Aging Eyes, Infant Eyes, and Excitable Tissues

From the original article in 2006. Author: Ray Peat.

The eyes and the lungs are sensitive tissues that are easily harmed by inappropriate environmental exposure. They are especially sensitive in infancy and old age.

For 60 years there have been controversies about the cause of retinopathy of prematurity, which has blinded tens of thousands of people.

Degeneration of the retina is the main cause of blindness in old people. Retinal injury is caused by ordinary light, when the eyes are sensitized by melatonin, prolactin, and polyunsaturated fats. Bright light isn't harmful to the retina, even when it is continuous, if the retina isn't sensitized.

Melatonin and prolactin are induced by stress, and darkness is a stress because it impairs mitochondrial energy production.

The polyunsaturated fats which accumulate in the brain and retina damage mitochondria.

Iron, which accumulates prenatally, and then again with aging, reacts with unsaturated fats during stress to destroy cells.

The popular supplements melatonin, tryptophan, fish oils, St. John's wort, and the various omega -3 oils, all increase the risk of retinal light damage and macular degeneration. Serotonin uptake inhibiting antidepressants are suspected to be able to cause it.

Processes similar to those that damage the over-sensitized retina can occur in other cells, as a result of stress. The substances that sensitize the retina to light-damage, can also increase the incidence of new or metastatic cancers.

Iron supplements and the use of supplemental oxygen, especially with a vitamin E deficiency exacerbated by excessive unsaturated fats in the diet, are still commonly used exactly when they can do the most damage.

One of the recognized achievements of biology has been the demonstration of life's universality, in the sense that organisms of all sorts use the same fundamental genetic code, and that yeasts, lizards, apes, and people have remarkably similar cellular systems, as well as a great amount of genetic similarity.

There has been another, less well recognized, sort of convergence going on in physiology and pathophysiology. Hans Selye's concept of stress, "the syndrome of being sick," Otto Warburg's argument that a "respiratory defect" was behind all kinds of cancer, and the idea of free radical damage as a common factor in disease and aging, helped to create a more general way of looking at the nature of disease that superceded medicine's theories of disease pathogens and genetic mutations, which created thousands of "disease entities," none of which had much to do with the individuality of the patient or his environment.

The understanding that plants and animals have much biochemistry in common has gradually changed the assumptions of the science establishment, which until recently insisted that only "ionizing radiation" could affect animals or other organisms that lacked chlorophyll--and insisted that ionizing rays acted only on the DNA. Visible light, the textbooks said, was not "chemically active," and so couldn't possibly affect animals' cells. In animals, coloration was seen mainly as decoration and disguise, rather than as a functional part of their biochemistry.

(Chemically, the meaning of "a pigment" is that it's a chemical which selectively absorbs radiation. **Old observations such as Warburg's, that visible light can restore the activity of the "respiratory pigments," showed without doubt that visible light is biochemically active.** By the 1960s, several studies had been published showing the inhibition of respiratory enzymes by blue light, and their activation by red light. The problem to be explained is why the science culture simply couldn't accept crucial facts of that sort.)

The retina, of course, was allowed (in the views of mainline science) to respond to ordinary light, but the few people who studied the biological effects of seasonal or daily cycles of light have until recently stayed very close to the nerve pathways leading from the retina to the pineal gland, because those pathways could be described in terms of an evolutionarily specialized "third eye." Even with a doctrine of a genetically specialized link between the retina and a little of the animal's physiological chemistry, the great, slow-witted science establishment has done its best to avoid thoughts of any deep interaction between an organism and its environment, by insisting that the organism runs according to a genetically determined "clock" which is located in a few cells in a certain area of the brain, and that nervous impulses from the retina have only the small privilege of "setting the clock."

It didn't matter to the academic and medical worlds that a professor, Frank A. Brown, had long ago disproved the idea of an innate genetic "clock," because philosophy is much stronger than evidence. Leibniz had said that everything in the world runs on its own inner clock, without needing to perceive its surroundings, and this idea that everything in the world is a "windowless monad" resonated through the world of science, because it justified the pompous authoritarian attitudes of the experts who knew that anything that wasn't already in their heads couldn't be considered knowledge. **If an organism's "essence is contained in its genes," then it clearly doesn't interact in any meaningful way with most of its environment.** This is the sort of culture that imbued research on the biology of light cycles.

When I moved from Mexico, first to Montana and then to Oregon in 1966, I became very conscious of how light affects the

hormones and the health. (For example, in Montana I experienced an interesting springtime shedding of body hair.) Many people who came to cloudy Eugene to study, and who often lived in cheap basement apartments, would develop chronic health problems within a few months. Women who had been healthy when they arrived would often develop premenstrual syndrome or arthritis or colitis during their first winter in Eugene.

The absence of bright light would create a progesterone deficiency, and would leave estrogen and prolactin unopposed. Beginning in 1966, I started calling the syndrome "winter sickness," but over the next few years, because of the prominence of the premenstrual syndrome and fertility problems in these seasonally exacerbated disorders, I began calling it the pathology of estrogen dominance. In the endocrinology classes I taught at the National College of Naturopathic Medicine, I emphasized the importance of light, and suggested that medicine could be reorganized around these estrogen-related processes. If the sparrows of Times Square mated in the winter because of the bright lights, it seemed clear that bright artificial light would be helpful in regulating human hormones.

In our lab at the University of Oregon, our hamsters would try to hibernate, even though they were in temperature-controlled laboratories with regular cycles of artificial light. (The ceiling lights provided only dim illumination inside their cage boxes, so they were probably in a chronic state of light deprivation, which probably increased their sensitivity to the weak environmental cues that Frank Brown had investigated, possibly microwaves that easily penetrated the lab walls.) During the winter, when they were infertile, I found that their thymus glands practically disappeared. The mechanism seemed to include the increase of pineal gland activity (probably increasing melatonin synthesis) in the winter, under the intensified activity of the "sympathetic nervous system" (with increased activity of adrenalin and other catecholamines), and the melatonin was apparently a signal for suppressing fertility during the stressful winter. In some animals (Shvareva and Nevretdinova, 1989), estrogen is increased during hibernation, contributing to the reduction of body temperature.

In 1994 A.V. Sirotkin found that melatonin inhibits progesterone production but stimulates estrogen production, and it's widely recognized that melatonin generally inhibits the thyroid hormones, creating an environment in which fertilization, implantation, and development of the embryo are not possible. This combination of high estrogen with low progesterone and low thyroid decreases the resistance of the organism, predisposing it to seizures and excitotoxic damage, and causing the thymus gland to atrophy.

Cyclical exposure to melatonin can have an effect on the reproductive system opposite to that of chronic exposure, and the way exogenous melatonin is delivered to the animal can have unexpected effects on the actual amount of melatonin circulating in the blood (Wright and Alves, 2001). The actual amount of melatonin in the tissues, its relation to the normal cycling of the animal, and the influence of temperature, are often disregarded in melatonin research, making it hard to interpret many of the publications.

There is a lot of talk about melatonin's function as an antioxidant, but, like so many other "antioxidants," melatonin can act as a pro-oxidant at physiologically relevant concentrations; some studies have found that it, like estrogen, increases the activity of the pro-oxidative free radical nitric oxide (which acts like melatonin on pigment cells, causing them to lighten). The promoters of estrogen are also making claims that estrogen is a protective antioxidant, though that isn't true of physiological concentrations of estrogen, which can catalyze intense oxidations. The market culture seems to guide most research in these substances.

Almost any kind of stress increases the formation of melatonin.

In some animals, melatonin has been shown to be responsible for whitening of the hair during the winter. In some species it acts directly on the pigment cells, but in other species it seems to inhibit the action of the melanocyte stimulating hormone.

In snowy climates, it's "ecologically" rational for animals to turn white in the winter, for camouflage. But tadpoles also turn white in the dark, or under the influence of melatonin, and the biological meaning of that isn't so clear. It's possible that being white would reduce their loss of heat through radiation, but I think it is more likely that it relates to an increased ability of weak radiation to penetrate their tissues, rather than being stopped near the surface by the melanin in the skin. The absence of melanin makes them more sensitive to light. Bright light suppresses their melatonin, and makes them turn dark brown or black, and this protects them from bright sunlight.

In the retina, melatonin increases the sensitivity of the cells to dim light. It, along with prolactin, another nocturnal hormone, helps to produce dark adaptation of the eyes.

Melatonin increases the concentration of free fatty acids during the night (John, et al., 1983; John and George, 1976)), so it's interesting that one of the long-chain highly unsaturated fatty acids, DHA (docosahexaenoic acid), also increases the light sensitivity of the retina.

Melatonin lowers body temperature, causes vasoconstriction in the brain, heart, and other organs, and slows reactions. An antagonist to melatonin acts as an antidepressant, reducing "behavioral despair" resulting from stress. (Dubocovich, et al., 1990.) So, in the behavioral sense, melatonin reduces sensitivity, yet it increases the eyes' sensitivity to light, causing them to be injured by light that would otherwise be harmless.

Since a hibernating animal under the influence of melatonin can become very cold, the light-sensitizing function of melatonin is probably related to the biological need to be roused out of the torpor occasionally. (Hibernators apparently have to warm up occasionally to sleep in the ordinary manner.) Melatonin is said to intensify dreaming, which is part of the process of arousal from sleep.

All of the stress-related hormones increase during the night. One of the ways these hormones of darkness act is to increase the sensitivity to light, in a process that is an important adaptation for organisms in dim light. In the night, our ability to see (and respond to) dim light is increased. But dark-adapted eyes are very sensitive to injury by bright light. Light that

ordinarily wouldn't harm the eyes, will do serious damage when the eyes are dark adapted.

In thinking about the effects of stress and oxygen deprivation, I read the studies demonstrating that the formation of the oxygen-wasting age pigment, lipofuscin, is increased by estrogen, by oxygen deprivation (in carp living below the ice, or even in fetuses), by metals such as iron, by x-rays, and by highly unsaturated fats.

Free fatty acids that are mobilized from storage tissues in the night and in the winter also tend to increase with aging, as the ability to tolerate stress decreases. Poor circulation and lipofuscin tend to be associated, in a vicious cycle. This means that the retina becomes easier to injure by light in old age, for some of the same reasons that the infant's retina is susceptible.

The fetus accumulates a very large amount of iron, and it absorbs melatonin from the maternal circulation. Prolactin is sometimes elevated in the newborn. Premature babies are often given extra oxygen, which tends to cause vasoconstriction by displacing carbon dioxide. Melatonin's ability to cause vasoconstriction means that stress makes supplemental oxygen more toxic. Synthetic glucocorticoids are often given to premature babies, adding to the risk of retinal damage.

When the mother has been given iron supplements during pregnancy, along with unsaturated oils in the diet, the baby is likely to be born with a vitamin E deficiency and suppressed thyroid function, increasing the probability that it will be jaundiced, leading to treatment of the jaundice with exposure to very bright light.

Although Yandell Henderson had already, in 1928, explained the need for carbon dioxide to be used with oxygen for resuscitating infants or adults, medical researchers and hospital workers could never accept the idea, probably because of a fundamental misunderstanding of the Henderson-Hasselbalch equation. Animal experiments show that supplemental oxygen, without carbon dioxide, causes vasoconstriction, reducing the tissues' supply of glucose as well as oxygen. In combination with too much light, especially blue light, it damages the retina. At hyperbaric pressure, oxygen causes seizures, as well as damage to the lungs and other tissues.

The contribution of bright light to retinal damage in babies has been denied in several recent publications, and these articles undoubtedly provide useful material for defense lawyers to use when hospitals are sued for causing blindness. One publication based on experiments with kittens concludes that bright light does not harm the newborn's retina, but the comparison is between continuous light and intermittent light, rather than between bright light and dim light. Twelve hours of total darkness, rather than sparing the eye by reducing its exposure to light, would sensitize the eye. The only reason such appalling things can be published is that their conclusions protect the hospitals.

A few good studies of the effect of bright light on the retina, and the fact that dark-skinned people with more protective pigment in their eyes have a lower incidence of retinopathy of prematurity, make it clear that the ordinary laws of physics and chemistry actually do apply to the infant eye.

Light and stress, especially with excess iron, damage the retina when the cells contain too much PUFA, since these fats react with light and free radicals. The nocturnal/stress hormones, especially prolactin and melatonin, make the retina more sensitive to light, and more easily damaged. (It's too much darkness that sets up the problem, since the eyes will adapt to excess light, but darkness increases their sensitivity.)

The use of lasers to operate on eyes produces intense inflammation of the eye, but even at low dose the diffusing light causes retinal/macular damage.

Cytochrome oxidase is one of the enzymes damaged by stress and by blue light, and activated or restored by red light, thyroid, and progesterone. It's a copper enzyme, so it's likely to be damaged by excess iron. It is most active when it is associated with a mitochondrial lipid, cardiolipin, that contains saturated palmitic acid; the substitution of polyunsaturated fats lowers its activity. Mitochonrial function in general is poisoned by the unsaturated fats, especially arachidonic acid and DHA.

Creating a "deficiency" of DHA, even when an oil of known toxicity is used to replace the omega -3 oils, prevents retinal damage from light. Despite evidence of this sort, Mead Johnson is going ahead with the marketing of its baby formula containing added DHA which is industrially extracted from algae. (Although the researchers who claim that DHA is beneficial haven't answered my letters, a representative of the company that manufactures it did answer my question about the actual composition of the oil, and acknowledged that they don't have any idea what the minor ingredients might be.)

When animals are made "deficient" in all the exogenous polyunsaturated fatty acids, linoleic and arachidonic acid as well as linolenic and DHA, they become remarkably resistant to all sorts of stress and toxins.

The polyunsaturated fats make the lungs more sensitive to excess oxygen or hyperventilation, they make the eyes more sensitive to light, and they make the brain more sensitive to fatigue.

The use of synthetic glucocorticoid hormone is standard in treating very premature babies, although it is known to contribute to eye damage. This is because it is considered necessary to improve the lung function of premature babies with respiratory distress. But there is no clear evidence that it is beneficial for lung function in the long run, and very clear evidence that it damages the brain and other organs. There is widespread agreement regarding the use of the glucocorticoids ***prenatally*** to accelerate lung development in women who seem likely to deliver prematurely. Natural cortisol is a factor that promotes lung development prenatally. But cortisol is also a signal produced by a stressed fetus, that triggers the birth process. Cortisol, or the synthetic glucocorticoid, inhibits progesterone production, and stimulates estrogen production, activating uterine contractions and other processes that terminate the pregnancy.

Apparently, it doesn't occur to many people that administering the glucocorticoid triggers premature birth, creating the problem they are intending to treat.

Recognizing causal connections between premature birth and respiratory distress and retinopathy of prematurity, it would be obvious that the greatest effort should be made to prevent the problems by improving the health of pregnant women. Hospitals, however, are invested in high technology systems for treating these problems, and even though their results are dismal, they can't make money by getting pregnant women to eat enough protein to prevent preeclampsia, which is a major cause of premature birth, or by treating the problems with salt, magnesium, progesterone, thyroid, and aspirin when the women haven't had a good diet.

Historically, preeclampsia has been blamed on the mother's or fetus's "bad genes," and that cultural bias was the setting in which these high technology prenatal and neonatal systems developed. High technology "neonatology" derives from the same ideology that motivated Josef Mengele's genetic research in Auschwitz. The idea of genetic determination is still motivating resistance to reasonable preventive approaches.

Thyroid, i.e., T3, is very effective in accelerating lung development in the fetus, and it doesn't have any of the harmful effects of the synthetic glucocorticoids. It normalizes the hormones, increasing progesterone and decreasing estrogen, which are needed for full-term gestation, the opposite of the glucocorticoids' effects. While the cortisol-like drugs damage the brain and other organs, thyroid and progesterone protect them.

Old organisms, like newborns, are easily injured by all sorts of inappropriate excitation. As in premature babies, the aged eyes, lungs, and brain are especially sensitive to damage by stress. *But all organs are subject to the same kinds of damage.* Medical treatments for respiratory distress and macular degeneration in old people are often the same as those used so inappropriately for babies. ***The good health practices that can prevent the inflammatory and degenerative diseases can often make it possible for damaged tissues to recover, even in old age.***

The pituitary hormones, especially prolactin and TSH, are pro-inflammatory, and darkness increases TSH along with prolactin, so to compensate for a light deficiency, the pituitary should be well-suppressed by adequate thyroid. Armour thyroid or Thyrolar or Cynoplus, Cytomel, would probably be helpful. (Eye-drops containing T3 might be a way to restore metabolic activity more quickly.) Limiting water intake (or using salt generously) helps to inhibit prolactin secretion. The saturated fats protect against the body's stored PUFA, and keeping the blood sugar up keeps the stored fats from being mobilized. Aspirin (or indomethacin) is generally protective to the retina, analogously to its protection against sunburn. Adequate vitamin E is extremely important. There are several prescription drugs that protect against serotonin excess, but thyroid and gelatin (or glycine, as in magnesium glycinate) are protective against the serotonin and melatonin toxicities. Copper and magnesium deficiencies predispose to retinal damage. Red light is protective, blue light (or u.v.) is harmful, so wearing orange lenses would be helpful. Progesterone and pregnenolone, by reducing the stress reactions, should be helpful--in the eye diseases of infancy and old age, as they are in the respiratory distress syndromes.

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Curr Eye Res 2001 Jul;23(1):11-9. **Rod outer segments mediate mitochondrial DNA damage and apoptosis in human retinal pigment epithelium.** Jin GF, Hurst JS, Godley BF.

Endocrinol Exp 1976 Jun;10(2):131-7. **Diurnal variation in the effect of melatonin on plasma and muscle free fatty acid levels in the pigeon.** John TM, George JC. Pigeons maintained on standard diet and held under 12 h daily photo-period in a controlled environmental room, were given intravenous injections of melatonin. A low dose (1.25 mg/kg body weight) of melatonin when given in the middle of the **scotophase, produced a significant increase in plasma FFA when estimated at 20 min and 90 min post-injection, whereas no significant change was seen with injections given in the middle of the photophase. No significant change in muscle FFA level was obtained either during the photophase or the scotophase** when estimated at 90 min postinjection. With a higher dose (5 mg/kg body weight) of melatonin given in the scotophase, on the other hand, a significant increase **in both plasma as well as muscle FFA levels was obtained at 90 min** post-injection but there was no effect on plasma FFA at 20 min or 90 min post-injection in the photophase and at 20 min in the scotophase. It is concluded that melatonin has a lipid mobilizing action in the pigeon when administered during the scotophase.

Arch Int Physiol Biochim 1983 Jul;91(2):115-20. **Diurnal impact of locomotory activity and melatonin and N-acetylserotonin treatment on blood metabolite levels in the rainbow trout.** John TM, Beamish FW, George JC. In rainbow trout forced to swim continuously at sustained speeds for six weeks, selected doses of melatonin or N-acetylserotonin (1.25 and 5.0 mg/kg body weight) injections caused no change in haematocrit. Melatonin did not produce any significant change in plasma glucose level either in the photophase or in the scotophase. However, diurnal variations were observed in the effect of melatonin on plasma free fatty acids (FFA). Melatonin was ineffective in causing **any change in plasma FFA level during photophase but during scotophase, the higher dose (5.0 mg/kg) produced an increase in FFA while the lower dose (1.25 mg/kg) had no effect, N-acetylserotonin administration produced diurnal** variation in its effect on both plasma glucose and FFA. The higher dose of N-acetylserotonin brought about a drop in plasma glucose level during photophase, but both doses were ineffective during scotophase. N-acetylserotonin produced no change in FFA during photophase, but during scotophase tended to lower FFA level. It is suggested that exercise shortens the time required to cause a hypoglycemic effect of N-acetylserotonin during photophase, blocks FFA release-inhibiting action of melatonin observed in photophase, and minimizes the time required for the FFA mobilizing action of melatonin in scotophase.

J Neural Transm 1977;40(2):87-97. **The adrenal medulla may mediate the increase in pineal melatonin synthesis induced by stress, but not that caused by exposure to darkness.** Lynch HJ, Ho M, Wurtman RJ.

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

Br J Pharmacol 1977 Dec;61(4):607-14. **The action of melatonin on single amphibian pigment cells in tissue culture.** Messenger EA, Warner AE.

Oftalmol Zh 1989;(8):469-73. **[The early diagnosis, evaluation of treatment results and modelling of certain aspects of the pathogenesis of retinal dystrophy]** ; Mironova EM, Pavlova ON, Ronkina TI. The paper analyses results after a study of the functional state of pigmented epithelium and the retina in patients with a dry form of senile macular dystrophy as well as of experimental simulation of retinal dystrophy with the help of melatonin and its treatment by taurine. **Melatonin in 10(-3) M concentration leads to development of dystrophic changes** in pigmented epithelium and interacting with it structures, this being testified by remarkable lowering of EOG parameters and electron microscopic findings. Taurine in 10(-3) **M concentration blocks the action of exogenic melatonin as well as has a pronounced positive action on metabolism of dystrophic changes in the pigmented epithelium and photoreceptors. Examination of patients with different stages of a dry form of senile** macular dystrophy revealed statistically significant reduction of KA cEOG at the initial stage of the disease in the presence of normal ERG parameters. In 18% of patients, supernormal values of KA were recorded, that are likely to reflect the presence of "predystrophic hyperactivity" of the pigmented epithelium cells. In progression of the process, the further reduction of electrophysiologic values was recorded. The data obtained speaks about the important role of pigmented epithelium pathology in the pathogenesis of senile macular dystrophy and about high information value of the cEOG method for detection of early stages of the disease. It is believed that disturbances in melatonin metabolism can be one of causes leading to development of retinal dystrophy.

J Clin Endocrinol Metab 1977 Oct;45(4):768-74. **The effects of oral melatonin on skin color and on the release of pituitary hormones.** Nordlund JJ, Lerner AB. “We studied the effects of prolonged ingestion of melatonin, 1 g per day, on skin color and the serum levels of pituitary hormones in 5 human subjects with hyperpigmented skin. Melatonin lightened hyperpigmented skin of one patient with untreated adrenogenital syndrome, but had no effect on three patients' skin with idiopathic hyperpigmentation and one patient with treated Addison's disease.”

Invest Ophthalmol 1976 Oct;15(10):869-72. **Hormonal influences on photoreceptor damage: the pituitary gland and ovaries.**

Olafson RP, O'Steen WK. To determine whether the absence of pituitary or ovarian hormones would influence retinal degeneration, female albino rats were either hypophysectomized (HYPEX) or ovariectomized (OVEX) before pubery. Later, they were exposed to continuous light for periods up to 45 days. Retinas evaluated by light microscopic measurements showed damage to the outer nuclear layer (ONL) and photoreceptor layer in both the operated and intact, control rats. However, the degree of damage observed in retinas of HYPEX and OVEX rats was significantly less than that observed in retinas of intact rats exposed to the same lighting conditions. Therefore, hypophysectomy and ovariectomy, which influence the normal development of sexual maturation when performed on immature rats, significantly reduce photoreceptor damage in adult rats exposed to continuous light.

Invest Ophthalmol Vis Sci 1996 Oct;37(11):2243-57. **Retinal light damage in rats with altered levels of rod outer segment docosahexaenoate. Organisciak DT, Darrow RM, Jiang YL, Blanks JC.** PURPOSE: To compare retinal light damage in rats with either normal or reduced levels of rod outer segment (ROS) docosahexaenoic acid. METHODS: Weanling male albino rats were maintained in a weak cyclic light environment and fed either a nonpurified control diet or a purified diet deficient in the linolenic acid precursor of docosahexaenoic acid (DHA). Half the rats on the deficient diet were given linseed oil, containing more than 50 mol% linolenic acid, once a week to maintain ROS DHA at near normal levels. Diets and linseed oil supplementation were continued for 7 to 12 weeks. To replenish DHA in their ROS, some 10-week-old rats on the deficient diet were given linseed oil three times a week for up to 3 additional weeks. Groups of animals were killed at various times for ROS fatty acid determinations or were exposed to intense green light using intermittent or hyperthermic light treatments. The extent of retinal light damage was determined biochemically by rhodopsin or photoreceptor cell DNA measurements 2 weeks after exposure and morphologically by light and electron microscopy at various times after light treatment. RESULTS: **Rats maintained for 7 to 12 weeks on the linolenic acid-deficient diet had significantly lower levels of DHA** and significantly higher levels of n-6 docosapentaenoic acid (22:5n-6) in their ROS than deficient-diet animals supplemented once a week with linseed oil or those fed the nonpurified control diet. As determined by rhodopsin levels and photoreceptor cell DNA measurements, deficient diet rats **exhibited protection against retinal damage from either intermittent or hyperthermic light exposure. However, the unsaturated fatty acid content of ROS** from all three dietary groups was the same and greater than 60 mol%. In 10 week-old deficient-diet rats given linseed oil three times a week, ROS DHA was unchanged for the first 10 days, whereas 22:5n-6 levels declined by 50%. After 3 weeks of treatment with linseed oil, ROS DHA and 22:5n-6 were nearly the same as in rats supplemented with linseed oil from weaning. The time course of susceptibility to retinal light damage, however, was different. Hyperthermic light damage in rats given linseed oil for only 2 days was the same as for rats always fed the deficient diet. Six days after the start of linseed oil treatment, retinal light damage was the same as in rats given the linseed oil supplement from weaning. Morphologic alterations in ROS of linseed oil-supplemented rats immediately after intermittent light exposure were more extensive than in either the deficient-diet animals or those fed the control diet. The deficient-diet rats also exhibited better preservation of photoreceptor cell nuclei and structure 2 weeks after exposure. CONCLUSIONS: Rats fed a diet deficient in the linolenic acid precursor of DHA are protected against experimental retinal light damage. The relationship between retinal light damage and ROS lipids does not depend on the total unsaturated fatty acid content of ROS; the damage appears to be related to the relative levels of DHA and 22:5n-6.

Exp Neurol 1970 May;27(2):194-205. **Retinal and optic nerve serotonin and retinal degeneration as influenced by photoperiod.** O'Steen WK.

Invest Ophthalmol Vis Sci 1982 Jan;22(1):1-7. **Antagonistic effects of adrenalectomy and ether/surgical stress on light-induced photoreceptor damage.** O'Steen WK, Donnelly JE. Light-induced damage to retinal photoreceptors in influenced by the endocrine status of the animal during the period of exposure. Experimental manipulation of the pituitary gland and of prolactin levels has been shown to affect retinal damage in rats exposed to visible light. When rats are experimentally stressed, prolactin secretion from the pituitary gland occurs as does secretion of adrenocorticotropic hormone (ACTH), which stimulates the release of adrenal cortical hormones. Since prolactin appears to influence retinal damage and since stressed animals have increased serum levels of prolactin, a comparison of photoreceptor damage in animals in which the adrenal glands were removed or which had been experimentally stressed was undertaken in this study. Adrenalectomized rats had thicker outer nuclear layer (ONL) measurements than those found in sham-operated animals. Stressed rats had severely damaged retinas with cystic degeneration and significantly reduced ONL thickness measurements as compared to retinas of unstressed and adrenalectomized rats. **Therefore hormones of the pituitary-adrenal system appear to be involved in the damage to the retina by light, and this response may be related to an interaction or synergism between the adrenal gland, stress, and prolactin secretion.**

Brain Res 1990 Nov 26;534(1-2):99-105. **Water deprivation protects photoreceptors against light damage.** O'Steen WK, Bare DJ, Tytell M, Morris M, Gower DJ. "Photoreceptor cell death after light-damage and during aging in rats is associated with the hormonal status of the animal, as well as other environmental and intrinsic factors. Restricted caloric intake extends the life of rodents and is usually accompanied by a reduction in water consumption. In this study, male and female rats were placed on restricted water intake for either 3 or 7 days to induce dehydration." "Photoreceptor cells of 7-day, dehydrated male and female rats survived light-damage significantly better than those allowed water ad libitum; however, after 3 days of water restriction, only the male rats demonstrated protection from photodamage." "AVP increased by 350% during the 7-day period of dehydration. Protection of photoreceptors from light-damage in this study may be correlated with osmotically stimulated changes in the retinas of dehydrated animals."

Brain Res 1985 Oct 7;344(2):231-9. **Neuronal damage in the rat retina after chronic stress.** O'Steen WK, Brodish A. Long-term exposure to escapable foot shock has been used to determine if chronic stress influences neuronal cell death in the retina of albino and pigmented rats. Histopathologic and morphometric approaches analyzed changes in photoreceptors and neurons of the bipolar and ganglion cell layers of the retina. Albino Fischer rats when exposed to chronic stress for 4-8 h daily for 1 week to 6 months, developed severe retinal damage, as compared to unstressed control retinas, with reduction in photoreceptor and bipolar neurons, particularly in the superior central retina. The damage was observed in male and female rats, but males appeared to be more susceptible to the influence of stress than female animals. Ganglion cells were unaffected. Photoreceptor destruction did not occur in Long-Evans pigmented rats under identical experimental conditions. The results suggest that: **input of the sensory stimulus, light, to the retina of stressed rats augmented neuronal damage and might be required for its initiation;** and hormones and/or neurotransmitters associated with long-term chronic stress might be related to increased neuronal cell death in the mammalian retina.

Invest Ophthalmol Vis Sci 1977 Oct;16(10):940-6. **Effects of hypophysectomy, pituitary gland homogenates and transplants, and prolactin on photoreceptor destruction.** O'Steen WK, Kraeer SL. "Prepubertal removal of the pituitary gland, which in young animals influences sexual maturation, reduces significantly the amount of retinal photoreceptor destruction when the rats are exposed to continuous illumination in adulthood. When crude pituitary gland homogenate is administered to adult rats hypophysectomized prior to puberty, photoreceptor destruction is more severe. Transplantation of whole pituitary glands to the kidney capsule of hypophysectomized rats also reduces the effect of pituitary gland removal and results in more extensive damage to receptor cells than found in hypophysectomized, adult animals. **Hypophysectomized rats treated with prolactin had more severe retinal damage than untreated, hypophysectomized rats."** "Results of these studies indicate the hormones of the pituitary gland have a regulatory influence on the severity of light-induced, retinal photoreceptor damage in the rat."

Life Sci 1985 Nov 4;37(18):1743-6. **Stress-induced synthesis of melatonin: possible involvement of the endogenous monoamine oxidase inhibitor (tribulin).** Oxenkrug GF, McIntyre IM.

Mech Ageing Dev 2000 Jan 10;112(3):169-83. **Double bond content of phospholipids and lipid peroxidation negatively correlate**

with maximum longevity in the heart of mammals. Pamplona R, Portero-Otin M, Ruiz C, Gredilla R, Herrero A, Barja G.

Prostaglandins Leukot Essent Fatty Acids 2001 Feb;64(2):75-80. **Comparative studies on lipid peroxidation of microsomes and mitochondria obtained from different rat tissues: effect of retinyl palmitate.** Piergiacomi VA, Palacios A, Catala A.

Curr Eye Res 1992 Oct;11(10):939-53. **Oxygen-induced retinopathy in the rat: hemorrhages and dysplasias may lead to retinal detachment.** Penn JS, Tolman BL, Lowery LA, Koutz CA.

Vision Res 1995 May;35(9):1247-64. **Studies on the role of the retinal dopamine/melatonin system in experimental refractive errors in chickens.** Schaeffel F, Bartmann M, Hagel G, Zrenner E.

Exp Clin Endocrinol Diabetes 1997;105(2): 109-12. **Melatonin and serotonin regulate the release of insulin-like growth factor-I, oxytocin and progesterone by cultured human granulosa cells.** Schaeffer HJ, Sirotkin AV.

Zh Evol Biokhim Fiziol 1989 Jan-Feb;25(1):52-9. **[Seasonal characteristics of the functioning of the hypophysis-gonad system in the suslik** Citellus parryi] Shvareva NV, Nevretdinova ZG. "In females, FSH was found in the blood in October, being absent from November to **January; beginning from February, it may be found both in sleeping and active** animals." **"Estradiol secretion was noted in hibernating females, whereas progesterone was found in the blood only in May."**

J Pineal Res 1985;2(1):39-49. **Melatonin and N-acetylserotonin stress responses: effects of type of stimulation and housing conditions.** Seggie J, Campbell L, Brown GM, Grota LJ.

Acta Ophthalmol Scand 2001 Aug;79(4):428-30. **Presumed sertraline maculopathy.** Sener EC, Kiratli H.

Paediatr Perinat Epidemiol 1999 Apr;13(2):128-30. **Effects of premature exposure to light: a credibility struggle.** Silverman WA.

J Pineal Res 1994 Oct;17(3):112-7. **Direct influence of melatonin on steroid, nonapeptide hormones, and cyclic nucleotide secretion by granulosa cells isolated from porcine ovaries.** Sirotkin AV. **"It was found that melatonin is able to inhibit progesterone and stimulate estradiol secretion."** "The present observations suggest a direct effect of melatonin on the steroid, nonapeptide hormone, and cyclic nucleotide release from porcine ovarian cells."

J Pineal Res 1994 Oct;17(3):112-7. **Direct influence of melatonin on steroid, nonapeptide hormones, and cyclic nucleotide secretion by granulosa cells isolated from porcine ovaries.** Sirotkin AV.

Prog Clin Biol Res 1989;312:229-49. **Inhibitors of the arachidonic acid cascade in the management of ocular inflammation.** Srinivasan BD, Kulkarni PS.

J Nutr 2000 Dec;130(12):3028-33. **Polyunsaturated (n-3) fatty acids susceptible to peroxidation are increased in plasma and tissue lipids of rats fed docosahexaenoic acid-containing oils.** Song JH, Fujimoto K, Miyazawa T. **"Thus, high incorporation of (n-3) fatty acids (mainly DHA) into plasma and tissue lipids due to DHA-containing oil ingestion may undesirably affect tissues by enhancing** susceptibility of membranes to lipid peroxidation and by disrupting the antioxidant system."

Acta Ophthalmol (Copenh) 1992 Feb;70(1):115-22. **Effects of steady electric fields on human retinal pigment epithelial cell orientation and migration in culture.** Sulik GL, Soong HK, Chang PC, Parkinson WC, Elner SG, Elner VM

Ned Tijdschr Geneeskd 2001 Dec 29;145(52):2521-5. **[Administration of glucocorticosteroids to premature infants: increasing evidence of adverse effects]** [Article in Dutch] 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."**

Brain Res 1984 Feb 27;294(1):166-8. **Pineal methoxyindoles depress calcium uptake by rat brain synaptosomes.** Vacas MI, Keller Sarmiento MI, Cardinali DP.

Ann N Y Acad Sci 1994 Nov 17;738:408-18. **Serotonin binding proteins: an in vitro model system for monoamine-related neurotoxicity.** Vauquelin G, Del Rio MJ, Pardo CV.

J Hypertens Suppl 1985 Dec;3 Suppl 3:S107-9. **Seasonal variation in the development of stress-induced systolic hypertension in the rat.** Weinstock M, Blotnick S, Segal M. "Seasonal variation in blood pressure in human hypertensives prompted us to investigate whether such a phenomenon also occurs in rats made hypertensive by environmental stress." **"Systolic pressure increased by 14-25 mmHg after 6-8 weeks of stress from October to January. Artificial environmental light for 15 h prevented development of hypertension by stress,** which could also be reversed by acute administration of propranolol." "Hypertensive rats had significantly greater relative heart and adrenal weights. This phenomenon can be explained by amplification of **sympathetic pressor activity by stress hormones, adrenaline, corticosterone and prolactin, under the influence of melatonin."**

Invest Ophthalmol Vis Sci 1992 May;33(6):1894-902. **Melatonin increases photoreceptor susceptibility to light-induced damage.** Wiechmann AF, O'Steen WK. **"Pinealectomy has been shown to protect photoreceptors from light-induced damage, and melatonin treatment has been reported to increase the degree of photoreceptor damage in albino rats."** "The animals that received daily melatonin injections (100 micrograms) in the late afternoon (3 hr before lights off) for 1-3 days before photodamage showed an approximate 30% greater reduction compared with sham control animals in ONL thickness in the superior quadrant, the area most susceptible to light damage. Melatonin injections given after the photodamage did not affect ONL thickness. Although retinal susceptibility to light damage varied with time of day, the degree to which melatonin increased the degree of damage appeared unaffected by the time of day. These results suggest that melatonin may be involved in some aspects of photoreceptor sensitivity to light damage."

J Neurochem 1986 Oct;47(4):1181-9. **Effects of arachidonic acid on glutamate and gamma-aminobutyric acid uptake in primary cultures of rat cerebral cortical astrocytes and neurons.** Yu AC, Chan PH, Fishman RA.