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Medical Treatment of Cataract

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In formulating an approach to the medical treatment of cataract it is as well to consider what kind of task we are setting ourselves. Do we expect to prevent cataracts, retard their progression or even cause them to reverse? Prevention of radiation cataract would be highly desirable were the expectation of cataract production high. On the other hand we will not expect to prevent senile cataract but rather to halt progression of early cataract once detected. If we have a concept as to why adult diabetics are more at risk of cataract than non-diabetics, and we believe that we can apply a specific remedy, we will not aim to treat all diabetics, but only those with incipient cataract.

The identification of risk factors may suggest ways of reducing risk by reducing exposure, lowering blood sugar in diabetics, for example, or screening out harmful UV in regions of high sunlight (if you believe UV to be a risk factor) but there are other risk factors which cannot be handled in this way; few would advocate an attempt to raise blood cholesterol to reduce the risk of cataract.

Another approach lies in experimental studies which pin-point specific mechanisms and permit specific anticataract therapies to be devised. It is fruitful then, to consider factors which render the lens transparent and the influences which can lead to opacity.

Lens Anatomy and Physiology

The lens epithelium lies deep to the capsule anteriorly. Mitosis occurs pre-equatorially in the germinative zone and gives rise to the meridional rows of cells; these differentiate into new fibres which are added to the lens cortex. The human lens grows almost linearly in thickness throughout life. Epithelial respiration is chiefly aerobic, and is responsible for about 30 per cent of the energy supply of the lens. The superficial cortex whose fibres are nucleated, produces the remaining energy requirements by glycolysis; a lens incubated anaerobically and supplied with glucose, remains transparent. The nucleus of the lens shows minimal metabolic activity.

Lens transparency results from the optical homogeneity of its parts. Lens fibres resemble one another and are closely packed with a minimum of extracellular space. The high concentration of the crystallins (33 per cent of lens wet weight) within the fibres will minimise scatter from the membrane/cytoplasm interface. It has been calculated that the short-order interactions of the crystallins confer the optical properties of glass.

The ion-water balance of the lens is maintained by an outward sodium pump residing in the epithelium and superficial cortical fibres and its efficiency is maintained by a selective permeability of the epithelial and fibre membranes. Fibres and epithelial cells are connected electrically by gap junctions.

Lens growth is achieved by differentiation of meridional epithelial cells into spindle-shaped fibres which elongate to enter into the complex anterior and posterior sutural systems. This is accompanied by the synthesis of new structural, cytoskeletal and enzyme proteins, including beta and gamma crystallins (alpha already being present in epithelial cells), actin, vimentin, tubulin, and gap junctional protein. Once established, these fibres pass through a cycle of events in which their nuclei and organelles are lost (terminal differentiation) and certain proteins, having

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performed their function, are removed. Thus certain cytoskeletal proteins persist for a limited number of generations, while other proteins such as the crystallins and probably certain membrane proteins persist throughout the life of the lens. These latter, long-lived proteins are susceptible to various chemical influences acting over long periods of time.

Growth of the human lens is accompanied by a central compaction of fibres so that in the adult, fibres are added at approximately double the rate suggested by its increase in total thickness. It can be calculated that the first clear zone (C1α) of the lens (about 125 μm in width) is equivalent to about 3 years of growth. This zone is of interest in relation to certain forms of cataract. It is of almost constant width in the adult which implies that while new fibres are added to it superficially, deeper fibres take on features of the subjacent zone of dysjunction, C1β and thence of the second clear zone (C2). If new fibres failed to be added to the lens, lens growth would stop and (C1) would be obliterated over a period of about 3 years. This would be detectable photographically, as would the reverse process. The clear zone (C1α) is narrowed in posterior subcapsular cataract and widened in diabetes.

It is apparent that there must be many hundreds of interdependent elements responsible for the maintenance of lens transparency. Interference with some, such as ion-pumps or membrane permeability, respiration, or the tertiary structure of the crystallins has been shown experimentally to cause cataract and has suggested ways in which preventing damage of this kind could be of therapeutic use in human cataract.

The lens is already equipped with a protective machinery against certain kinds of damage. A number of scavenger molecules are present which protect against oxidative stress. Lens membranes contain vitamin E which protects against lipid peroxidation. Glutathione (GSH), a potent free radical scavenger, is synthesised in the lens from amino-acid precursors (1-glutamic acid, 1-cysteine, and 1-glycine). It is probably important in maintaining lens protein thiols in the reduced state, such as that of Na+ K+ ATPase or the lens crystallin thiols. It will maintain ascorbate in the reduced state and scavenges peroxides and radiation induced radicals. Vitamin C, already in high concentration in the aqueous is transported into the lens and achieves high concentration here also. It is a powerful reducing agent which can cooperate with GSH in scavenging carbon-centred radicals. It will scavenge superoxide. Other compounds have been cited as performing a similar role in the lens (carotenoids, choline, taurine thioredoxin-T). (Bron and Brown, 1987).

Experimental Cataract

Ion Pumps: Inhibition of NA+ K+ ATPase by ouabain results in lens swelling and cataract. Hydrogen peroxide also causes cataract, probably by oxidation of the active site thiol group of NA+ K+ ATPase, accessible at the surface of the cell membrane. Ultraviolet exposure also inhibits pump activity.

In the inherited Nakano mouse cataract the onset of opacity at 3 weeks of life has been attributed to the action of a genetically determined inhibitor of Na+ K+ ATPase. Glucocorticoids inhibit the pump *in vitro* as well as increasing permeability of the lens to cations.

Lens Permeability: A number of agents have been shown to induce lens swelling by increasing cell permeability. These include anticholinesterases (phospholine iodide) cationic antibiotics such as polymixin, and glucocorticoids. Biological detergents (such as lysolecithin) released into the vitreous during inflammation or by destruction of the inner retina have also been proposed as a cause of increased permeability.

Reduced calcium levels are a potent cause of cataract due to increased permeability and increased permeability may be induced by a binding of membrane thiols.

Inhibition of cation pumps or increased membrane permeability lead to swelling of the lens. This can also be brought about by an osmotic mechanism exemplified by sugar cataract.

Osmotic Damage: In experimental cataract produced by dietary feeding of galactose,

galactose diffuses in high concentration into the lens and in the presence of the enzyme aldose reductase is converted into its sugar alcohol, dulcitol to which the lens cells are poorly permeable. The osmotic load created causes cataract. This mechanism is responsible for cataract in galactosaemia and galactokinase deficiency and for juvenile diabetic cataract.

Research initiated by Kinoshita at the NIH, has led to the development of a series of compounds which will inhibit aldose reductase, prevent sugar cataract in the galactose fed rat and other models. One of these, Sorbinil will inhibit cataract formation in galactose fed rats when given by the topical or systemic route. These compounds are also active against sugar alcohol accumulation in the retina and nerve. Of over 30 compounds under study, there are at least 5 compounds undergoing clinical trials in the prevention of complications in diabetic patients.

Respiratory Inhibition: Inhibition of glycolysis with the compound 2. deoxyglucose, causes cataract. This agent competes with glucose for the enzyme hexokinase, preventing entry of glucose into the glycolytic pathway. This is probably a model for infantile hypoglycaemic cataract.

Aerobic respiration is inhibited by the compound 2.4 dinitrophenol which uncouples oxidative phosphorylation and prevents the generation of ATP by this route. This was withdrawn as a slimming agent when it was introduced in the 1930s because of the occurrence of cataracts.

Lipid Synthesis: Interference with the synthesis of cholesterol by the cholesterol-lowering drug triparanol (MER 29) led to the accumulation of desmosterol in the tissues with the occurrence of cataract and other side effects.

In the inherited disorder of cerebrotendinous xanthomatosis, in which cataract is accompanied by gross cerebral signs, cholesterol synthesis is blocked at the level of cholestanol.

Post-Translational Modification of Proteins

Long-lived proteins such as the crystallins which show little turnover and repair in the core of the lens, are subject to chemical modification from a number of influences. Such changes alter their surface charge, causing them to unfold and expose reactive groups such as thiols. Such unfolding increases with age, in the lens nucleus more than the cortex. Unfolded crystallins are vulnerable to oxidative damage leading to the formation of disulphide-linked high molecular weight aggregates. This process is thought to account in part for the increased scattering of light by a sclerotic nucleus.

Phosphorylation, amino acid racemisation, and methionine oxidation have been proposed as factors leading to unfolding, in addition to the formation of adducts with glucose and other sugars, or cyanate, a derivative of urea (glycosylation and carbamylation).

Cyanate and glucose form stable adducts with the free (epsilon) amino group of crystallin lysine; the end product following glycosylation is a brown compound containing crystallins covalently crosslinked by a derivative of the reaction, furoyl furanyl imidzole.[2] There is evidence that this accounts in part for nuclear brunescence.

Other compounds which will react non-enzymatically with crystallins in the same way include certain glucocorticoids, and ascorbate.

Oxidative Stress

Oxidative stress and free radical production have been increasingly demonstrated as cataractogenic mechanisms at the experimental level.

Cataract may be produced *in vitro* with H_2O_2 and the sensitivity of the lens to this damage is related to the levels of GSH available and ability of the lens to regenerate GSH. Oxidation of GSH by TBHP (tertiary butyl hydroperoxide) increases fibre and epithelial permeability. In various experiments, UV exposure will cause cataract. UV exposure generates reactive oxygen species and other reactive molecules in the lens (e.g. H_2O_2 and malonaldehyde), and lowers GSH and protein thiol levels.

In the Philly mouse, cataract is associated with the failure to express a 23 kD beta crystallin.

Therapeutic Approaches

Experimental

Some of the experimental approaches to the prevention of cataract are summarised in Table I. Ultraviolet radiation damage to lens Na+ K+ ATPase and membrane transport systems has been inhibited by predosing with vitamin C, which will also retard UV-induced crystallin aggregation *in vitro*. Thiol compounds have also been effective in preventing membrane damage by a sulphydryl reagent (PCMBS), and inhibiting 2.4 Dinitrophenol (DNP) cataract, and sugar cataract. Sulphur containing compounds have been effective in delaying cataract produced by ionising radiation in a number of studies, presumably by preventing free-radical damage to mitosing cells, when given prior to irradiation (Table II). Surprisingly, taurine is said to be effective, *after* irradiation.[21,22].

There is an extensive literature supporting the ability of aldose reductase inhibitors to retard or even prevent the occurrence of sugar cataract (e.g. galactose-induced or diabetic) in animals, when given by the oral or topical route.[7-10] The ability of free radical scavengers (e.g. vitamin E, A, glutathione, butylated toluene) to achieve a similar inhibitory effect may lie in their ability to protect or replace scavenger thiols such as reduced glutathione. Flux through the sorbitol pathway consumes NADPH, which is required for the regeneration of reduced glutathione. Aldose reductase inhibitors will therefore protect this thiol system by preventing oxidation of NADPH and some have independent radical scavenging ability.

Acetyl salicylate will inhibit the binding of cyanate or glucose to lens crystallins by itself acetylating these proteins. It will inhibit the cyanate-induced opacity which occurs on cooling rat lenses.[12] Bendazac has a similar action.[13]

Table II. *Protection against radiation cataract by thiol compounds*

Glutathione[16]
Cysteine[16,17]
Cystaemine[18]
Cystamine[19]
AET[20]
Taurine[21-23]

AET = 2—amino ethyl isothiouronium bromide

Clinical

Kador critically reviewed over fifty commercially available products purporting to be of value in the therapy of cataract.[24] For many of these, no adequate rationale for a mode of action could be entertained. In a small number of instances, randomised controlled trials have been performed, for limited periods, sometimes with intimation of efficacy resting on an effect on acuity alone. Some examples are given in Table III.

Table I. *Inhibition of experimental cataract*

Damage	*Agent*	*Protection*
Cation pump	Hydrogen peroxide	GSH[3]
	U-V radiation	Ascorbate[4]
	Genetic (Nakano Mouse)	Phakolysin[5]
Membrane Permeability	Binding of membrane thiols (PCMBS)	Cysteine, GSH[6]
Osmotic	Sugar Cataract	ARI[7-10]
		Vitamin E; A; GSH;[11] BT
Crystallin	Glycosylation	Acetylsalicylate[12]
Conformation	Carbamylation	Bendazac[13]
Crystallin Aggregation	U-V radiation	Ascorbate[14]
Aerobic respiration	2-4 DNP	GSH[15]
Mitosis	Ionising radiation	Sulphur compounds

ARI—Aldose Reductose Inhibitors; GSH—Reduced Glutathione; BT—Butylated toluene; DNP—dinitrophenol.

Table III. *Controlled trials of anticataract drugs*

Phakan	:	140 patients	9 months slight, if any effect[25]
Tiopronin	:	150 patients	12 months treated group improved[26]
Taurina	:	100 patients	6 months acuity improved[23]
Catalin	:	40 patients	18 months morphology improved[27]
Phakolysin	:	40 patients	5–6 months acuity improved[5]
Bendazac	:	37+80+50+60 patients	1–12 months treated groups fared better[30–33]

Phakan contains ascorbic acid, inositol, vitamin B6 and the precursor amino-acids of glutathione. Weigelin and Hockwin (1983) found it slightly more effective than placebo in treatment of senile cataract.[24] Taurine and tiopronin, two sulphur-containing drugs, were found to be more effective than vitamin drops or placebo in two other studies in senile cataract.[23,26] Two agents introduced to prevent the binding of quinoid compounds to lens sulphydryl groups have been found to retard progress of cataract in clinical trials, Catalin (a phenoxazine carboxylic acid)[27] and Phakolysin (azapentacene polysulphonate).[5] The theory of Ogino which attributed senile cataract to the formation of intralenticular quinones,[28] has not been supported, however. It is of note that although MacLean in an extended study found some action of Catalin in delaying cataract he did not advocate its general use.[29]

Bendazac lysine was found to improve acuity, or delay the progression of cataract in randomised double masked trials.[30–33]

Future Endeavours

A number of therapeutic considerations relating to the prevention of cataract are suggested by the foregoing.

(1) Drugs like acetyl salicylate and bendazac lysine which bind to the lens crystallins would theoretically be thought to be effective in retarding the progress of nuclear sclerosis. There is no experimental evidence that they would protect against damage to membrane permeability or cation pumps. But if epidemiological studies are correct,[34] then acetyl salicylate may have a wider protective effect than supposed. It is claimed that Bendazac is effective in cortical cataracts. Aminoguanidine is another agent whose value would seem at first sight to lie in retarding the progress of nuclear sclerosis. This hydrazine compound blocks the formation of advanced non-enzymatic glycosylation products in diabetic tissue.[35]

Since one mechanism proposed for steroid cataract involves binding to lens crystallins in much the same way as a cyanate or glucose, a possible approach to prevention of steroid cataract due to systemic administration in high dose, would be the topical administration of acetyl salicylate drops or related agent to diminish local binding to the lens while permitting steroid action where it was required. In the same way, if steroid cataract is due to the cellular products which it causes to be released (e.g. lipocortin) then use of a topical steroid blocking agent would be in order.

(2) Experimental studies suggest that free radical scavengers can protect against oxidative damage to the lens *in vitro* and *in vivo*. A fall in both ascorbate and reduced glutathione levels have been noted in the human lens with age, and also in both nuclear and cortical cataract. So far no convincing evidence of efficacy of topical preparations containing ascorbate and glutathione precursors has been presented. Possibly glutamine should replace glutamic acid in such preparations since glutamate enters the lens poorly—the use of topical free-radical scavengers would seem to have a special attraction administered over the period of therapy to those receiving ionic radiation in the head region.

(3) Aldose reductase inhibitors (ARIs): There is no evidence that the excess risk for cataract in adult diabetics has an osmotic mechanism. There is no major difference in the morphology between age-related cataract in diabetics and non-diabetics and it is likely that the diabetic mechanism converges on that responsible

for non-diabetic senile cataract. One possibility might be the consumption of NADPH that occurs in the formation of sorbitol from glucose. NADPH is also required to regenerate GSH from its oxidised form (GSSG). If deficiency of GSH was the basis for the over representation of diabetics at cataract surgery, then ARIs might be effective in reducing this risk by reducing the flux through the sorbitol pathway but would this affect in any way non-diabetic factors still active? It may be relevant that some aldose reductase inhibitors themselves have a free-radical scavenging activity.

Route of therapy

Topical therapy is the preferred route for a drug required to act on the anterior segment. High concentrations of lipid soluble drugs can be achieved in the aqueous after topical administration. It cannot be assumed, however, that adequate concentrations enter the lens, and therefore, it is necessary to determine that any topical drugs selected will reach the lens in adequate concentration.

The same applies to systemic drugs and here again, high lipid solubility is required for penetration into the uninflammed eye. In addition, anionic drugs are transported out of the eye against a diffusion gradient, and this would restrict entry by this route. Since anticataract therapy implies a lifetime treatment from say the fifth or sixth decade, the risks of adverse reaction or adverse drug interaction should be kept in mind when considering the systemic route.

Clinical Trials of Anticataract Drugs

To carry out a clinical trial it is necessary to be able to measure the quantity of cataract and its effect on vision. Details of methods are available elsewhere, but a summary is given here.[36]

Visual function

(1) *Visual acuity* is measured on Bailey-Lovie charts which offer an equal logarithmic step between each row of letters in terms of visual angle subtended at the eye. There are no uneven jumps between lines and there are the same number of letters on each line. The trial score is calculated by subtracting letter errors from the total number correctly seen. (Logmar score.)

(2) *Contrast sensitivity* is of interest in cataract patients as a measure of degradation of the retinal image; it will show a depression at middle and lower spatial frequencies when acuity, and responses at high frequency are unaffected. Glare testing should increase specificity.

Both these tests are affected by the patient's retinal function.

(3) Another index of the degrading effect of a cataract on the retinal image, can be achieved using the resolution target projection ophthalmoscope. This is based on the instrument of Cottlier in which the ability of the observer to resolve a series of projected targets of graded size and separation gives an indication of the resolving power of the lens. The model which we have devised (NAP Brown, Keeler Ltd.) projects targets whose size is separated in the same, equal logarithmic steps as in the Bailey-Lovie charts. This test is affected by the observer's retinal function, but not by the patient's retinal function.

Quantification of lens opacities is carried out in two ways

(1) Clinical grading at the slit lamp requires a trained observer to quantify the number and/or area covered by selected cataract features such as spoke and subcapsular opacities, or the density or colour of features such as nuclear sclerosis. This is done by matching against standard charts. Colour is matched against commercial Munsell colour chips and nuclear scatter against stepped neutral grey targets. Intra- and inter-observer agreement using this approach is good, for instance for spoke and posterior subcapsular opacity, with a weighted kappa value of 0.61 and 0.86 respectively (intra observer). (A kappa value of >0.75 is excellent, 0.6–<0.75 good, 0.4–<0.6 fair, <0.4 poor.)

(2) Photographic Documentation:
   (a) Slit-Image (Scheimpflug) photography provides a meridional cut through the thickness of the lens. In

some instruments multiple cuts can be made. We take a single sagittal cut through the lens. Reproducibility is aided by providing a separate fixation light for right and left eye, and by incorporating a fibre optic system along the incident light path which indicates in the viewing system alignment of the visual axis of the eye with the optical axis of the camera.

The slit-image provides data about lens thickness, zone thickness and scattering of light along the light path. The latter provides a measure of the density of cataract, which can be recorded densitometrically using image analysis techniques. Because nuclear scattering is homogenous, the nucleus is least sensitive to the effects of misalignment. A problem of the system is that opacities in the slit-beam throw shadows which lower the apparent density behind the opacity. Reduced pupil size affects recordability of the posterior lens surface. The method is highly reproducible on repeat testing in a subject.

(b) Retroillumination photography is achieved using a modified Kawara system. Crossed polaroids extinguish the light reflex from the corneal surface. The system provides a detailed picture of the lens opacities in silhouette and lends itself to image analysis.

Some problems are encountered. A Maltese cross pattern due to corneal birefringence is superimposed on the red reflex. This creates fluctuations in apparent density, unrelated to cataract. It is also not usually possible to keep both the anterior and posterior surface of the lens in focus simultaneously so that two photographs must be taken for analysis.

In both current systems, a window of neutral grey filter steps illuminated by the flash source appears on the film and controls for variable film exposure and development. An adjustment of apparent cataract density can be made on the basis of this during image analysis.

Recently Zeiss have developed an on-line video system with an image grabbing facility permitting analysis of high quality images of the lens in slit section or retroillumination. We are developing a similar system in Oxford.

Another technique which will be of future interest is the laser measurement of quasi-elastic light scattering by laser spectroscopy. This provides information about scattering from selected zones about the lens. It was originally interpreted as providing a direct statement of the size of protein aggregates within the lens fibres and changes were noted with ageing, and in diabetes. However, the response is affected by other factors and the interpretration of the results is now less certain. Nonetheless, the ability of the system to monitor scattering rapidly is of interest to clinical trials of anti cataract drugs.

Study Design

Clinical trials of this kind require a randomised double-masked, placebo-controlled design. The placebo should resemble the active drug in appearance and taste, the placebo excipient should not be expected to have an effect on lens metabolism (e.g. lactose). A preliminary run-up with all patients on placebo will ensure adequate baseline values; a staggered run-up will mask the onset of the trial.

The size and duration of the trial must be based on a knowledge of the natural history of cataract, and the estimated efficacy of the drug; e.g. if a significant change in grade is expected in 40 per cent of untreated lenses over 2 years, then in a study of 100 treated and 100 untreated patients, a 37.5 per cent protection by an anticataract drug would be needed to show a statistically significant difference over 2 years at the 5 per cent level (or a 45 per cent protective effect to show significance at the 1 per cent level). This information is not yet available to us.

Inclusion criteria: These will specify age range, sex, cataract type and degree, upper and lower limits of acuity.

Exclusion criteria: These could include diabetes, hypertension, severe systemic disease of any kind, use of steroids, heavy smoking, use of aspirin-like drugs.

Expectations

Over a period of time the techniques available will provide different kinds of information according to the kinds of cataract studied.

In diabetes, the non-cataractous lens is thicker than normal, perhaps because of increased growth, perhaps because of increased water uptake. Effective therapy might halt or even reverse this process in addition to preventing the advance of opacities. A similar expectation might exist for cortical spoke cataract where the spoke opacity is usually surrounded by a 'water cleft' and implies a localised excess of water. Such lenses might go through a stage of swelling which could be inhibited by appropriate therapy. A search for *decreased* sagittal lens thickness or zone thickness would be important.

In posterior subcapsular cataract various mechanisms have been suggested to explain the discoid morphology. One view suggests that there is focal damage to the fibre ends—for example by binding of a toxic agent—e.g. steroid to fibre proteins. In this case, the opacity would build up posteriorly, encroaching into the posterior clear zone but not the anterior clear zone. Effective therapy would restore the posterior clear zone and the opacity would move (relatively and actually) forwards, with a clear gap between capsule and opacity. The restoration of normal C1P thickness might take about 3 years (125 μm) but slit photography would be expected to detect a difference earlier.

Another view of posterior subcapsular cataract would be that it is the result of posterior migration of epithelial cells from the equator which undergo transformation into fibre-like, bladder cells (Wedl) when they reach the posterior part of the lens. This is the postulated mechanism in the subcapsular cataract due to X-radiation. Here, mitosis is stopped by the radiation and opacity appears when mitosis resumes. In this lag period the clear zone (C1) would be expected to disappear anteriorly and posteriorly because of the failure to add new fibres while C1 continues to convert to C2 internally. Thus lens growth would stop (or even reverse because of continued compaction) and C1 would disappear. Resumed mitosis and fibre differentiation would reverse this process, but C1 might not be restored to a normal appearance if fibre formation was abberrant.

If there is a process which simply switches off differentiation, then again C1 would thin anteriorly and posteriorly and epithelial cells would migrate backwards to form a posterior opacity, simply from the force of continued mitosis.

In these three hypothetical examples improvement would be heralded by a relative (and perhaps absolute) forward movement of the opacity.

For nuclear sclerosis our expectation should be of a slowing down of the rate of browning or of increased scattering. In other forms of cataract a slowing down of the rate of formation of new opacities or of increasing density of existing opacity will be the goal.

Conclusions

The causes of senile and other forms of cataract are being unravelled by experimental and epidemiological studies. Some risk factors for cataract could be reduced by environmental and health measures. Drugs which inhibit post-translational protein modification or protect from oxidative stress should be tested in senile cataract. Similar drugs may be of value in prophylaxis against toxic cataracts. The efficacy of medical therapy can only be assessed within the framework of well-designed clinical trials.

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