Ray Peat's Newsletter

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Lungs, shock, inflammation, and aging

There is a growing effort by the food and drug industries, and many physicians, to promote the use of certain polyunsaturated fatty acids, those with their double bonds farthest from the acidic end of the molecule. These fats, which are found in fish, algae, and many vegetables, are the most easily oxidized of the common fatty acids. With stress, such as premature birth, and with aging, these fats produce free radical decomposition products at a high rate. They contribute to "shock lung" and to multiple organ failure.

After I had done my dissertation on the changes in oxygen metabolism that occur during aging and under the influence of estrogen, and not long after I had seen the therapeutic effects of progesterone in epilepsy, arthritis, depression, and multiple sclerosis, I met a woman who was disabled with some kind of inflammatory muscle and joint disease. Her face, arms, and upper torso were emaciated, but her hips and thighs were huge. This pattern of fat distribution is typical of the extreme and prolonged influence of estrogen.

In discussing her health history, she said that her movement problems began at the age of 21, when her physician-father began giving both her and her mother regular injections of estrogen.

Having a doctor in the family, they had the most complex medical studies done in trying to diagnose their problems. The thing that stood out in her description of the tests was the pulmonary oxygen diffusion test, which she said showed that both she and her mother had oxygen diffusing capacity that were "95% below normal." I think she might have meant that they were in the lowest 5 percent of the population, since I can't think of another interpretation that would be compatible with life. Right around that time, I read a study in which mice were given a large dose of estrogen, which, after just 40 minutes, caused a similarly radical decrease in their oxygen diffusing capacity.

In the late 1960s, I had been interested in the use by athletes of a drink made by foaming oxygen into a solution of gelatin, to increase their blood oxygenation and their performance. I tried to talk to a few physician-researchers about this, and they firmly said that it was nonsensical, because "blood is always fully oxygenated when it leaves the lungs." Looking in the science library at the university, I found a recent (c. 1968) study in which the blood's oxygenation was found to decline with aging, commonly down to about 50%. But despite the mouse study, I didn't find any studies regarding estrogen's effects on oxygen diffusion in humans. I believed that the reason was the same as the denial that athlete's blood might not be fully oxygenated, namely, a stupefying degree of authoritarianism and a need to absolutize anything that was in a medical textbook.

About 15 years later, I visited a friend who was 82 years old, who lived in Toluca, Mexico. When I first saw him, I could see that he didn't recognize me. He was sitting down, breathing heavily, and his face was purplish. He had been diagnosed as having emphysema, and hadn't been able to work for several weeks. Since he was very fat, I guessed that he might be suffering from the

". . . at a maximum level of exertion, the heart at high altitude is relying less on glycolysis (anaerobic energy production), and getting more of its energy from oxygen, than it would at sea level." This means that sea-level metabolism is more like cancer metabolism, because of the high oxygen/carbon dioxide ratio.

same sort of estrogen-provoked diffusion problem that I had run across previously. I left his daughter some progesterone and pregnenolone to give him, and left Toluca for several days. The next time I saw him, his skin had a better color, and his humor had returned. When I came back again two weeks after he had started taking progesterone and pregnenolone, his color was entirely normal, he had resumed working in his office (in a building that didn't have an elevator), and he insisted on taking me around the city, causing me to pant because of the altitude, about 8,500 feet above sea level.

In the 1950s, Gilbert Ling found that, under the influence of increased carbon dioxide, excitable cells don't "depolarize" electrically[1] to the extent that they do under a normal atmosphere. This principle has been applied to treat epilepsy, by breathing air with a few percent of carbon dioxide added, and more often, the principle has been used in the "diagnosis" of epilepsy, by using hyperventilation to induce seizures, by displacing too much carbon dioxide. Carbon dioxide spontaneously forms carbamino groups by reacting with the amino groups in proteins, and increasing the oxygen pressure causes the carbon dioxide to be displaced.

The binding of the acidic carbon dioxide to the protein molecule shifts electrons in the protein, making it more acidic. This shift in the protein changes the way the protein interacts with other molecules, including water, sodium, potassium, and calcium. Under the relatively acidic conditions when carbon dioxide is abundant, with the cell proteins' average electrons slightly "retracted," free radical production is inhibited, and cells are more resistant to radiation damage or other excitatory damage.

Carbon dioxide, along with the carbonic acid it forms as it reacts with water, regulates the organism's handling of water.

Carbon dioxide's association with cells has many effects, including the regulation of hormones and nerve transmitters. For example, carbon dioxide causes cells to bind serotonin, so that a loss of carbon dioxide causes serotonin to be released, with the effect that blood vessels become more permeable, and leak fluid (including serum proteins) into the surrounding spaces.

In the lungs, this leakage of fluid is very inconvenient.

In any tissue, the leakage of serum creates an additional barrier to the diffusion of oxygen from the blood to the tissue cells. The hypoxic cells release lactic acid and other mediators of inflammation, and the walls of the capillaries and other blood vessels thicken, making the proper circulation of the blood more difficult. These effects are usually overlooked in the brain and the heart, but in the lung they are hard to miss. Following a stressful death, the lungs are waterlogged, with a great increase in weight, a condition called "shock lung" or "wet lung."

The antiexcitatory action of carbon dioxide is opposed by oxygen, so oxygen can, in this context, be considered as a cell excitatory agent. At increased pressure, pure oxygen causes seizures, and even at normal pressure, the lungs are more likely to be damaged when there is more oxygen. Since the lungs' delicate membranes are in direct contact with air, it's obvious that they are in a vulnerable situation, easily losing too much carbon dioxide in the presence of excessive oxygen.

At high altitudes, once a person has adapted to the lower oxygen pressure, the tissues retain more carbon dioxide, and this prevents cells from being activated to the same extent that's possible at low altitude, so there is less lactic acid produced. The carbon dioxide makes the blood circulate more easily, so the heart works less to circulate the blood at the same rate that it would circulate at sea level, or even at a higher rate, and even **at a maximum level of exertion, it is relying less on glycolysis (anaerobic energy production), and getting more of its energy from oxygen, than it would at sea level.**

[1] In the normal resting state, a cell is "polarized." In the depolarized state, a cell is vulnerable, and if it is too frequently depolarized, it can be damaged or killed in the process called "excitotoxicity," and other related degenerative processes. Cancer cells are chronically "depolarized," and this is related to their low-efficiency metabolism.

Some people, who have a respiratory problem at sea level, react to high altitude by breathing so hard that they lose even more carbon dioxide than they were losing at low altitude, and they may develop lung edema, and even brain edema and seizures. With lung edema, breathing becomes harder, and the heart works harder. It has been discovered repeatedly over the years that altitude sickness can be treated successfully with supplemental carbon dioxide. The now-standard treatment for mountain sickness is the drug acetazolamide, which causes the body to retain carbon dioxide. Despite the drug's success in preventing and curing altitude sickness, there is a weird reluctance to acknowledge that mountain sickness is produced by an insufficiency of carbon dioxide. The same drug is now often used to treat sleep apnea, despite the textbooks' opinion that sleep apnea is caused by too much carbon dioxide, rather than by the alkalosis resulting from insufficient carbon dioxide.

If we think of the presence of lactic acid as evidence of metabolic inefficiency, then an athlete, or anyone who exercises strenuously, has a low degree of efficiency, especially at sea level. Despite the presence of oxygen that isn't being consumed at a maximum rate, glycolysis becomes very intense, producing lactic acid that apparently helps to limit the full use of the available oxygen. It is probably the high oxygen pressure, wasting carbon dioxide, that turns on the lower efficiency lactic acid-producing glycolysis.

"Hypoxemia of exercise," the failure of the blood to be fully oxygenated during strenuous activity, is very similar to the chronic hypoxemia that occurs in the "respiratory distress syndrome." Women ahtletes have a greater tendency to exercise hypoxemia then men. In the luteal phase, when progesterone should be dominant, women breathe more effectively than during the estrogen-dominated follicular phase of the cycle. Since estrogen, like exercise, causes blood vessels to leak fluid, this isn't surprising. Stress, such as exercise or sickness, causes a significant rise of estrogen, along with the other mediators of inflammation, even in men.

Both exercise and estrogen dominance cause fatty acids to be liberated from the tissues. The unsaturated fatty acids increase the permeability of capillaries, and the ratio of unsaturated fatty acids to saturated fatty acids corresponds closely to the degree of lung malfunction and respiratory distress. (Baughman, et al., 1984) The medium chain saturated triglycerides, extracted from coconut oil, can be used for intravenous feeding without causing the respiratory distress and lung damage produced by the unsaturated vegetable oils that were formerly used.

The long chain polyunsaturated fatty acids, including linoleic, linolenic, arachidonic, and docosahexaenoic (DHA) acids, cause mitochondrial breakdown, thyroid suppression, vascular permeability, brain edema, and increased radiation sensitivity.

DHA is the most unstable of these unsaturated fatty acids. But there is at present a very poweful marketing campaign which argues that DHA should be added to baby formula and should be taken by adults, because we supposedly "evolved on a diet rich in n-3 fatty acids," and because our tissues generally contain a much lower concentration of the n-3 fats than of the n-6 fats.

There is evidence that the low ratio of these n-3 fatty acids, such as DHA (docosohexaenoic acid), to the n-6 fats, such as arachidonic acid, is the result of the fact that the n-3 fats are extremely unstable, and break down rapidly in the tissues, producing lipid peroxides, free radicals, and the characteristic ethane, which can be measured in the breath. Stress accelerates the decomposition of these fats, and the resulting ethane can be detected in higher amounts during respiratory distress, and in premature babies and in older people.

Mead Johnson has announced that it will add DHA to their baby formula, arguing that it is an essential nutrient for eye and brain development. But animals that are fed a diet that is "deficient in" DHA are less susceptible to eye damage than animals that have "sufficient" DHA. But more generally, animals that are deficient in ***all of the so-called "essential fatty acids"*** are extremely resistant to all sorts of injury, shock, and poisoning.

Since all of the polyunsaturated fats inhibit thyroid function, and since the thyroid hormone is essential for the development of the brain and

lungs, increased use of polyunsaturated oils will increase the incidence of hypothyroidism, leading to the birth of more premature babies with lung disease. With a high concentration of polyunsaturated fats in the lungs, the exposure of the newborn's lungs to oxygen will create an inflammatory reaction. This is probably why the respiratory distress of prematurity usually takes a few days to appear. Considering what is known about oxygen, lungs, and DHA, I think it would be reasonable to say that increased use of DHA would be the ideal way to increase infant lung disease.

The unsaturated fats and estrogen contribute to the increased release of serotonin and nitric oxide (NO). Nitric oxide is produced during inflammation, and, like ethane, can be detected in the breath when the lungs are inflamed. Nitric oxide, as a pro-inflammatory free radical, stimulates the peroxidation of the unsaturated fats. Both NO and serotonin inhibit mitochondrial respiration, shifting metabolism toward glycolysis.

Since the processes that damage the lungs are so similar in aging, stress, and prematurity, I think an examination of the factors that cause premature birth will be useful for understanding the general problem of "lung stress."

Preeclampsia, or a syndrome of pregnancy induced hypertension, occurs in about 10% of pregnancies, and it's the main cause of maternal death and sickness of the newborn.

Thomas Brewer, about 50 years ago, made it clear that a protein deficiency is the main cause of preeclampsia. Protein deficiency causes a general inflammatory condition, with increased serotonin.

In women with preeclampsia, there are abnormally high levels of serotonin, nitric oxide, and lipid peroxidation.

In a study of more than 3000 women (Clausen, et al., 2001), the consumption of sugar and polyunsaturated fat was strongly associated with the development of preeclampsia. Women who don't eat enough protein are likely to substitute sugar and fat for the absent protein, so this study is consistent with Brewer's work, but it's very important to see that it was polyunsaturated fats, not saturated or monounsaturated fats, that caused the problem. Eclampsia (pregnancy- related seizures) and preeclampsia are caused by oxidative stress, produced by the excessive unstable fats. The increased serotonin and nitric oxide are exactly what would be expected to result from the high consumption of polyunsaturated fats, especially with a deficiency of protein in the diet.

Protein deficiency, like an excess of polyunsaturated fats, causes a thyroid deficiency. Supplements of thyroid, given during gestation, accelerate the maturation of the baby's lungs, and prevent the respiratory distress syndrome.

The use of adequate protein and saturated fats during pregnancy will prevent many of the problems of pregnancy and infancy, but since the unsaturated fats remain stored in the tissues for many years, and are mobilized during stress, it's important to eat correctly long before pregnancy. The requirement for vitamin E remains high for years after the diet has contained an excess of the polyunsatured fats.

The diet which protects the developing fetus happens to be the diet that protects adults from all sorts of stress, and prevents many of the worst symptoms of aging.

Supplemental thyroid, pregnenolone, and progesterone can partly make up for defects in the diet, by maintaining a better balance between carbon dioxide and lactic acid, and by restraining the various mediators of stress, such as NO, serotonin, and estrogen.

REFERENCES

Lipids 1997 May;32(5):535-41. Comment in: Lipids. 1998 Sep;33(9):947. **Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans.** Allard JP, Kurian R, Aghdassi E, Muggli R, Royall D. The purpose of this study was to investigate in healthy humans the effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intake, alone or in combination with dL-alpha-tocopherol acetate (vitamin E) supplements on lipid peroxidation. Eighty men were randomly assigned in a double-blind fashion to take daily for 6 wk either menhaden oil (6.26 g, n-3 fatty acids) or olive oil supplements with either vitamin E (900 IU) or its placebo. Antioxidant vitamins, phospholipid composition, malondialdehyde (MDA), and lipid peroxides were measured in the plasma at baseline and week 6. At the same time, breath alkane output was measured. Plasma alpha-tocopherol concentration increased in those receiving vitamin E ($P < 0.0001$). In those supplemented with n-3 fatty acids, **EPA and DHA increased in plasma phospholipids ($P < 0.0001$) and**

plasma MDA and lipid peroxides increased ($P < 0.001$ and $P < 0.05$, respectively). Breath alkane output did not change significantly and vitamin E intake did not prevent the **increase in lipid peroxidation during menhaden oil supplementation. The results** demonstrate that supplementing the diet with n-3 fatty acids resulted in an increase in lipid peroxidation, as measured by plasma MDA release and lipid peroxide products, which was not suppressed by vitamin E supplementation.

Am J Med Sci 1995 Dec;310(6):226-8. **Isolated reduction in single-breath diffusion capacity in young, healthy, asymptomatic women.** Ansari A, Collier J, Mohsenifar Z

Free Radic Biol Med 1994 Dec;17(6):569-76. **Breath ethane generation during clinical total body irradiation as a marker of oxygen-free-radical-mediated lipid peroxidation: a case study.** Arterbery VE, Pryor WA, Jiang L, Sehnert SS, Foster WM, Abrams RA, Williams JR, Wharam MD Jr, Risby TH.

Biull Eksp Biol Med 1976 Oct;82(10):1181-3. **[Role of the biological activity of serotonin in the production of the "shock lung" syndrome.]** Bazarevich GI, Deviataev AM, Likhtenshtein AO, Natsvlishvili BP, Sadeko MK.

Am J Obstet Gynecol 2001 Aug;185(2):451-8. **High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia.** Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE, Henriksen T. OBJECTIVE: Preeclampsia is associated with high body mass index, insulin resistance, and hypertriglyceridemia. Our objective was to investigate prospectively whether diet in the first half of pregnancy is associated with the risk for preeclampsia. STUDY DESIGN: This prospective, population-based, cohort study of pregnant women investigated dietary intake early in the second trimester with a quantitative food frequency questionnaire. RESULTS: The questionnaire was completed by **3133 women** (83%). Preeclampsia developed in 85 women. Adjusted odds ratio (95% CI) for preeclampsia was 3.7 (1.5-8.9) for energy intake of >3350 kcal/d compared with < or =2000 kcal/d. Adjusted odds ratio (95% CI) for preeclampsia was 3.6 (1.3-9.8) for sucrose intake (percent of total energy) of >25% compared with < or =8.5% and 2.6 (1.3-5.4) for polyunsaturated fatty acids intake (percent of total energy) of >7.5% compared with < or =5.2%. Other energy-providing nutrients were not associated with the risk for preeclampsia. CONCLUSION: The current study suggests that high intakes of energy, sucrose, and polyunsaturated fatty acids independently increase the risk for preeclampsia.

Minerva Anestesiol 1994 Jun;60(6):295-303. **[Expired ethane as a non-invasive marker of the course of experimental multiple organ dysfunction syndrome (MODS)]** di Filippo A, Scardi S, Consalvo M, Ridolfi N, Pellegrini G, Paternostro E, Novelli GP.

Thorax 1999 Feb;54(2):161-8. **Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension.** Egermayer P, Town GI, Peacock AJ. Canterbury Respiratory Research Group, Christchurch School of Medicine, New Zealand.

Eur J Obstet Gynecol Reprod Biol 2000 Sep;92(1):63-6. **Lipid-mediated endothelial dysfunction: a common factor to preeclampsia and chronic vascular disease.** Gratacos E

Hypertension 2001 Apr;37(4):1184-90. **8-iso-prostaglandin F(2alpha) increases expression of LOX-1 in JAR cells.** Halvorsen B, Staff AC, Henriksen T, Sawamura T, Ranheim T. **"Oxidative stress is believed to play a role in the pathophysiology of preeclampsia. 8-iso-prostaglandin F(2alpha) (8-iso-PGF(2alpha)) is a marker of oxidative stress in vivo, is biologically active in vitro, and is elevated in preeclamptic plasma and gestational tissue."** "We speculate a potential role of isoprostanes and LOX-1 in preeclampsia in the development of "acute atherosis" of gestational spiral arteries."

J Physiol (Lond) 1998 Mar 1;507 (Pt 2):619-28. **Exercise-induced arterial hypoxaemia in healthy young women.** Harms CA, McClaran SR, Nickele GA, Pegelow DF, Nelson WB, Dempsey JA

J Neurosci Res 1989 Oct;24(2):247-50. **Brain mitochondrial swelling induced by arachidonic acid and other long chain free fatty acids.** Hillered L, Chan PH.

J Neurosci Res 1988;19(1):94-100. **Effects of arachidonic acid on respiratory activities in isolated brain mitochondria.** Hillered L, Chan PH.

J Neurosci Res 1988 Aug;20(4):451-6. **Role of arachidonic acid and other free fatty acids in mitochondrial dysfunction in brain ischemia.** Hillered L, Chan PH.

J Neurosci Res 1989 Oct;24(2):247-50. **Brain mitochondrial swelling induced by arachidonic acid and other long chain free fatty acids.** Hillered L, Chan PH.

Biol Neonate 1978;34(1-2):61-7. **Relationship between fatty acids and lipid peroxidation in lungs of neonates.** Kehrer JP, Autor AP.

Monaldi Arch Chest Dis 1996 Dec;51(6):533-7. **Nitric oxide in exhaled air is a new marker of airway inflammation.** Kharitonov SA, Barnes PJ.

Arch Toxicol 1998 Mar;72(4):244-6. **Expiration of ethane in rats under variously elevated inspiratory O2-concentrations.** Kritzler K, Schoch G, Topp H.

Bull Acad Natl Med 2000;184(2):415-28; discussion 428-30. **[Pulmonary toxicity of oxygen]** Mantz JM, Stoeckel ME.

J Neurotrauma 1998 Oct;15(10):825-35. **Cellular accumulation of extravasated serum protein and DNA fragmentation following vasogenic edema.** Murakami K, Kawase M, Kondo T, Chan PH

Clin Physiol 1987 Oct;7(5):423-30. **The transfer factor (diffusing capacity) as a predictor of hypoxaemia during exercise in restrictive and chronic obstructive pulmonary disease.** Nordenfelt I, Svensson G. Thirty patients (17 with restrictive, eight with chronic obstructive pulmonary disease and five with combined pulmonary changes) were studied. Ordinary pulmonary function tests were made and in addition the transfer factor (diffusion capacity) was measured at rest and compared to the arterial oxygen tension at rest and during maximal exercise. There

was a significant correlation (r = 0.89) **between the transfer factor at rest and the oxygen tension during maximal exercise in both the patients with restrictive and those with obstructive lung disease, but no correlation was found between the transfer factor and the resting oxygen tension. Exercise induced hypoxaemia (PO2 less than 8-8.5 kPa) occurred in some patients and this could be predicted with an excellent sensitivity and specificity if a discrimination point for the transfer** factor of 50 per cent of predicted or less was chosen. Determination of the transfer factor at rest is thus a good screening test for exertional hypoxaemia and can be used to select patients for exercise testing when the purpose is to detect hypoxaemia.

Am J Physiol 1994 Jul;267(1 Pt 1):C177-88. **Cell fatty acid composition affects free radical formation during lipid peroxidation.** North JA, Spector AA, Buettner GR.

Nippon Kyobu Geka Gakkai Zasshi 1996 Jul;44(7):936-44. **[Immunosuppressive effect of intravenously injected docosahexaenoic acid on single lung allotransplantation in the rat]** Sasaki H, Hirose H, Sakai S, Zhang YQ, Hamazaki T.

J Toxicol Environ Health 1995 Sep;46(1):23-9. **Effect of oxygen concentration on production of ethane and thiobarbituric acid-reactive substances by peroxidizing lung and liver homogenates and formation of ethanol by peroxidizing docosahexaenoic acid preparations under hyperoxic conditions.** Schweich MD, Gosselain J, Lison D, Lauwerys R. Industrial Toxicology and Occupational Medicine Unit, School of Medicine, Catholic University of Louvain, Brussels, Belgium. The oxygen dependence of ethane formation was investigated in rat lung and liver homogenates, incubated in sealed flasks, in which the peroxidation was stimulated by the addition of ferrous ions. For both tissues, the production of ethane was maximal under a 20% oxygenated gas phase, while hyperoxic conditions led to a decreased ethane in the gas phase. The formation of thiobarbituric **acid-reactive substances (TBA-RS), another marker of the lipid peroxidation process, in the homogenates of lung and liver was strongly stimulated at 100% compared to 20% oxygen. Experiments were also carried out on iron-stimulated peroxidation of pure docosahexaenoic acid preparations, which under air led to a large production of ethane.** As for tissue homogenates, the TBA-RS content was increased in the presence of 100% oxygen. Those conditions, however, did not induce an increase in ethane production but led to the formation of ethanol. **Therefore, the quenching of ethyl radical by molecular oxygen seems to be a very attractive hypothesis to explain the lack of increased ethane production in favor of ethanol when iron-induced lipid peroxidation was stimulated by oxygen.**

Am J Respir Crit Care Med 2000 Aug;162(2 Pt 1):369-73. **Exhaled ethane, a marker of lipid peroxidation, is elevated in chronic obstructive pulmonary disease.** Paredi P, Kharitonov SA, Leak D, Ward S, Cramer D, Barnes PJ.

J Surg Res 1987 Aug;43(2):118-27. **Serotonin receptor blockade improves cardiac output and hypoxia in porcine ARDS.** Sielaff TD, Kellum JM, Sugerman HJ, Kuemmerle JF, Tatum JL.

Dev Pharmacol Ther 1984;7(2):133-9. **Synergistic effect of triiodothyronine and dexamethasone on male and female fetal rat lung surfactant synthesis.** Torday JS, Dow KE

Pediatr Res 1994 Jul;36(1 Pt 1):55-9. **Immaturity-dependent free radical activity in premature infants.** Varsila E, Pitkanen O, Hallman M, Andersson S. "During the first 2 postnatal d ethane [24.1 (SEM 7.8) pmol x kg-1 x min-1] and pentane [24.2 (SEM 4.1) pmol x kg-1 x min-1] were stable but increased during d 5 to maxima of 79.1 (15.8) pmol x kg-1 x min-1 and 62.1 (8.1) pmol x kg-1 x min-1, respectively. Maximum ethane and pentane correlated with gestational age (r = -0.42, p = 0.03 and r = -0.52, p = 0.005, respectively) and birth weight (r = -0.38, p = 0.05 and r = -0.59, p = 0.001, respectively). **Infants with high maximum expired ethane and pentane (exceeding 40 pmol x kg-1 x min-1) had higher odds of dying or having bronchopulmonary dysplasia than those with low ethane and pentane (odds ratio, 6.5; 95% confidence interval, 1.1 to 38.5; p < 0.05 for ethane and odds ratio, 5.6; 95% confidence interval, 1.1 to 29.3; p < 0.05 for pentane). We conclude that degree of prematurity is the single most important factor explaining free radical-mediated lipid peroxidation in premature infants.** A therapeutic intervention to limit the effects of free radicals should be started during the 1st postnatal d in premature infants to be effective."

Respir Physiol 2000 Mar;120(1):1-11. **Reduced maximal cardiac output at altitude--mechanisms and significance.** Wagner PD.

Ned Tijdschr Geneeskd 2001 Dec 29;145(52):2521-5. **[Administration of glucocorticosteroids to premature infants: increasing evidence of adverse effects]** van Bel F. **Neonatal glucocorticosteroid therapy is increasingly being used for the prevention of chronic lung disease in very premature infants. In the short term this therapy is usually successful. There is, however, increasing evidence for long-term adverse effects. In particular there seems to be an increased chance of abnormal brain development, which later results in locomotory dysfunction,** developmental delay and cerebral palsy. From experimental studies there are indications that cardiovascular and immunological complications may occur during adult life. Long-term follow-up of neonates treated with glucocorticosteroids seems warranted so that adverse effects that may occur later can be detected and where possible treated. Moreover, the development of alternative treatments should be considered such as the use of less potent glucocorticosteroids.

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