The transparency of life: Cataracts as a model of age-related disease

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

Cataracts can disappear when the eye's metabolic condition is corrected. A supply of energy is essential to maintain the transparent structure.

Lactic acid increases as carbon dioxide decreases, during a typical energy deficiency. Deficient thyroid, and the resulting excess of cortisol relative to pregnenolone and progesterone, define the energy deficiency.

Increased lactate relative to CO2 in the cell alters cell pH and electrical charge, causing swelling. Swelling and increased water content characterize the cataract.

High altitude is inversely related to cataracts, despite the known role of sunlight in causing cataracts; this is a strong confirmation of the protective role of carbon dioxide.

In the markets around Lake Patzcuaro, they sell green transparent fish, about 6 inches long. When cooked, the meat is white, like ordinary fish. Most fish filets are a little translucent, but are at least cloudy, and usually pink by transmitted light. I don't know how the transparent fish work, because it seems that the blood and the network of blood vessels needed to sustain muscle activity would diffuse the light. Anyway, cooking disrupts the mysteriously ordered state of water and proteins that makes them transparent, roughly the way egg-white loses its transparency when it is cooked. I have never heard a convincing explanation for the opacity of cooked egg-white, either, but anything that disrupts the original structuring of the protein-water interaction will destroy the transparency.

Around 1970, I used a technique called nuclear magnetic resonance (NMR), which is the basis for the procedure known as MRI (magnetic resonance imaging), to compare the state of water in old (uterine) tissue and young tissue. Old tissue predictably contains less water than young tissue, but I found that the water in the old tissue was in a relatively free and uncontrolled state. When tissue swells and takes up water, more of the water is likely to be in this uncontrolled state, and this is one of the things that makes MRI so useful, because tumors, for example, show up vividly because of their large amount of uncontrolled ("unbound") water. I suspect that the measurements I made on uterine tissue showed a localized effect, that opposed the general trend toward increased dryness with aging. In the case of cataracts, this is clearly the case**:** Most of the lens becomes drier with age, but at a certain point there is a reversal, and some of the tissue takes up too much water. That's why I refer to cataracts as a model of age-related disease, rather than as a model of aging. In this sense, I am including them among the inflammatory diseases of aging--colitis, arthritis, and cancer, for example. MRI now can show developing cataracts before they are visible, because of increased water content in the area.

The lens of the eye is a fairly dense, tough, transparent living structure, which can develop opaque areas, cataracts, as a result of old age, poisoning, radiation, disease, or trauma. The varieties of cataract relate to the causes. Most of the oxidative metabolism of the lens is in or near the epithelial layer that surrounds it. Old-age cataracts most often begin in this region.

Although the efficient oxidative energy metabolism occurs near the surface of the lens, **there is a constant flow of fluid through the lens,** entering it mainly in the front and back, and leaving on its "sides" or equator (considering the front and back as the poles, the direction light passes through). Oxygen and nutrients are supplied to the lens by way of this circulation of fluid, entering mostly from the aqueous humor in front (which also supplies the cornea), but also from the vitreous humor behind the lens.

When the flow of nutrients and energy is impaired, the organized state of the protein and water system in the cell is damaged, and an excess of water is taken up by the cells, as the protein content decreases. The loss of organization causes light to be dispersed, with a loss of transparency.

The lens of the eye is usually treated as something so specialized that it is hardly considered to be part of our living substance, just as dentistry has tended to treat teeth as inert things to be approached mechanically, rather than physiologically. **The lens's circulatory system is very interesting, because of what it says about the nature of living substance. In the absence of blood vessels, it provides its own flow of nutrients.** This flow is reminiscent of the flow of substances through the dentine channels of the teeth, through the axons of nerves (two-way transport in a very narrow channel), and, in some ways recalls the flow of fluids in plants, called "guttation" (drop formation), which is disturbing to botanists, because it is contrary to the textbook descriptions of proper physiology.

The flow of material through lens cells, dentine canals, and nerve axons should allow us to gain a perspective in which these observable processes become a model for other biological situations in which "transport" occurs**:** Kidney, intestine, or the skin of frogs, for example, in which water, ions, and other solutes are moved in considerable quantities.

When cells metabolize, they create gradients. In the cell, electrical, chemical, osmotic, and thermal gradients, for example, are constantly being produced or maintained. The whole substance of the cell is involved in its life processes. Because of prejudices introduced 200 years ago, the life of the cell has been relegated to its "membrane" (where hypothetical "membrane pumps" reside) and its nucleus. **When the term "cell" (hollow space) came into use instead of "corpuscle' (little body), a mind-set came into existence that discounted the importance of most of the living material,** and claimed that it was a mere "random solution." Random solutions don't do much. The wonderful "membrane," under the direction of the nucleus (and its set of instructions), took care of everything.

Whenever assimilation or excretion took place, it was explained by inventing a property possessed by the cell "membranes."

Therefore, we have physiology textbooks that have an unfounded explanation for everything. Before Copernicus, planetary movements were described as arbitrary "epicycles." They didn't make sense, but people studied them and felt that they were important. "Membrane physiology" is the modern equivalent of the Ptolemaic epicycles.

We know that glucose can be metabolized into pyruvic acid, which, in the presence of oxygen, can be metabolized into carbon dioxide. Without oxygen, pyruvic acid can be converted into lactic acid. The production of lactic acid tends to increase the pH inside the cell, and its excretion can lower the pH outside the cell.

The decrease of carbon dioxide that generally accompanies increased lactic acid, corresponds to increased intracellular pH. Carbon dioxide binds to many types of protein, for example by forming carbamino groups, changing the protein conformation, as well as its electrical properties, such as its isoelectric point. With increased pH, cell proteins become more strongly ionized, tending to separate, allowing water to enter the spaces, in the same way a gel swells in an alkaline solution.

The Bohr-Haldane effect describes the fact that hemoglobin releases oxygen in the presence of carbon dioxide, and releases carbon dioxide in the presence of oxygen. When oxygen is too abundant, it makes breathing more difficult, and one of its effects is to cause carbon dioxide to be lost rapidly. At high altitude, more carbon dioxide is retained, and this makes cellular respiration more efficient.

The importance of carbon dioxide to cell control process, and to the structure of the cell and the structure of proteins in general suggested that degenerative diseases would be less common at high altitude. Wounds and broken bones heal faster at high altitude, but the available statistics are especially impressive in two of the major degenerative conditions, cancer and cataracts.

The two biggest studies of altitude and cataracts (involving 12,217 patients in one study, and 30,565 lifelong residents in a national survey in Nepal) showed a negative correlation between altitude and the incidence of cataract. At high altitude, cataracts appeared at a later age. **In Nepal, an increase of a few thousand feet in elevation decreased the incidence of cataracts by 2.7 times. At the same time, it was found that exposure to sunlight increased the incidence of cataracts, and since the intensity of ultraviolet radiation is increased with altitude, this makes the decreased incidence of cataracts even more important.**

All of the typical causes of cataracts, aging, poisons, and radiation, decrease the formation of carbon dioxide, and tend to increase the formation of lactic acid. **Lactic acid excess is typically found in eyes with cataracts.**

The electrical charge on the structural proteins will tend to increase in the presence of lactic acid or the deficiency of carbon dioxide, and the increase of charge will tend to increase the absorption of water.

The lens can survive for a considerable length of time *in vitro* (since it has its own circulatory system), so it has been possible to demonstrate that changes in the composition of the fluid can cause opacities to form, or to disappear.

Oxidants, including hydrogen peroxide which occurs naturally in the aqueous humor, can cause opacities to form quickly, but they will also disappear quickly in a solution that restores metabolic energy. The lens regulates itself powerfully**;** for example, it will swell when put into a hypotonic solution, but will quickly adapt, returning to approximately its normal size.

Several years ago, I saw what appeared to be oxidant-induced cataracts. Two women had a very sudden onset of cataracts, and I asked about their diet and supplements**;** it turned out that one of them had begun taking 500 mg of zinc daily a few months earlier, and the other had begun taking 600 mg of zinc and 250 mg of iron, on her doctor's recommendation, just a couple of months before the cataracts appeared.

For some reason, there have been many nutritional supplements sold as cataract remedies in the form of eye drops. I suppose a trace of the material could diffuse through the cornea into the aqueous humor, where it might make a difference in the lens's nutrient supply, but it seems more reasonable to treat the body as a whole, nourishing every part in a balanced way.

Besides living at a high elevation or breathing extra carbon dioxide, the most certain way to increase the amount of carbon dioxide in the eye, and to prevent an excess of lactic acid, is to make sure that your thyroid function is adequate.

One man who took thyroid, USP, and vitamin E told me that his cataracts had regressed, but I haven't known other people who tried this.

If a person already has distinct cataracts, it might be worthwhile to experiment with a relatively high degree of hypercapnia, for example, breathing a 5% mixture of CO_2 in air.

Carbon dioxide, at higher levels than are normal at sea level, has a profound effect on free radicals, reducing the free radical activity in the blood to approximately zero, before reaching the level that produces acidosis.

There are several situations in which carbon dioxide affects the hydration, water content, of biological materials, that I think give an insight into its effects on the lens. Hydrophilic glycoproteins are involved in each case. These are proteins with attached chains of sugar molecules that make them associate with a large amount of water. In the cornea, increased carbon dioxide strongly protects against swelling. The bulk of the cornea is a connective tissue that is relatively simple and passive compared to the compact cellular structure of the lens, and it is conventional to describe the thin layers of cells on the inside and outside of the cornea as being responsible for the water content of the underlying substance. However, even when the epithelial cells are removed, it has been demonstrated that carbon dioxide is able to prevent corneal swelling. (M.V. Riley, et al., "The roles of bicarbonate and CO_2 in transendothelial fluid movement and control of corneal thickness," *Invest. Ophthalmol. Vis. Sci. 36(1),* 103-112, 1995.)

Bronchial mucous secretions are an even simpler system, so it is very interesting that carbon dioxide is recognized as the most powerful regulator of their behavior. (This has important implications for “cystic fibrosis,” or mucoviscidosis.) Goodman and Gilman (page 1068, *Pharmacological Basis of Therapeutics,* 2nd Edition, Macmillan Co., 1956), say

"Among inhalants, steam and carbon dioxide have been found to be excellent expectorants. Relative humidity above 85 per cent liquefies sputum, decreases its viscosity...." "Carbon dioxide is the most effective agent of all. It not only lowers the viscosity of tenacious sputum, thereby facilitating expectoration, but it decreases the volume of sputum by promoting its active resorption by bronchial mucosa." "A five to ten per cent concentration of carbon dioxide is adequate and well tolerated if administered at intervals." "Oxygen has been shown to be an antiexpectorant and has effects opposite to those of carbon"

Oxygen tends to displace carbon dioxide from tissue, and is a source of free radicals.

One of the best-known free radical scavenging substances that has been widely used as a drug is iodide. It has been used to treat asthma, parasites, syphilis, cancer, Graves’ disease, periodontal disease, and arteriosclerosis. Diseases that produce tissue overgrowth associated with inflammation--granulomas--have been treated with iodides, and although the iodide doesn’t necessarily kill the germ, it does help to break down and remove the granuloma. Leprosy and syphilis were among the diseases involving granulomas* that were treated in this way. In the case of tuberculosis, it has been suggested that iodides combine with unsaturated fatty acids which inhibit proteolytic enzymes, and thus allow for the removal of the abnormal tissue.

In experimental animals, iodide clearly delays the appearance of cataracts. (Buchberger, et al., 199l.)

Inflammation, edema, and free radical production are closely linked, and are produced by most things that interfere with energy production.

Endotoxin, produced by bacteria, mainly in the intestine, disrupts energy production, and promotes maladaptive inflammation. The wide spectrum of benefit that iodide has, especially in diseases with an inflammatory component, suggests first that it protects tissue by blocking free radical damage, but it also suggests the possibility that it might specifically protect against endotoxin.

There are subtler differences in transparence that probably have a variety of causes, but differences in water content or hydration might be involved in the lower transparency that has been seen in women's lenses. Estrogen, which tends to produce edema and hypotonic body fluids, also increases prolactin production. Prolactin is involved in water and electrolyte regulation, and it has been found to **accelerate the development of experimental cataracts.** (M. C. Ng, et al, 1987.) These hormones are associated with the calcification of soft tissues, and cataracts contain very high levels of calcium. (Avarachan and Rawal, 1987; Hightower and Reddy, 1982.)

Estrogen is strongly associated with free radical processes, calcium mobilization, and acetylcholine release, all of which are involved in the process of excitoxicity. Alvarez, et al., (1996) have shown a possible involvement of acetylcholine in calcium mobilization in the lens.

Serotonin is another regulatory substance strongly associated with prolactin and estrogen, and it also can be involved in disrupting the metabolism of the lens. This is one of the potential dangers in using supplemental tryptophan. (Candia, et al., 1980.)

Old age commonly involves some changes in the color of tissues--loss of pigment from hair and skin, with appearance of new pigment (age pigment, lipofuscin), which may appear as “liver spots.” But there is also a tendency of the toenails, fingernails, teeth, and lenses to turn yellow or brown. Some of this dark material seems to be age pigment, derived from unsaturated fatty acids, but other components have been identified, for example, tryptophan from damaged proteins. The Maillard reaction (similar to the browning that occurs in bread crust) has often been mentioned in relation to aging, and involves the combination of protein amino groups with sugars. But the browning of the lens tends to be associated with the general age related drying of the lens, it isn’t irregularly distributed, and it doesn’t significantly harm vision.

When I first heard about the age-related browning of the lens, I thought that the experience of colors would be affected, so I devised a test in which the relative darkness of blue and yellow could be judged in comparison with a graded strip of shades of grey.

After people of ages ranging from 10 to 80 had given exactly the same matches, I realized that the nervous system probably corrects for the “yellow filter” effect of the brown lens.

The browning of tissues will be the subject of another newsletter.

Among the interesting causes of cataracts**:** Tamoxifen and hypotonic fluids, sodium deficiency**;** toxicity of tryptophan**;** oxidants (metals, hydrogen peroxide, PUFA); diabetes, photosensitizers and sunlight**;** excess calcium, deficient magnesium. Excess cortisol. Radiation. Arachidonic and linoleic acids in other situations have been found to block cells' regulation of their water content. Hypothyroidism tends to increase the activity of serotonin, estrogen, prolactin, calcium, and the tendency of tissues to retain water, and to decrease the level of ATP.

Among the factors that probably have a role in preventing cataracts**:** Thyroid, progesterone, pregnenolone, vitamin E, iodide, pyruvate. Increasing the carbon dioxide lowers the cell’s pH, and tends to resist swelling. Palmitic acid (a saturated fat that can be synthesized by our tissues) is normally oxidized by the lens. Calcium blockers experimentally prevent cataracts, suggesting that magnesium and thyroid (which also act to exclude calcium from cells) would have the same effect.

Thyroid hormone is essential for maintaining adequate carbon dioxide production, for minimizing lactic acid, cortisol and

prolactin, for regulating calcium and magnesium, for avoiding hypotonicity of the body fluids, and for improving the ratio of palmitic acid to linoleic acid.

References

"Inhibition of ionic transport and ATPase activities by serotonin analogues in the isolated toad lens," Candia OA; Lanzetta PA; Alvarez LJ; Gaines W, Biochim Biophys Acta (602)2, 389-400, 1980. "Tryptamine, 5-methyltryptamine and 5-methoxytryptamine had dual effects: 1 mM in the posterior bathing solution depressed the potential difference of the posterior face of the lens, which resulted in an increase in the translenticular potential difference and short-circuit current; 1 mM in the anterior solution (in contact with the lens epithelium) produced a quick and pronounced reduction of the potential difference of the anterior face. This resulted in a 90-100% decline of the translenticular short-circuit current. Serotonin and tryptamine were then tested for their effect on the ATPases of lens epithelium. Both amines inhibited the enzymes with tryptamine at 5 mM completely inhibiting all ATPase activity. **Since tryptophan is transported from the aqueous humor into the lens and may be converted by lens enzymes to serotonin and tryptamine, these findings may have physiological implications in cataractogenesis."**

"Effects of Ca2+ on rabbit translens short-circuit current: evidence for a Ca2+ inhibitable K+ conductance,"Alvarez LJ; Candia OA; Zamudio AC, Curr Eye Res, 1996 Dec, 15:12, 1198-207. PURPOSE: To characterize the effects of medium Ca2+ levels on rabbit lens electrical properties. Overall, these results suggest that **lens Ca2(+)-mobilizing agents (e.g. acetylcholine)** could trigger the inhibition of epithelial K+ conductance(s) by the direct action of Ca2+ on K+ channels."

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"D600 increases the resistance associated with the equatorial potassium current of the lens," Walsh SP; Patterson JW, Exp Eye Res, 1992 Jul, 55:1, 81-5 "This effect is similar to that produced by quinine and by a calcium-free medium, and is attributed to the prevention of an increase in the calcium-dependent conductance produced by pCMPS."

"Effects of hydrogen peroxide oxidation and calcium channel blockers on the equatorial potassium current of the frog lens," Walsh SP; Patterson JW, Exp Eye Res, 1994 Mar, 58:3, 257-65. "Hydrogen peroxide, in concentrations of 10-1000 microM, produces two major changes in the current-voltage relationships associated with the equatorial potassium current of the lens. First, the resting and reversal potentials become more negative than they were prior to treatment with hydrogen peroxide and second, the membrane resistance related to the equatorial current is decreased. The shift in the resting and reversal potentials is in the opposite direction from that produced by ouabain. Based on the Nernst equation, the shift in the reversal potential suggests that there is an **increase in the concentration of potassium in the lens. The 86Rb uptake and efflux are increased. These observations suggest that hydrogen peroxide stimulates the Na,K-pump. The decrease in membrane resistance is inhibited by 100 microM of quinine, a calcium-dependent potassium channel blocker, and does not decrease in a calcium-free medium. This suggests that the decrease in resistance may be secondary to an increase in lenticular calcium.** These effects of hydrogen peroxide are similar to those of p-chloromercuriphenylsulfonate (pCMPS), a nearly impermeant sulfhydryl binding agent, **and suggest that permeant hydrogen peroxide may increase calcium influx by acting on sulfhydryl groups on the outer surface of lens membranes. Verapamil, a calcium channel blocker, is reported to prevent cataract formation.**"

"Effect of prolactin on galactose cataractogenesis," Ng MC; Tsui JY; Merola LO; Unakar NJ phthalmic Res 19:2, 82-94, 1987. "Prolactin has been known to affect the water and electrolyte balance. Because increased lens hydration has been shown to be a common phenomenon in most, if not all types of cataracts, we have been interested in investigating a possible role of prolactin in sugar cataract induction and progression. For this study, we have used morphological and biochemical approaches. The prolactin delivery method involved intraperitoneal implantation of one or more pellets in Sprague-Dawley female rats. Following implantation of the desired number of prolactin or control (nonprolactin) pellets, animals were either fed galactose and lab chow, or lab chow diet. Gross morphological observations of whole lenses, slit-lamp examination of lenses and light microscopic analysis of lens sections showed that in the galactose-fed prolactin group, galactose associated alteration progressed faster and total opacification (mature cataract development) was achieved earlier than in the nonprolactin group. The levels of galactose and dulcitol were higher in the lenses of galactose-fed prolactin treated rats as compared to lenses from nonprolactin (control) rats. No significant difference in lens Na+-K+ ATPase activity between the prolactin and nonprolactin group was observed. Our results indicate that prolactin accelerates galactose-induced cataractogenesis in rats."

"A hypothetical mechanism for toxic cataract due to oxidative damage to the lens epithelial membrane," Bender CJ Med Hypotheses, 1994 Nov, 43:5, 307-11 Lenticular opacities can be induced by numerous external agents that **coincide with those that catalyze oxidative damage to lipids.** One of the consequences of lipid peroxidation is that the affected membrane is rendered more permeable to protons. A proton leak in the tight epithelium of lens **would uncouple the Na+/K(+)-ATPases that regulate the water** and ionic content of the bounded tissue. Once regulatory control of the osmotic pressure is lost, **the phase state of the** cell's soluble proteins would change, **leading to refractive changes or, in extreme cases, precipitation**. The same does not occur in cornea because the stroma is an extracellular polymer blend rather than solution of soluble polymers. Polymeric phase transitions in the cornea require that divalent cations pass the epithelial membrane, which can occur only through the action of ionophores.

Tsubota K; Laing RA; Kenyon KR Invest Ophthalmol Vis Sci, 1987 May, 28:5, 785-9, **Abnormalities in glucose metabolism are thought to be among the main causes of cataract formation.** The authors have made noninvasive biochemical measurements of the lens that provide information concerning glucose metabolism in the lens epithelium. The autofluorescence of reduced pyridine nucleotides (PN) and oxidized flavoproteins (Fp) within the rabbit lens were noninvasively measured as a function of depth using redox fluorometry. The peak of the autofluorescence at 440 nm (excited at 360 nm) and 540 nm **(excited at 460 nm) were determined at the lens epithelium. When 8 mM sodium pentobarbital, a known inhibitor of mitochondrial respiration, was applied to the lens, the autofluorescence peak at 440 nm increased and that at 540 nm decreased. The 440 nm autofluorescence is thought to be from** reduced pyridine nucleotides, whereas the 540 nm autofluorescence is from the oxidized flavoprotein. Blocking lens respiration with pentobarbital caused an increase in the PN/Fp ratio by a factor of 3 within 3.5 hr after pentobarbital application."

[Use of pyrimidine bases and ATP for conservative treatment of early cataracts] Larionov LN Oftalmol Zh, 1977, 32:3, 221-2

"Concentrations of some ribonucleotides, L-lactate, and pyruvate in human senile cataractous lenses with special reference to anterior capsular/subcapsular opacity," Laursen AB Acta Ophthalmol (Copenh), 1976 Dec, 54:6, 677-92 The concentrations of some ribonucleoside tri- and diphosphates, adenosine-5'-monophosphate, L-lactate and pyruvate were determined in human senile cataractous lenses removed during cataract operations. Pyruvate concentrations were found to be negligible (median = 56 mumol/kg lens wet weight) in 15 human senile cataractous lenses. On the basis of correlations between the biomicroscopic appearances of the senile cataractous lenses (N = 80) and the concentrations and ratios of the metabolites in question, the following classification was found to be justified: 1. Immature cataractous lenses

without anterior capsular/subcapsular opacity: high levels of ribonucleoside triphosphates (RTP), high sums of RTP, ribonucleoside diphosphates (RDP), and adenosine 5'-monophosphate (AMP) as well as **high levels of L-lactate and high ratios of L-lactate in the lens/L-lactate in the aqueous**. 2. Immature cataractous lenses with anterior capsular/subcapsular opacity; intermediate levels of RTP, intermediate values for the sums of RTP, RDP, and AMP, **high L-lactate levels, and intermediate values of the ratios of L-lactate in the lens/L-lactate in the aqueous.**"

Sulochana KN; Ramakrishnan S; Vasanthi SB; Madhavan HN; Arunagiri K; Punitham R, "First report of congenital or infantile cataract in deranged proteoglycan metabolism with released xylose," Br J Ophthalmol, 1997 Apr, 81:4, 319-23."'Of 220 children of both sexes below 12 years of age, with congenital or infantile cataract treated in Sankara Nethralaya, Madras, India, during a period of 2 years, 145 excreted fragments of GAG (heparan and chondroitin sulphates) in their urine. There was no such excretion among the control group of 50 children. **The same was found accumulated in the blood and lenses of affected children.** In addition, xylose was present in small amounts in the urine and blood and xylitol was present in the lens. There was a significant elevation in the **activity of beta glucuronidase in lymphocytes and urine,** when compared with normals. All the above findings suggest deranged proteoglycan metabolism. As the urine contained mostly GAG fragments and very little xylose, Benedict's reagent was not reduced. This ruled out galactosaemia.CONCLUSION: An increase of **beta glucuronidase activity might have caused extensive fragmentation of GAG** with resultant accumulation in the blood and lens and excretion in urine. Small amounts of xylose may have come from xylose links between GAG and core protein of proteoglycans. Owing to their polyanionic nature, GAG fragments in the lens might abstract sodium, and with it water, thereby increasing the hydration of the lens. Excessive hydration and the osmotic effect of xylitol from xylose might cause cataract. While corneal clouding has been reported in inborn acid mucopolysaccharidosis, congenital or infantile cataract with deranged metabolism of proteoglycans (acid mucopolysaccharide-xylose-protein complex) is reported in children for the first time."

"State of electrolytes, osmotic balance and the activity of ATPase in the lenses of selenite--induced cataracts," Avarachan PJ; Rawal UM Indian J Ophthalmol, 1987, 35:5-6, 210-3. "Selenite-cataracts incorporated many morphological characteristics observed in human senile catracts. Progressive elevation of sodium, marked loss of potassium, **several fold increment of calcium; considerable loss of magnesium levels,** a dose-response reduction of total-ATPase activity **and significant hydration are the important features** observed in the lens during the progressive treatment of selenite. The sodium-potassium imbalance is found to be a secondary effect during the development of cataract and is suggested to bring about by **an abnormal accumulation of calcium ions** and inactivation of transport enzyme. The calcium activated proteases could be the promoting factor for the proteolysis and insolubilization of lens proteins in the inducement of selenite cataract. The impact of selenite on the SH containing ATPase anzymes could be the cause of impairment in energy metabolism, derangement of electrolytes and osmotic imbalance which, in turn, accelerate the cortical involvement of lens opacities."

"Glucose metabolism by human cataracts in culture," Wolfe JK; Chylack LT Jr Exp Eye Res 43:2, 243-9, 1986. "Metabolism in human senile cataracts has been studied using uniformly labeled [14C]glucose. Intracapsularly extracted lenses were cultured in TC-199 media with a glucose concentration of 5.5 mM. Results show that lactate production accounts for 97% of the glucose metabolized. Under these standard incubation conditions there is negligible accumulation of alpha-glycerol phosphate, glucose-6-phosphate, and sorbitol. The rate of lactate production was found to be relatively uniform over a range of cataract severities which were determined from the CCRG classification. The effects of several perturbants in the medium were measured. **An ATP concentration of 3 mM was found to inhibit lactate production."**

M. V. Riley, et al., "The roles of bicarbonate and CO_2 in transendothelial fluid movement and control of corneal thickness," Invest. Ophthalmol. Vis. Sci. 36(1), 103-112, 1995. **"The equilibrium thickness of deepithelialized corneas swollen with HCO_3^-/CO_2 on both surfaces was 35 microns less than that of corneas swollen in HPO_4^-." "Normal corneal thickness can be maintained in vitro only in media that contain HCO_3^- at concentrations of more than 20 mM."**

"The effect of X-irradiation on the sodium-potassium-activated adenosine triphosphatase (Na-K-ATPase) activity in the epithelium of the rat lens. A histochemical and biochemical study," Palva M Acta Ophthalmol (Copenh), 1978 Jun, 56:3, 431-8. "The epithelial Na-K-ATPase activity of the rat lens was studied after X-irradiation at intervals of three to ninety days. The enzyme was demonstrated histochemically by light microscopy and it was measured biochemically by a fluorometric method. Neither histochemical nor biochemical changes of Na-K-ATPase content of the lens epithelium were observed during the development of cataract. In whole-mount preparations the enzyme activity was localized in the cell membranes. However, one month after radiation a few peripheral cells had in addition a precipitated over the whole cell. **The unaltered Na-K-ATPase content in the epithelium** suggests that the hydration of the lens after X-irradiation is primarily caused by **changes in the passive permeability properties of the cell membranes and not by a decreased capacity of the activity cation pump."**

McNamara NA; Polse KA; Bonanno JA **"Stromal acidosis modulates corneal swelling."** Invest Ophthalmol Vis Sci, 1994 Mar, 35:3, 846-50 "PURPOSE. Studies have shown that stromal acidosis reduces the rate of corneal thickness recovery after induced edema, providing the first human in vivo evidence that corneal pH can influence corneal hydration control. This finding raises the question of the possible effect that pH may have on induced corneal swelling. To explore this question, the corneal swelling response to hypoxia was measured while stromal pH was controlled. METHODS. Corneal edema and stromal acidosis was induced in ten subjects by passing a mixture of nitrogen and carbon dioxide gas across the eyes through tight-fitting goggles. **One eye of each subject received 100% N_2, whereas the contralateral eye received a mixture of 95% N_2 and 5% CO_2. Exposures of 95% N_2 + 5% CO_2 lower pH on average to 7.16 versus 7.34 for 100% N_2 alone.** Before and after 2.5 hours of gas exposure, central corneal thickness (CCT) was measured. RESULTS. **Eyes exposed to the lower pH environment (eg, N_2 + CO_2) developed less change in CCT** compared to the eyes receiving N_2 alone. Overall increase in CCT was 29.9 +/- 5.3 microns for eyes exposed to the 95% N_2 + 5% CO_2 gas mixture, versus 37.1 +/- 4.8 microns for 100% N_2 **eyes ($P < 0.0001$). CONCLUSIONS. The corneal swelling response to hypoxia can be reduced by lowering stromal pH. Because changes in corneal pH alone have not been found to alter steady-state CCT, it is proposed that pH** exerts its effect only under non-steady-state conditions (ie, corneal swelling and deswelling). This suggests that acidosis may produce changes in the **rate of lactate metabolism** or alter endothelial hydraulic conductivity."

Buchberger W; Winkler R; Moser M; Rieger G, "Influence of iodide on cataractogenesis in Emory mice," Ophthalmic Res, 1991, 23:6, 303-8. Cataract development was studied in two groups of Emory mice by periodical biomicroscopic examinations (beginning at 5 weeks of age) and by a final evaluation of water-soluble SH groups in the lenses. The experimental group was given 256 micrograms iodide/kg body weight with the drinking water throughout the study. The untreated control group received tap water. **Iodide treatment induced a delay of cataract formation...."** "A still significant difference in the degree of cataract was also found between the two groups at week 47 of age. No difference was found in the content of water-soluble SH groups. The results are discussed in relation **to the known antioxidant and .OH-scavenging effect of iodide and to the oxidative changes in the lens occurring during progression of cataract development.**"

"[The chemical nature of the fluorescing products accumulating in the lipids of the crystalline lenses of mice with hereditary cataract]," Shvedova AA; Platonov ES; Polianskii NB; Babizhaev MA; Kagan VE Biull Eksp Biol Med, 1987 Mar, 103:3, 301-4. **"The content of diene conjugates (lipid hydroperoxides) was shown to be significantly higher in lipids extracted from the lenses of mice with hereditary cataract than in the controls. The same holds true for characteristics of fluorescence of the end-product of lipid peroxidation."** "It was established that high-molecular weight fluorescent fractions corresponded to lipid components of **lipofuscin-like pigments.** NMR and mass spectrometry of low-molecular weight fractions suggested that they contained predominantly products of free

radical oxidation of **long chain polyunsaturated fatty acids (C22:6). "**

"Formation of N'-formylkynurenine in proteins from lens and other sources by exposure to sunlight," Pirie A Biochem J, 1971 Nov, 125:1, 203-8.

"Lipid fluorophores of the human crystalline lens with cataract." Babizhayev MA Graefes Arch Clin Exp Ophthalmol, 1989, 227:4, 384-91 "It has been established that the development of cataract is accompanied by the formation of various fluorophores in the lipid fraction of the lens. These lipid-fluorescing products have been separated chromatographically according to polarity and molecular weight. It is shown that the initial stages of the development of cataract are characterized by the appearance of lipid fluorophores in the near ultraviolet and violet regions of the spectrum **(excitation maximum 302-330 nm, emission maximum 411 nm) with low** polarity and a small molecular weight; the maturing of the cataract is **characterized by an increase in the intensity of the long-wave fluorescence of the lipids in the blue-green region (430-480 nm) and by the formation of** polymeric high-molecular-weight fluorescing lipid products with high polarity. It has been demonstrated that the appearance of lipid fluorophores in the **crystalline lens is associated with the free radical oxidative modification of the phospholipids and fatty acids in cataract."**

"Incidence of cataracts in the mobile eye hospitals of Nepal," Brandt F; Malla OK; Pradhan YM; Prasad LN; Rai NC; Pokharel RP; Lakhe S, Graefes Arch Clin Exp Ophthalmol, 1982, 218:1, 25-7 The incidence of cataract in Nepal was determined from data collected in 14 mobile eye hospitals (called 'eye camps'). Of a total of **12,217** patients examined in the out-patient department (OPD), cataract surgery was performed on 2,163. The percentage of cataract patients in the OPD was **less in the mountains (13.8%) than in the Tarai plains (19.8%).** In the inhabitants of the mountains, the majority of whom belong to the Tibeto-Birman race, **cataracts appeared at a significantly later age in both males and females compared to the people of the plains, who are mostly Indo-Aryan.** Cataracts were discovered in both groups at a younger age in women than in men."

"Associations among cataract prevalence, sunlight hours, and altitude in the Himalayas." Brilliant LB; Grasset NC; Pokhrel RP; Kolstad A; Lepkowski JM; Brilliant GE; Hawks WN; Pararajasegaram R., Am J Epidemiol 118:2, 250-64 1983. "The relationship between cataract prevalence, altitude, and sunlight hours was investigated in a **large national probability sample survey of 105 sites** in the Himalayan kingdom of Nepal, December 1980 through April 1981. Cataract of senile or unknown etiology was diagnosed by ophthalmologists in 873 of **30,565 full-time life-long residents** of survey sites. Simultaneously, the altitude of sites was measured using a standard mountain altimeter. Seasonally adjusted average daily duration of sunlight exposure for each site was calculated by a method which took into account latitude and obstructions along the skyline. Age- and sex-standardized **cataract prevalence was 2.7 times higher in sites at an altitude of 185 meters or less than in sites over 1000 meters. Cataract prevalence was negatively correlated with altitude** (r = -0.533, p less than 0.0001). However, a positive correlation between cataract prevalence and sunlight was observed (r = 0.563, p less than 0.0001). Sites with an average of 12 hours of sunlight exposure had 3.8 times as much cataract as sites with an average of only seven hours of exposure. Sunlight was blocked from reaching certain high altitude sites by tall neighboring mountains. "

"The untenability of the sunlight hypothesis of cataractogenesis," Harding JJ Doc Ophthalmol 88:3-4, 345-9, 1994-95. "The excess prevalence of cataract in **third world countries led early this century to the hypothesis that sunlight causes cataract. The hypothesis, which ignored differences in diet, culture, poverty and prevalence of other diseases** such as diarrhoea, received little support until about thirty years ago when biochemical studies were set up to explore the browning of lens proteins, which is a common feature of cataract on the Indian subcontinent. Initially these studies were encouraging in that exposure to sunlight caused some changes seen in cataractous lenses, but eventually the hypothesis was rejected because the first change in the laboratory was the destruction of tryptophan, **but this was not found in brown cataract lenses.** A brown nuclear cataract could not be produced artificially in the laboratory using sunlight or UV exposure. Exposure of laboratory animals has produced lens opacities, but in most experiments the doses required have also caused keratitis, conjunctivitis, iritis and inflammation. The cornea seems more sensitive than the lens, which is not surprising, as it gets the first chance to absorb damaging UV. The biochemical rejection of the hypothesis coincided with the re-start of the epidemiological studies. Most of these are simply latitude studies and are no more than a repeat of what was available sixty years ago. They do not help to find a cause. **Two studies showed that cataract was less common at higher altitude in the Himalayas, but unfortunately led to opposing conclusions**. On the basis of common knowledge that UV exposure was greater at higher altitude, the first altitude study led to the rejection of the sunlight hypothesis."

"Anticataract action of vitamin E: its estimation using an in vitro steroid cataract model," Ohta Y; Okada H; Majima Y; Ishiguro I Ophthalmic Res, 1996, 28 Suppl 2:, 16-25 "The aim of this study was to estimate the anticataract action of vitamin E using an in vitro methylprednisolone (MP)-induced cataract model. The same severity of early cortical cataract was induced in lenses isolated from male Wistar rats aged 6 weeks by incubation with MP (1.5 mg/ml) in TC-199 medium. The cataractous lenses showed slight increases in lipid peroxide (LPO) content and Na+/K+ ratio and slight decreases in reduced glutathione (GSH) content and glyceraldehyde-3-phosphate dehydrogenase (GAP-DH), a sensitive index of oxidative stress, and Na+,K(+)-ATPase activities. When the cataractous lenses were further incubated in TC-199 medium with and without vitamin E (250 micrograms/ml) for 48 h, the progression of cataract was prevented in the vitamin E-treated lenses, but not in the vitamin E-untreated lenses. The vitamin E-untreated lenses showed a decrease in vitamin E content and an increase in water content in addition to further increases in LPO content and Na+/K+ ratio and further decreases in GSH content and GAP-DH and Na+,K(+)-ATPase activities. In contrast, the changes of these components and enzymes except for GSH were attenuated in the vitamin E-treated lenses. From these results, it can be estimated that vitamin E prevents in vitro cataractogenesis in rat lenses treated with MP by protecting the lenses against oxidative damage and loss of membrane function. "

"Prevention of oxidative damage to rat lens by pyruvate in vitro: possible attenuation in vivo," Varma SD; Ramachandran S; Devamanoharan PS; Morris SM; Ali AH,.Curr Eye Res, 1995 Aug, 14:8, 643-9 "Studies have been conducted to assess the possible preventive effect of pyruvate against lens protein oxidation and consequent denaturation and insolubilization. Rat lens organ culture system was used for these studies. The content of water insoluble proteins (urea soluble) increased if the lenses were cultured in medium containing hydrogen peroxide. Incorporation of pyruvate in the medium prevented such insolubilization. The insolubilization was associated primarily with loss of gamma crystallin fraction of the soluble proteins. PAGE analysis demonstrated that insolubilization is related to -S-S- bond formation which was preventable by pyruvate. Since pyruvate is a normal tissue metabolite the findings are considered pathophysiologically significant against cataract formation. This was apparent by the **prevention of selenite cataract in vivo by intraperitoneal administration of pyruvate.**"

"Glucocorticoid-induced cataract in chick embryo monitored by Raman spectroscopy," Mizuno A; Nishigori H; Iwatsuru M Invest Ophthalmol Vis Sci, 30:1, 132-7, 1989. "Glucocorticoid-induced cataract lens in chick embryo was monitored by laser Raman spectroscopy. The lens opacity that appeared in chick embryo is a reversible one. Raman spectra show no significant change in the relative content of water or secondary structure of the proteins upon lens opacification. The intensity ratios of tyrosine doublet bands in Raman spectra between clear and opaque lens portions are changes. **This change is reversible,** and **is interpreted as a protein-water phase separation that occurred during lens opacification**."

"[NMR study of the state of water in the human lens during cataract development]" Babizhaev MA; Deev AI; Nikolaev GM, Biofizika 30:4, 671-4,1985. "Water proton spin-spin relaxation times (T2) and the content of bound, "non-freezable" at -9 degrees C water in both normal human lenses and human lenses of different stages of cataract progression (cataracta incipiens, nondum matura, mature hypermatura) were measured

by NMR spin echoes method. By the stage of cataracta nondum matura, increase of bound water content and simultaneous, almost half decrease of the relaxation time (T2), were observed. However, on the following stages of cataract evaluation (almost mature, mature cataracts) **a gradual decrease of bound water content is noted,** but only for the mature cataract stage the water content significantly differs from that of the normal one. On the stage of hypermature cataract the presence of two unexchanged with each other fractions of water is found. The obtained data are **explained by lens protein reconstructions during the cataract progression.**"

Hightower KR; Reddy VN "Ca++-induced cataract." Invest Ophthalmol Vis Sci, 1982 Feb, 22:2, 263-7 "Cataracts in cultured rabbit lenses were produced by elevation of internal calcium. Experimental procedures were successful in increasing levels of total and bound Ca++, often without significant changes in sodium, potassium, or water content. Although the excess in calcium was predominantly associated with water-soluble proteins and was freely diffusible, a significant amount was bound to membranes and cytosol water-insoluble proteins. Thus, in lenses with a 10-fold increase in total Ca++, the bound Ca++ increased twofold, nearly 35% of which remained fixed to water-insoluble and membrane proteins after exhaustive (72 hr) dialysis. In contrast, over 95% of the Ca++ in water-soluble protein fractions was removed by dialysis."

[Use of pyrimidine bases and ATP for conservative treatment of early cataracts] Larionov LN Oftalmol Zh, 1977, 32:3, 221-2.

"Noninvasive measurements of pyridine nucleotide and flavoprotein in the lens," Tsubota K; Laing RA; Kenyon KR Invest Ophthalmol Vis Sci 28:5, 785-9, 1987. "**Abnormalities in glucose metabolism are thought to be among the main causes of cataract formation.** The authors have made noninvasive biochemical measurements of the lens that provide information concerning glucose metabolism in the lens epithelium. The autofluorescence of reduced pyridine nucleotides (PN) and oxidized flavoproteins (Fp) within the rabbit lens were noninvasively measured as a function of depth using redox fluorometry. The peak of the autofluorescence at 440 nm (excited at 360 nm) and 540 nm **(excited at 460 nm) were determined at the lens epithelium. When 8 mM sodium pentobarbital, a known inhibitor of mitochondrial respiration, was applied to the lens, the autofluorescence peak at 440 nm increased and that at 540 nm decreased. The 440 nm autofluorescence is thought to be from** reduced pyridine nucleotides, whereas the 540 nm autofluorescence is from the oxidized flavoprotein. Blocking lens respiration with pentobarbital caused an increase in the PN/Fp ratio by a factor of 3 within 3.5 hr after pentobarbital application."

"Concentrations of some ribonucleotides, L-lactate, and pyruvate in human senile cataractous lenses with special reference to anterior capsular/subcapsular opacity," Laursen AB Acta Ophthalmol (Copenh) 54:6, 677-92,1976. "The concentrations of some ribonucleoside tri- and diphosphates, adenosine-5'-monophosphate, L-lactate and pyruvate were determined in human senile cataractous lenses removed during cataract operations. Pyruvate concentrations were found to be negligible (median = 56 mumol/kg lens wet weight) in 15 human senile cataractous lenses. On the basis of correlations between the biomicroscopic appearances of the senile cataractous lenses (N = 80) and the concentrations and ratios of the metabolites in question, the following classification was found to be justified: 1. Immature cataractous lenses without anterior capsular/subcapsular opacity: high levels of ribonucleoside triphosphates (RTP), high sums of RTP, ribonucleoside diphosphates (RDP), and adenosine 5'-monophosphate (AMP) as well as **high levels of L-lactate and high ratios of L-lactate in the lens/L-lactate in the aqueous**. 2. Immature cataractous lenses with anterior capsular/subcapsular opacity; intermediate levels of RTP, intermediate values for the sums of RTP, RDP, and AMP, **high L-lactate levels, and intermediate values of the ratios of L-lactate in the lens/L-lactate in the aqueous."**

"Lipid fluorophores of the human crystalline lens with cataract," Babizhayev MA Graefes Arch Clin Exp Ophthalmol, 1989, 227:4, 384-91. [Initial stages of cataracts are characterized by the fluorescence of the products of fatty acid free radical oxidation.]
