disord. 2003 Apr;27(4):433-42. **Uncoupling proteins-2 and 3 influence obesity and inflammation in transgenic mice.** Horvath TL, Diano S, Miyamoto S, Barry S, Gatti S, Alberati D, Livak F, Lombardi A, Moreno M, Goglia F, Mor G, Hamilton J, Kachinskas D, Horwitz B, Warden CH. "... female transgenics of both lines had significantly smaller femoral fat depots than the control (littermate) mice.... Transgenic baseline interleukin4 (IL-4) and interleukin6 (IL-6) levels were low with lower or later increases after endotoxin injection compared to wild-type littermates. Endotoxin-induced fever was also diminished in transgenic male animals."

Am J Physiol. 1998 Apr;274(4 Pt 1):G669-76. **Estrogen increases sensitivity of hepatic Kupffer cells to endotoxin.** Ikejima K, Enomoto N, Iimuro Y, Ikejima A, Fang D, Xu J, Forman DT, Brenner DA, Thurman RG.

Oncol Res. 2004;14(7-8):363-72. **Apoptosis of human T-cell acute lymphoblastic leukemia cells by diphenhydramine, an H1 histamine receptor antagonist.** Jangi SM, Asumendi A, Arlucea J, Nieto N, Perez-Yarza G, Morales MC, de la Fuente-Pinedo M, Boyano MD

Vascul Pharmacol. 2002 Apr;38(4):219-27. **Analysis of inflammatory gene induction by oxidized phospholipids in vivo by quantitative real-time RT-PCR in comparison with effects of LPS.** Kadl A, Huber J, Gruber F, Bochkov VN, Binder BR, Leitinger N.

J Invest Surg. 1997 Sep-Oct;10(5):287-93. **Glucose suppresses the activity of rat oxyntic histidine decarboxylase without affecting gastrin levels.** Kaneko T, Nagamachi Y, Matsuzaki S.

Reproduction. 2001 Jan;121(1):3-19. **Cytokine control in human endometrium.** Kelly RW, King AE, Critchley HO.

Endocrinology. 1993 May;132(5):2213-20. **Insulin/hypoglycemia-induced adrenocorticotropin and beta-endorphin release: involvement of hypothalamic histaminergic neurons.** Kjaer A, Knigge U, Madsen EL, Soe-Jensen P, Bach FW, Warberg J. "We have previously found that histamine (HA) is involved in the mediation of restraint- and ether stress-induced release of the POMC-derived peptides ACTH and beta-endorphin."

Adv Anat Embryol Cell Biol. 2001;161:III-XIII, 1-151. **Cooperation of liver cells in health and disease.** Kmiec Z.

Ann Surg. 2003 Feb;237(2):246-55. **Protective effects of medium-chain triglycerides on the liver and gut in rats administered endotoxin.** Kono H, Fujii H, Asakawa M, Yamamoto M, Matsuda M, Maki A, Matsumoto Y.

Arch Surg. 2003 Jul;138(7):727-34. **Administration of progesterone after trauma and hemorrhagic shock prevents**

hepatocellular injury. Kuebler JF. Yokoyama Y. Jarrar D, Toth B. Rue LW 3rd, Bland KI, Wang P, Chaudry IH.

Acta Gastroenterol Latinoam. 1988;18(3):161-71. **|Hepatic fibrosis and progesterone|** Lanari A, Garegnani TC, Heinrichs G, Castresana MP. "To study the progesterone (Prog.) action on the hepatic fibrosis, we produced fibrosis on 55 New Zealand male rabbits, by oral ingestion of carbon tetrachloride (Cl4C) and ethanol. They developed it in six months." "A group of these animals also received the Prog since the onset (0.66 mg/3 times a week, IM) and the rest received it 180 days after the beginning of the experiment. We could see in the biopsies of the animals who received Prog since the beginning or after 180 days: protection of the hepatocytes, no vacuolization of the cell, no inflammatory infiltrate, no fat metamorphosis, very thin fibrous hands. If one of these alterations had appeared with the toxic, the Prog action would have diminished it gradually until its disappearance." --"The Prog in the fibroblasts culture and in the treatment of desmoid tumours, on operative adhesions, destroy the fibroblasts and for this action diminished the volume of the tumour and the adhesions."

Drug Des Deliv. 1989 Mar;4(2):85-91. **New possibilities for anti-migraine drugs: prostanoid antagonists and progesterone-mimicking stabilizers of excitable cells.** Leathard HL.

Am J Physiol. 1979 Mar;236(3):R215-20. **Body water compartments with human aging using fat-free mass as the reference standard.** Lesser GT, Markofsky J.

Circ Shock 1990 Jun;31(2):159-70. **Resistance of essential fatty acid-deficient rats to endotoxin-induced increases in vascular permeability.** Li EJ, Cook JA, Spicer KM, Wise WC, Rokach J, Halushka PV.

Res Commun Chem Pathol Pharmacol. 1980 Dec;30(3):581-4. **Studies on the prevention of CCl4 induced liver necrosis by agents having effects on cell membrane.** Marzi A, de Toranzo EG, Castro JA. **[Nupercaine, promazine and benadryl|**

J Pharmacobiodyn. 1980 Sep;3(9):435-43. **Effect of normal C10:0-C20:0 fatty acids and their related compounds on gastric secretion and experimental ulceration in rats.** Mimura T, Tsujibo H, Nishikawa M, Yamabe Y, Aonuma S.

J Biol Chem. 2005 Feb 18;280(7):6181-96. Epub 2004 Nov 15. **Estrogen-induced spermatogenic cell apoptosis occurs via the mitochondrial pathway: role of superoxide and nitric oxide.** Mishra DP, Shaha C.

Zentralbl Allg Pathol. 1979;123(3):195-201. **|Liver biopsy findings after intake of oral contraceptives|** Molleken K. "115 liver biopsies of women who had taken oral contraceptives have been examined. In 106 of these case (68.4%) morphological modifications were found which may be considered as effects of the hormonal contraceptives."

J Nutr. 2003 Nov;133(11):3422-7. **A diet rich in coconut oil reduces diurnal postprandial variations in circulating tissue plasminogen activator antigen and fasting lipoprotein (a) compared with a diet rich in unsaturated fat in women.** Muller H, Lindman AS, Blomfeldt A, Seljeflot I, Pedersen JI.

Fertil Steril 1999 May;71(5):869-72. **Serum ionized magnesium and calcium in women after menopause: inverse relation of estrogen with ionized magnesium.** Muneyyirci-Delale O, Nacharaju VL, Dalloul M, Altura BM, Altura BT.

Life Sci 1996;58(17):1461-7 **The endogenous estrogen metabolite 2-methoxyestradiol induces apoptotic neuronal cell death in vitro.** Nakagawa-Yagi Y, Ogane N, Inoki Y, Kitoh N.

Hepatology 1997 Dec;26(6):1538-45. **Dietary saturated fatty acids down-regulate cyclooxygenase-2 and tumor necrosis factor alfa and reverse fibrosis in alcohol-induced liver disease in the rat.** Nanji AA, Zakim D, Rahemtulla A, Daly T, Miao L, Zhao S, Khwaja S, Tahan SR, Dannenberg AJ" The therapeutic effects of saturated fatty acids may be explained, at least in part, by reduced endotoxemia and lipid peroxidation, which in turn result in decreased levels of TNF-alpha and Cox-2."

Hepatology 1999 Oct;30(4):934-43. **Activation of nuclear factor kappa B and cytokine imbalance in experimental alcoholic liver disease in the rat.** Nanji AA, Jokelainen K, Rahemtulla A, Miao L, Fogt F, Matsumoto H, Tahan SR, Su GL.

J Physiol Pharmacol. 1999 Sep;50(3):443-54. **Endotoxaemia in rats: role of NO, PAF and TXA2 in pulmonary neutrophil sequestration and hyperlactataemia.** Olszanecki R, Chlopicki S.

Horm Metab Res. 1998 Aug;30(8):500-3. **Influence of orchidectomy and ovariectomy on the blood-brain barrier permeability during bicuculline-induced seizures.** Oztas B, Kaya M.

Int J Tissue React. 1983;5(4):415-20. **The gastric anti-ulcer activity of naringenin, a specific histidine decarboxylase inhibitor.** Parmar NS.

Am J Physiol Endocrinol Metab. 2004 Oct;287(4):E767-71. **Estrogens sensitize anterior pituitary gland to apoptosis.** Pisera D, Candolfi M, Navarra S, Ferraris J, Zaldivar V, Jaita G, Castro MG, Seilicovich A.

Int J Cardiol. 2000 Nov-Dec;76(2-3):125-33. **Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure.** Rauchhaus M, Koloczek V, Volk H, Kemp M, Niebauer J, Francis DP, Coats AJ, Anker SD.

Food Chem Toxicol. 1998 Aug;36(8):663-72. **The association of increasing dietary concentrations of fish oil with hepatotoxic effects and a higher degree of aorta atherosclerosis in the ad lib.-fed rabbit.** Ritskes-Hoitinga J, Verschuren PM, Meijer GW, Wiersma A, van de Kooij AJ, Timmer WG, Blonk CG, Weststrate JA.

Endocrinology 1997 Apr;138(4):1434-9. **Thyroxine administration prevents streptococcal cell wall-induced inflammatory responses.** Rittenhouse PA, Redei E

Nitric Oxide 1997;1(6):453-62. **Effects of female hormones (17beta-estradiol and progesterone) on nitric oxide production by alveolar macrophages in rats.** Robert R, Spitzer JA

J Lipid Res. 2004 Aug;45(8):1418-28. Epub 2004 Jun 01. **Lipid peroxidation induced by DHA enrichment modifies paracellular permeability in Caco-2 cells: protective role of taurine.** Roig-Perez S, Guardiola F, Moreto M, Ferrer R.

J Endocrinol. 1989 Jun;121(3):513-9. **Indomethacin inhibits the effects of oestrogen in the anterior pituitary**

gland of the rat. Rosental DG, Machiavelli GA, Chernavsky AC, Speziale NS, Burdman JA.

Biochim Biophys Acta. 1994 Sep 8;1223(2):185-94. **Inhibition of cytokine-stimulated thymic lymphocyte proliferation by fatty acids: the role of eicosanoids.** Rotondo D, Earl CR, Laing KJ, Kaimakamis D.

J Nutr Sci Vitaminol (Tokyo). 2000 Dec;46(6):316-20. **Coffee and fitness--coffee suppresses lipopolysaccharide-induced liver injury in rats.** Sakamoto W, Nishihira J, Fujie K, Mizuno S, Ozaki M, Yukawa S.

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)...."

Proc Natl Acad Sci U S A. 1992 Nov 15;89(22):10628-32. **Activation of kappa B-specific proteins by estradiol.** Shyamala G, Guiot MC.

J Neurochem. 2001 Jan;76(1):47-55. **Potentiation by histamine of synaptically mediated excitotoxicity in cultured hippocampal neurones: a possible role for mast cells.** Skaper SD, Facci L, Kee WJ, Strijbos PJ.

Gastroenterology 2000 Feb;118(2):422-30. **Drug- and estrogen-induced cholestasis through inhibition of the hepatocellular bile salt export pump (Bsep) of rat liver.** Stieger B, Fattinger K, Madon J, Kullak-Ublick GA, Meier PJ.

Liver. 1992 Jun;12(3):147-51. **Estradiol-17 beta modifies the induction of spermidine/spermine N1-acetyltransferase activity in the liver of lipopolysaccharide-treated mice.** Sugimoto H, Matsuzaki Y, Yuasa K, Kaneko M, Yamada S, Hamana K, Matsuzaki S.

Gastroenterol Jpn. 1979 Aug;14(4):336-43. **Role of plasma histamine in liver injury--clinical and experimental investigations.** Suzuki O, Ishii K, Nagata H, Miyairi M, Mizuno Y, Kiryu Y, Tsuchiya M.

Contraception 1992 May;45(5):473-81. **Increased capillary permeability for plasma proteins in oral contraceptive users.** Toilan A, Kvenild K, Strand H, Oian P, Maltau JM.

J Nutr 1998 Nov;128(11):1861-8-. **Flaxseed and its lignan precursor, secoisolariciresinol diglycoside, affect pregnancy outcome and reproductive development in rats.** Tou JC, Chen J, Thompson LU. "Flaxseed is the richest source of the mammalian lignan precursor secoisolariciresinol diglycoside (SDG)." "Flaxseed had no effect on pregnancy outcome except that the 10% flaxseed diet lowered birth weight ($P < 0.05$), compared with other treatments, and produced hormonal effects. The female offspring had shortened anogenital distance, greater uterine and ovarian relative weights, earlier age and lighter body weight at puberty, lengthened estrous cycle and persistent estrus ($P < 0.05$), whereas the males had reduced postnatal weight gain and, at postnatal d 132, greater sex gland and prostate relative weights ($P < 0.05$), suggesting estrogenic effects." "Because flaxseed affects the reproductive development of offspring, caution is suggested when consuming flaxseed during pregnancy and lactation."

Braz J Med Biol Res. 2003 Apr;36(4):491-4. Epub 2003 Apr 8. **Hormone replacement therapy increases levels of antibodies against heat shock protein 65 and certain species of oxidized low density lipoprotein.** Uint L, Gebara OC, Pinto LB, Wajngarten M, Boschcov P, da Luz PL, Gidlund M.

Mol Hum Reprod. 1996 Jun;2(6):433-8. **Nuclear factor-kappa-B/steroid hormone receptor interactions as a functional basis of anti-inflammatory action of steroids in reproductive organs.** van der Burg B, van der Saag PT.

J Surg Res. 1999 Jun 15;84(2):143-9. **Sodium salicylate inhibits macrophage TNF-alpha production and alters MAPK activation.** Vittimberga FJ Jr, McDade TP, Perugini RA, Callery MP.

Toxicol Appl Pharmacol. 2000 Jul 1;166(1):24-35. **Induction of proliferative lesions of the uterus, testes, and liver in swiss mice given repeated injections of sodium arsenate: possible estrogenic mode of action.** Waalkes MP, Keefer LK, Diwan BA.

Clin Sci (Lond) 1987 Mar;72(3):383-5. **Effect of dietary linoleate content on the metabolic response of rats to Escherichia coli endotoxin.** Wan JM, Grimble RF.

Gaoxiong Yi Xue Ke Xue Za Zhi. 1995 Apr;11(4):213-9. **Drug-induced liver disease--a review of 14 cases.** Wang CK, Liu JD, Lin SY, Liao LY, Cheng NY, Wang CS, Siauw CP, Chen PH.

Life Sci 1984 Mar 26;34(13):1281-6. **Stimulation of uterine ornithine decarboxylase in organ culture by decreasing osmolality: possible relation to in vivo mechanisms.** Webster RA, Zaloudek CJ, Inman BC Ornithine decarboxylase (ODC) activity increases

Recent Prog Horm Res 1997;52:279-303. **Aging of the female reproductive system: a window into brain aging.** Wise PM, Kashon ML, Krajnak KM, Rosewell KL, Cai A, Scarbrough K, Harney JP, McShane T, Lloyd JM, Weiland NG.

Proc Soc Exp Biol Med. 1951 Nov;78(2):626-9. **Hemodilution as a result of estrogen therapy; estrogenic effects in the human female.** Witten CL, Bradbury JT.

Cancer Res. 1991 Sep 1;51(17):4511-5. **Inhibition of glucuronidation of benzo(a)pyrene phenols by long-chain fatty acids.** Zhong Z, Kauffman FC, Thurman RG.

****