# Ray Peat's Newsletter

*The Questioner who sits so sly Shall never know how to Reply -- W. Blake*

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## Contexts for asthma

***Asthma in children involves many of the biological processes that cause disability and degeneration in the process of aging, and since the incidence of asthma in children is increasing, it has serious implications for the whole population.***

***Increased exposure to estrogen (including prenatal exposure), increased consumption of unsaturated vegetable oils, use of food or drug additives including guar gum, carob, carrageenan, and sulfites, and the use of adrenergic ("beta-agonist") inhalant drugs have coincided with the increased death rates from asthma. Estrogen and unsaturated fats are clearly involved in producing the symptoms of asthma.***

***Living at high altitude decreases asthma prevalence and mortality. Exercise increases the incidence of asthma. These facts provide insight into the biochemical events of asthma.***

***The inflammatory-excitatory processes of asthma are parallel to those of depression, diabetes, premenstrual syndrome, arthritis, migraine, MS, SLE, multiple organ failure, aging, and death.***

***Protecting cellular energy and stability can prevent or alleviate asthma. Thyroid, progesterone, and carbon dioxide are therapeutically useful, but reducing exposure to polyunsaturated oils and estrogens should be the basic approach.***

**Medical theories of asthma give a better insight into the nature of medicine than into the nature of the asthmatic condition.**

Evasion and misdirection were woven into the culture of pharmacology by the competition to sell products. The objective result has been something approaching genocide. The U.S. government has served as the agent of the drug industry, by outlawing generic remedies whenever a corporation sought to fill that niche with its newly patented substance. This practice is so fundamental that, when inquiry is made about getting FDA approval for a substance, the response is that you must first have a patent on the substance. On its face, this indicates that the agency is in a conspiracy against the public health, to permit only proprietary remedies to be used legally.

"Medical empiricism" traditionally referred to the use of remedies that worked, without trying to build a speculative or theoretical explanation for the way they worked or for the physiological nature of disease. "Scientific medicine" decided to call that approach quackery, and to build a theory of disease that would explain how remedies worked.

As it worked out, this meant that certain kinds of remedy were "validated" by certain types of theory. Commercial and cultural interests therefore fostered and promoted the theories that they found most profitable. Impressively "scientific" words were invoked to justify procedures that otherwise would have been considered barbaric. As microscopic technique developed, "humoral" theories of disease were replaced by cellular theories, and the cellular theories came to encompass the "genetic" theories of disease.

The specific, concrete nature of the "gene" concept became part of the "allopathic" tradition of medicine, in which a specific drug was appropriate for, "indicated" for, a specific symptom or disease. The holistic ideas associated with the homeopathic tradition disappeared from organized medicine in the United States. A fragmented and compartmentalized "health science" has been the result.

In the 17th century the term *diathesis* (constitutional predisposition) was coined to "explain" disease, and the term was replaced in the 20th century by the phrase "genetic cause."

Medical writers (and medical editors) are similar to politicians and college sophomores in their habitual use of the classical logical fallacies. When students use defective reasoning, the presumption is that they are confused, but when politicians and physicians argue fallaciously, the interpretation must include other possibilities.

If a certain theoretical explanation has become unnecessary and impossible, then a growing advocacy of that theory strongly implicates ulterior motives, and suggests corrupt influences.

Although there were individuals who believed that asthma was a "psychosomatic" disease or the result of an infection, the official medical position has been that it is a diathesis, a congenital disposition, a "genetic disease" (e.g., Castro, et al., 2001; Ishikawa and Tsujimoto, 2001). A genetic theory of disease is ideal for the drug business, since incurability guarantees continuing sales. Fads in asthma theory coincide with the availability of products. The defective genes have at various times been thought to produce excessive activity in the parasympathetic nervous system, or incontinent mast cells that leak histamine, or enzyme defects that produce too much Slow-Reactive-Substance or leukotriene, or weak adrenal glands, or genetic imbalances that affect the immune system in relatively simple or in more complex ways.

Sudden increases in asthma mortality in the 1960s and 1970s in various countries corresponded to increased use of certain synthetic adrenergic drugs (instead of adrenaline), called bronchodilators, as inhalants. The concept that they were "beta-agonists" was used to rationalize their use, even after animal experiments showed that they caused serious heart damage, and other harmful effects.

When the medical model of asthma shifted its emphasis from "smooth muscle spasm" to "inflammation," a shift that in the U.S. dates from a series of publications in the 1980s (Ackerman, 1989), there was the usual sense of accomplishment, as authors and medical professors spread the word about the latest inhaled steroid products, replacing the "synthetic adrenaline" inhalants that had been increasingly used during the years that asthma mortality had been rising so rapidly. That this change of medication was thirty years tardy wasn't mentioned. (G. Rona's group began publishing warnings in the early 1960s about the heart and vascular damage caused by adrenergic drugs such as isoproteronol.) Even as new medications came into use, there wasn't much change in medical knowledge about asthma. ***And even though there is evidence that oral glucocorticoids drastically reduce death from acute asthma (Abramson, et al., 2001), and that inhaled glucocorticoids have serious systemic side effects, the drug industry created another set of mystifications, claiming that inhaling certain synthetic steroids would act selectively upon the bronchial tubes and lungs.***

As far as I can tell, the only significant event that caused the change of emphasis in the medical model of asthma from "bronchial contraction" to "bronchial inflammation" was the promotion of steroids to replace the "bronchodilators." The description of the disease seems to change according to the drug that's being marketed.

Decades ago, the public accepted the medical doctrine that asthma, and allergies in general, were caused by genetic defects. With the tremendous increase in the death rate from asthma in recent decades (coinciding with similar increases in other supposedly "genetic" diseases), many people are de-emphasizing that theory, because an impossibly high rate of mutation would have been needed to create those "new genetic defects." However, few people are looking for a radically new theory of asthma.

Asthma would be a good place to make a fresh start in understanding chronic disease, and the first step has to be to abandon the unfounded and corrupt theory of genetic causation, and to begin the construction of a functional, environmental theory of its cause. If asthma can be understood functionally, there is a good chance that it can be prevented or cured.

Elite athletes are generally considered to have "good genes," and exercise is commonly said to promote good health, so a new orientation is

needed to accommodate the fact that **"elite" athletes, winter or summer athletes, including participants in the Olympics, have a high incidence of asthma--roughly three times higher than the general population.**

It turns out that exercise induces the signs and symptoms of asthma, not only in "asthmatics," but in normal people too.

**Anaerobic exercise (getting out of breath) increases the release of, or activity of, a large variety of inflammatory mediators, beginning with lactic acid and interleukin-6 released from the exercised muscle itself, and including factors released from various cells in the blood, and hormones including estrogen, prolactin and sometimes TSH.**

**Figures from Mexico show that, in the states with high altitude, the prevalence of asthma is about ten times lower than the states that are close to sea level.** Mountain therapy has been used for a long time to treat asthma and other chronic diseases, especially in Russia. In the United States, many publications have confirmed that high altitude alleviates asthma, but it is called "antigen avoidance therapy," despite evidence that shows improvement at high altitude even in the presence of the usual antigens, such as skin mites. All of the main mediators of inflammation decrease with increasing altitude.

The incidence of asthma in girls surpasses that in boys around puberty, and it is common for asthma to be worse premenstrually. The use of oral contraceptives often makes asthma worse. During pregnancy, asthma sometimes gets worse, sometimes better. At menopause, asthma is likely to get worse, and to appear in women who didn't previously suffer from asthma. The use of estrogen at menopause increases the incidence of asthma. Progesterone, and related hormones, alleviate asthma, and this probably accounts for the variable effects of pregnancy on asthma, since pregnancy can improve the ratio of progesterone to estrogen, but often, with poor nutrition, estrogen dominance is exacerbated by pregnancy. Estrogen exposure early in life can cause asthma later. The common use of DES during pregnancy in the 1950s was one of the factors that caused the increase of asthma in children in the 1960s.

Estrogen increases most of the mediators of inflammation, which are generally inhibited by progesterone. Estrogen also shifts many processes toward excitation, and it's often hard to distinguish the mediators of inflammation from the mediators of excitation. Free polyunsaturated fatty acids, for example, which are increased under the influence of estrogen (or exercise, diabetes, nighttime, aging, histamine, parasympathetic dominance, etc.), produce both inflammation and excitation. Associated with the processes of inflammation and excitation is the tendency of estrogen and other inflammatory mediators, such as nitric oxide and serotonin, to impair mitochondrial respiration. This effect on the cells' energy production is probably responsible for many of the things that occur in asthma, such as edema and smooth muscle contraction. Acute or chronic interference with mitochondrial respiration can produce a tremendous variety of symptoms, depending on the location, and the degree of the energy deprivation. Exercise, probably acting through some of the same mediators, also impairs mitochondrial respiration.

These factors that impair respiration tend to shift mitochondrial metabolism away from the oxidation of glucose and the production of carbon dioxide, to the oxidation of fats and the production of lactic acid.

The clear distinction between inflammation and excitation (and excitotoxicity) is largely an artifact of the drug industry's influence on medical theory.

The "spasmolytic" drugs that are intended to prevent contraction of the bronchioles can cause histamine release as well as increasing cortisol production, and they increase the level of free fatty acids as well as raising the blood sugar.

Simply shifting the cells' energy production away from the oxidation of glucose can produce excitability, inflammation, increased leakiness of blood vessels, changes in mucus, discharge of histamine and serotonin, hormonal changes, etc.

The doctrine of "preventing excessive weight gain" in pregnancy that dominated obstetrics-gynecology in the U.S. in the 1950s and 1960s probably contributed to the increased prevalence of asthma in the 'sixties and 'seventies, because

protein deficiency creates an inflammatory state, and a state of estrogen dominance. (Measurement of inflammatory proteins in the blood has been proposed as a way to confirm protein deficiency.)

One of the major "acute phase proteins," C-reactive protein, is defensive against bacteria and parasites, but it is suspected to contribute to tissue degeneration. When its presence is the result of exercise, estrogen, or malnutrition, then its association with asthma is likely to be causal, rather than coincidental.

Some of the "acute phase proteins" in the blood, that are associated with inflammation, rise progressively with aging, and are induced by estrogen. One of these stress-related proteins, serum amyloid P-component, is called the "female protein" in hamsters. This type of protein is implicated in atherosclerosis, Alzheimer's disease, heart attacks, and kidney disease.

The respiratory system is so intimately related to the circulatory system and other systems that the traditional classification of diseases can be misleading. Ordinarily, asthma is distinguished from bronchitis, emphysema, "Acute Respiratory Distress Syndrome" or "shock lung," pulmonary edema, surfactant deficiency, etc., as if each problem were clearly distinguishable by its intrinsic properties. Actually, there is considerable overlap, and the diagnostic distinction can depend on the patient's history and situation, rather than on the actual pathology. Even "High Altitude Pulmonary Edema" has important similarities to "bronchial asthma."

Even though breathing might be the immediate focus of attention, there is no health problem which isn't systemic. The old medical use of cathartics for asthma, epilepsy, headaches, arthritis, cancer, etc., was often based on good observation. Before medicine became "scientific," many cases of asthma and epilepsy were successfully treated with vermifuges, but now the role of parasites in these conditions is rarely considered.

The specific location of symptoms--bronchial asthma, migraine, hemorrhoids, sneezing, etc.--brought on by an allergen, such as worms or certain foods or constipation or intestinal gas, is influenced by nervous reflexes. Reflexes are exaggerated by stresses such as hypoglycemia or alkalosis. Experimenters, for example, found that inflating a balloon in the intestine of an anesthetized animal wouldn't produce any observable reactions when the blood sugar was normal, but when the blood sugar was lowered, bronchospasms or other localized reflexive reactions would be produced.

The allergic reaction produced by any substance is intensified by hypoglycemia, and weakened by elevated blood sugar. Decreasing or increasing sodium has a similar, but weaker, effect. (G. Jasmin, 1968)

Knowing something about the situation that preceded a breathing difficulty can be useful, especially as a guide to eliminating environmental problems, but the fact that so many conditions involve the same physiological/pathological components means that a few therapies can be rationally used for many "different diseases."

For example, **caffeine, thyroid, carbon dioxide, progesterone, and several other anti-serotonin drugs (e.g., tianeptine and ketanserin)** can be therapeutic for asthma, even when the specific causes aren't known.

Buteiko's recognition of the importance of carbon dioxide (and the avoidance of hyperventilation) in the prevention of asthma is validated by the fact that high altitude normally alleviates asthma, that carbon dioxide inhalation at high altitude relieves altitude sickness (indicating that altitude sickness, like asthma, is the result of relative hyperventilation), and that acetazolamide, which increases carbon dioxide retention and is used to prevent or treat high altitude sickness, also alleviates asthma.

Practically everything which is stressful will shift metabolism away from the adequate production of carbon dioxide. The use of oxygen supplementation to treat asthma or other respiratory difficulty without also supplementing carbon dioxide is unphysiological and dangerous.

In the 19th century in the U.S., cocaine was officially recognized as a therapy for asthma, and in South America coca is the traditional remedy for altitude sickness, but there has been very little scientific investigation of the therapeutic use of cocaine. It increases progesterone production and probably has antihistamine action. Atropine,

which is very similar in chemical structure to cocaine, was a standard drug for asthma until the synthetic antihistamines and bronchodilators displaced it. Although it's known mainly as an "anticholinergic," atropine can protect against the excessive liberation of free fatty acids that interferes with the use of glucose. Camphor, amantadine, procaine and other soothing anticholinergics or antihistamines had a similar fate, as far as asthma therapy is concerned. The antihistamine Benadryl is usually helpful in asthma and other inflammatory or spasmodic conditions.

Eucalyptus oil, containing cineole or eucalyptol, is a traditional remedy for asthma, that inhibits the products of unsaturated fatty acid metabolism and the cytokines most associated with asthma symptoms.

The uncontrolled release of many inflammatory and excitatory substances can be prevented by good nutrition, emphasizing adequate protein and magnesium intake, and the use of sugars and saturated fats, rather than starches and unsaturated fats. Vitamin E protects against the inflammatory actions of the unsaturated fats. The short-chain saturated fatty acids of coconut oil have been reported to have antihistamine actions. **The selection of proteins should minimize the amino acids tryptophan (which is the precursor of serotonin) and cysteine (which, like tryptophan, suppresses thyroid function), by including gelatin and fruits.** Gelatin is 22% glycine, which protects the lungs and other organs against toxins and inflammatory agents, and many fruits are also "deficient" in tryptophan and cysteine.

The overlapping effects of estrogen, polyunsaturated fats, exercise, serotonin, histamine, lactic acid, nighttime, and hyperventilation, tend to be cumulative and self-stimulating. Degenerative changes in tissues are accelerated by all of these stress mediators.

When these factors aren't corrected, the standard officially recognized treatments for asthma--despite the acute relief they can provide--will probably increase long-range morbidity and mortality. For short-term relief, combinations of safer materials can probably be found that will give the same immediate results, while helping to correct the underlying problems.

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Eur Respir J 1997 Feb;10(2):482-91. **The role of pulmonary surfactant in obstructive airways disease.** Hohlfeld J, Fabel H, Hamm H. "Pulmonary surfactant research has an increasing impact on treatment **considerations in adult respiratory disorders,**

**above all acute respiratory distress syndrome (ARDS).**" "In addition to its surface activity, airway surfactant improves bronchial clearance and regulates airway liquid balance, thus indirectly modulating airway wall thickness and airway diameter. Surfactant has furthermore been shown to modulate the function of respiratory inflammatory cells. Its immunomodulatory activity includes suppression of cytokine secretion and transcription factor activation. This may be of importance in the inflammatory network of asthma."

Respir Physiol 1998 Apr;112(1):113-9. **Worsening of hypoxemia with nitric oxide inhalation during bronchospasm in humans.** Takahashi Y, Kobayashi H, Tanaka N, Honda K, Kawakami T, Tomita T. **"Our results show that NO inhalation worsens desaturation during bronchospasm in humans after MCh nebulization."**

Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 1997 Sep;118(1):5-10. **Inhibitory effect of sex steroids on guinea-pig airway smooth muscle contractions.** Perusquia M, Hernandez R, Montano LM, Villalon CM, Campos MG. perusqui@servidor.unam.mx We assessed the possible inhibition of airway smooth muscle contraction by progesterone and pregnanolones (5 alpha and 5 beta-reduced). Progesterone and 5 **beta-pregnanolone prevented histamine- or carbachol-induced contraction in isolated guinea-pig trachea and potency was related to their respective chemical structure; progesterone was the most potent inhibitor in a concentration-dependent manner.** The steroids also exhibited calcium antagonist activities in this tissue as assessed by their action on calcium entry in depolarized preparations; this event involved the immediate blockade of the extracellular calcium influx in the muscle cell membrane, indicating a nongenomic action. Classical GABAA antagonists did not block the progesterone response, implying no involvement of the GABAA-receptor complex. Our results **suggest a bronchodilating effect induced by sex steroids, and probably by other related compounds, before the genomic mechanisms take place. This nongenomic** action of steroids could have potential therapeutic usefulness in the treatment of asthma.

Am J Respir Crit Care Med 1997 Apr;155(4):1273-7. **Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill.** Tan KS, McFarlane LC, Lipworth BJ.

Verh K Acad Geneeskd Belg 1991;53(5):497-505. **[Consumption of coca in history.]** [Article in French] Appelboom T. "The **medical use of cocaine for the treatment of hayfever and asthma (Dr. Tucker's elixir) had in between officially been agreed by the famous scientific societies in America."**

Cardiology 2001;95(1):31-4. **Insulin resistance is increased by transdermal estrogen therapy in postmenopausal women with cardiac syndrome X.** Assali AR, Jabara Z, Shafer Z, Solodky A, Herz I, Sclarovsky E, Strasberg B, Sclarovsky S, Fainaru M. ". . . it remains to be examined how short-term transdermal estrogen therapy (TET) affects insulin **sensitivity** (SI) in patients with cardiac syndrome X (CSX), who are characterized by elevated insulin resistance." **"SI decreased by 32 +/- 8.3%, from 5.94 +/- 1.14 at baseline to 3.61 +/- 0.40 [(10(-4) x min(-1))/(microU/ml)] during TET** ($p = 0.03$)."

Am J Physiol Lung Cell Mol Physiol 2001 Sep;281(3):L668-76. **Airway inflammation in nonasthmatic amateur runners.** Bonsignore MR, Morici G, Riccobono L, Insalaco G, Bonanno A, Profita M, Paterno A, Vassalle C, Mirabella A, Vignola AM. marisa@ifr.pa.cnr.it **"Elite athletes show a high prevalence of symptoms and signs of asthma, but no** study has assessed the acute effects of endurance exercise on airway cells in nonasthmatic athletes." "After the marathon, exhaled NO (n = 9 subjects) was higher [27 +/- 9 parts/billion (ppb)] than at baseline (12 +/- 4 ppb; $P < 0.0005$). Polymorphonuclear neutrophil (PMN) counts in induced sputum were much higher in runners (91.2 +/- 3.6% of total cells postmarathon and 78.7 +/- 9.1% at baseline) than in sedentary control subjects (9.9 +/- 5.9%; $P < 0.001$)." "Our data indicate that sputum PMNs are increased in nonasthmatic runners both after a marathon and at baseline and suggest that NO may modulate exercise-associated inflammatory airway changes."

J Allergy Clin Immunol 2000 Sep;106(3):444-52. **Allergy and asthma in elite summer sport athletes.** Helenius I, Haahtela T. **"In the summer Olympic Games, 4% to 15% of the athletes showed evidence of asthma or used antiasthmatic medication. Asthma is most commonly found in endurance** events, such as cycling, swimming, or long-distance running. The risk of asthma is especially increased among competitive swimmers, of which 36% to 79% show bronchial hyperresponsiveness to methacholine or histamine. The risk of asthma is closely associated with atopy and its severity among athletes. A few studies have investigated occurrence of exercise-induced bronchospasm among highly trained athletes. The occurrences of exercise-induced bronchospasm vary from 3% to 35% and depend on testing environment, type of exercise used, and athlete population tested. Mild eosinophilic airway inflammation has been shown to affect elite swimmers and cross-country skiers. This eosinophilic inflammation correlates with clinical parameters (ie, exercise-induced bronchial symptoms and bronchial hyperresponsiveness). Athletes commonly use antiasthmatic medication to treat their exercise-induced bronchial symptoms."

Am J Respir Crit Care Med 2001 Sep 1;164(5):785-9. **Repeated hyperventilation causes peripheral airways inflammation, hyperreactivity, and impaired bronchodilation in dogs.** Davis MS, Freed AN. "Winter athletes have an increased incidence of asthma, suggesting that repetitive hyperventilation with cold air may predispose individuals to airways disease. We used a canine model of exercise-induced hyperpnea to examine the effects of repeated hyperventilation with cool, dry air (i.e., dry air challenge [DAC]) on peripheral airway resistance (Rp), reactivity, and inflammation." ". . . other mechanisms in addition to increased smooth muscle tone may contribute to the development of repetitive hyperventilation-induced bronchial obstruction and hyperreactivity."

Exerc Immunol Rev 2001;7:66-89. **Free radicals, exercise, apoptosis, and heat shock proteins.** Fehrenbach E, Northoff H. "Evidence is accumulating that free radicals have important functions in the signal network of cells. . . ." **"Excessive exercise will also induce DNA damage in peripheral leukocytes."** "Massive intervention into the redox state by pharmaceutical doses of exogenous antioxidants should be regarded with caution due to the ambiguous role of free radicals in regulation of growth, apoptosis, and cytotoxicity by immunocompetent cells."

Med Sci Sports Exerc 2000 Aug; 32(8):1384-9. **Influence of carbohydrate on cytokine and phagocytic responses to 2 h of rowing.** Henson DA, Nieman DC, Nehlsen-Cannarella SL, Fagoaga OR, Shannon M, Bolton MR, Davis JM, Gaffney CT, Kelln WJ, Austin MD, Hjertman JM, Schilling BK. "This study examined the influence of carbohydrate (C) versus placebo (P) beverage ingestion on the phagocytic and cytokine responses to normal rowing training by 15 elite female rowers." "Concentrations of blood neutrophils and monocytes, phagocytic activity, and plasma IL-1ra were significantly lower postexercise after C versus P ingestion." **"These data indicate that carbohydrate compared with placebo ingestion attenuated the moderate rise in blood neutrophils, monocytes, phagocytosis, and plasma IL-1ra**

concentrations that followed 2-h bouts of training in elite female rowers."

J Clin Hypertens (Greenwich) 2001 May-Jun;3(3):145-52. **Gender differences in vascular compliance in young, healthy subjects assessed by pulse contour analysis.** Winer N, Sowers JR, Weber MA. "Reductions in the oscillatory or reflected component of the diastolic waveform have been observed in various clinical conditions, including hypertension, diabetes mellitus, and congestive heart failure, and may reflect endothelial dysfunction at the site of resistance vessels." **"These data indicate that female sex hormones have unexpected negative effects on small vessel compliance. They may help to explain why premenopausal women hospitalized for myocardial infarction have higher mortality rates than men of the same age."**

J Leukoc Biol 1993 Apr;53(4):420-6. **Polyunsaturated fatty acids increase neutrophil adherence and integrin receptor expression.** Bates EJ, Ferrante A, Harvey DP, Poulos A. Department of Immunology, Women's and Children's Hospital, Adelaide, Australia. Fish oils are abundant in polyunsaturated fatty acids of the n-3 series (in particular eicosapentaenoic, 20:5 and docosahexaenoic acid, 22:6). Such fatty acids are generally considered to be beneficial in the prevention of cardiac disease and to have anti-inflammatory properties. **Neutrophil adherence is an essential early event in an acute inflammatory response, and we have demonstrated that both 20:5 and 22:6 stimulate adherence in vitro. Arachidonic acid (20:4, n-6) was also stimulatory. Significant simulation of adherence was seen from 5 to 80 microM (nontoxic concentrations) 22:6, 20:5, or 20:4. At the lower fatty acid concentrations tested (< or = 40 microM) 20:5 was less active than 22:6 or 20:4 at stimulating adherence. Above 40 microM there was no difference in the ability of the three fatty acids to stimulate adherence**. At the lower fatty acid concentrations tested (< or = 10 microM) 22:6 was less active than 20:4, whereas above 10 microM they were equally active. Immunofluorescent flow cytometric analysis of neutrophil integrin (adherence) receptors showed that **the complement C3bi receptor (CD11b) was up-regulated by these fatty acids.** There was no change in CD11a or CD11c. Saturated fatty acids of the same chain length were without effect on adherence or receptor expression. The findings suggest that **these polyunsaturated fatty acids may, under certain conditions, be proinflammatory with respect to their acute effects on the interaction of neutrophils with microbes, endothelium, and other tissues.**

Nippon Yakurigaku Zasshi 2001 Sep;118(3):170-6. **[New strategy on medical research after completion of genome sequencing].** [Article in Japanese] Ishikawa K, Tsujimoto G.

J Investig Allergol Clin Immunol. 2001;11(2):73-8. **Susceptibility genes for asthma and allergy: hits and questions.** Castro J, Telleria JJ, Blanco-Quiros A.

J Asthma. 1989;26(6):331-3, 335-40. **The new gestalt: asthma as a chronic inflammatory disease.** Ackerman SJ.

Med Sci Sports Exerc 2001 Apr;33(4):549-55. **Anaerobic exercise induces moderate acute phase response.** Meyer T, Gabriel HH, Ratz M, Muller HJ, Kindermann W.

Epilepsia 2000 May;41(5):510-5. **Estradiol facilitates kainic acid-induced, but not flurothyl-induced, behavioral seizure activity in adult female rats.** Woolley CS.

Endocrinology 1992 Aug;131(2):662-8. **Estradiol selectively regulates agonist binding sites on the N-methyl-D-aspartate receptor complex in the CA1 region of the hippocampus.** Weiland NG. **"Estradiol alters cognitive function and lowers the threshold for seizures in women and laboratory animals. Both of these activities are modulated by the excitatory neurotransmitter glutamate in the hippocampus."** "Two days of estradiol treatment increased the density of NMDA agonist, but not of competitive nor noncompetitive NMDA antagonist binding sites exclusively in the CA1 region of the hippocampus. The density of noncompetitive NMDA antagonist sites, however, was decreased in the dentate gyrus by estradiol treatment." "The increase in NMDA agonist sites with ovarian hormone treatment should result in an increase in the sensitivity of the hippocampus to glutamate activation which may mediate some of the effects of estradiol on learning and epileptic seizure activity."

Epilepsia 1985 May-Jun;26(3):252-7. **Comparative effects of estradiol benzoate, the antiestrogen clomiphene citrate, and the progestin medroxyprogesterone acetate on kainic acid-induced seizures in male and female rats.** Nicoletti F, Speciale C, Sortino MA, Summa G, Caruso G, Patti F, Canonico PL. We have investigated the comparative effects of estradiol benzoate (EB), the antiestrogen clomiphene citrate (CC), and the progestin medroxyprogesterone acetate (MPA) on seizures induced by systemic injection of kainic acid (15 mg/kg i.p.) in male and female rats. **Subcutaneous administration for 10 days of EB (10 micrograms/kg) or high doses of CC (50 mg/kg) significantly potentiated kainate-induced seizures,** with this effect being more pronounced in male animals. Doses of 2.5 mg/kg of CC potentiated kainate-induced seizures in male rats but were ineffective in female rats. **Low doses of CC (0.5 mg/kg) exhibited a mild anticonvulsant effect in both sexes. Repeated administration of MPA (2.5 mg/kg) partially protected female animals against kainate-induced seizures;** in male animals, MPA induced a 30% increase in the seizure severity score, although the difference from the score of control male rats **was not significant.** These data suggest that sex steroids influence kainate-induced seizures in a sex-dependent manner and that the effects of the antiestrogen CC are dose dependent. This should be taken into account in view of a possible use of CC and MPA in hormonal therapy for seizure disorders.

Biochem Soc Symp 1999; 66:149-66. **Mitochondrial dysfunction in sepsis.** Singer M, Brealey D. **"The current mainstream view of organ failure induced by sepsis revolves around inflammation and loss of vascular control. However, there has been a resurgence in interest in bioenergetic failure due to mitochondrial**

**dysfunction.** This concept is not new--studies date back 30 years. . ." "As a generalization, there does appear to be depression of mitochondrial function with longer-duration models of greater severity." "The potential roles of nitric oxide, intracellular calcium and reactive oxygen species are highlighted."

J Clin Invest 1985 Jul;76(1):66-74. **Hamster female protein, a sex-limited pentraxin, is a constituent of Syrian hamster amyloid.** Coe JE, Ross MJ. Female protein (FP) is a pentraxin of Syrian hamster which is a homologue of two human pentraxins, C-reaction protein (CRP) and amyloid P component (AP).

Am J Pathol 2001 Mar;158(3):1039-51. **Generation of C-reactive protein and complement components in atherosclerotic plaques.** Yasojima K, Schwab C, McGeer EG, McGeer PL. "C-reactive protein (CRP) and complement are hypothesized to be major mediators of inflammation in atherosclerotic plaques."

Jpn J Pharmacol 1979 Aug;29(4):509-14. **Anti-inflammatory action of progesterone on carrageenin-induced inflammation in rats.** Nakagawa H, Min KR, Nanjo K, Tsurufuji S. Effect of progesterone (1 mg/kg) on the inflammation in rats induced by carrageenin was studied. **Progesterone inhibited the vascular permeability and the formation of granulation tissue in the early phase of the inflammation. In the chronic proliferative phase, progesterone suppressed the vascular permeability and there was an active resorption of the granulation tissue.** Increased degradation of noncollagen protein was observed in the treated group without apparent influence on the metabolism of collagen or on the synthesis of noncollagen protein. **The mode of action of progesterone was compared with that of a potent anti-inflammatory steroid, hydrocortisone acetate.**

Circulation 1999 Aug 17;100(7):717-22. **Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study.** Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, Sakkinen PA, Tracy RP. "**Postmenopausal hormones rapidly increased the concentration of the inflammation factor C-reactive protein. Such an effect may be related to adverse early effects of estrogen therapy.**"

J Clin Endocrinol Metab 2001 Sep; 86(9):4216-22. **Differential effects of E and droloxifene** on C-reactive protein and other markers of inflammation in healthy postmenopausal women. Herrington DM, Brosnihan KB, Pusser BE, Seely EW, Ridker PM, Rifai N, MacLean DB. "**E treatment resulted in 65.8% higher levels of C-reactive protein (P = 0.0002) and 48.1% higher levels of IL-6 (P < 0.001),** . . ."

Arterioscler Thromb Vasc Biol 2001 Feb;21(2):255-61. **Tamoxifen and cardiac risk factors in healthy women: Suggestion of an anti-inflammatory effect.** Cushman M, Costantino JP, Tracy RP, Song K, Buckley L, Roberts JD, Krag DN.

Circulation 1999 Aug 17;100(7):713-6. **Hormone replacement therapy and increased plasma concentration of C-reactive protein.** Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE.

JAMA 2001 Jul 18;286(3):327-34. **C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.** Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM.

Thromb Haemost 1999 Jun;81(6):925-8. **Increased C-reactive protein levels during short-term hormone replacement** therapy in healthy postmenopausal women.

Immunol Lett 1991 Jan;27(1):75-9. **Parallel relationship between the increase in serotonin in the liver and the hypoglycaemia induced in mice by interleukin-1 and tumour necrosis factor.** Endo Y.

Clin Sci (Colch) 2000 Jan;98(1):47-55. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Jeukendrup AE, Vet-Joop K, Sturk A, Stegen JH, Senden J, Saris WH, Wagenmakers AJ.

Circulation 1999 Aug 24;100(8):793-8. **Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin.** Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P.

Annu Rev Med 2000;51:245-70. **Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty.** Ershler WB, Keller ET.

Vestn Ross Akad Med Nauk 2000;(10):37-45. **[Increased proinflammatory cytokine production by human peripheral lymphocytes treated with glucocorticoids].** [Article in Russian] Kalashnikova EA, Kokarovtseva SN, Pakhul'skii AL.

Exerc Immunol Rev 2001;7:18-31. **Exercise and cytokines with particular focus on muscle-derived IL-6. Pedersen BK, Steensberg A, Fischer C, Keller C, Ostrowski K, Schjerling P.**

Brain Behav Immun 2001 Mar;15(1):7-24. **Cytokine-induced sickness behavior: where do we stand?** Dantzer R. "There is **clinical and experimental evidence that activation of the brain cytokine system is associated with depression.** . . ."

Atherosclerosis 1990 Jun;82(3):247-52. **Inhibition of cyclooxygenase-independent platelet aggregation by low vitamin E concentration.** Violi F, Pratico D, Ghiselli A, Alessandri C, Iuliano L, Cordova C, Balsano F.

BioDrugs 2001;15(2):81-6. **The potential role of tocopherol in asthma and allergies: modification of the leukotriene pathway.** Centanni S, Santus P, Di Marco F, Fumagalli F, Zarini S, Sala A.

Prostaglandins Med 1980 Feb;4(2):79-85. **Inhibition of human platelet cyclooxygenase by alpha-tocopherol.** Ali M, Gudbranson CG, McDonald JW. "**A dose-dependent reduction in thromboxane B2 and prostaglandin D2 synthesis was observed with** approximately 60% inhibition at 5.0 IU or alpha-tocopherol. Alpha-tocopherol produced a time-dependent, irreversible inhibition."

Prostaglandins Leukot Essent Fatty Acids 1991 Oct;44(2):89-92. **Inhibition of PGE2 production in macrophages from vitamin E-treated rats.** Sakamoto W, Fujie K, Nishihira J, Mino M, Morita I, Murota S.

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