

*Review*

# The ageing lens and cataract: a model of normal and pathological ageing

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Cataract is a visible opacity in the lens substance, which, when located on the visual axis, leads to visual loss. Age-related cataract is a cause of blindness on a global scale involving genetic and environmental influences. With ageing, lens proteins undergo non-enzymatic, post-translational modification and the accumulation of fluorescent chromophores, increasing susceptibility to oxidation and cross-linking and increased light-scatter. Because the human lens grows throughout life, the lens core is exposed for a longer period to such influences and the risk of oxidative damage increases in the fourth decade when a barrier to the transport of glutathione forms around the lens nucleus. Consequently, as the lens ages, its transparency falls and the nucleus becomes more rigid, resisting the change in shape necessary for accommodation. This is the basis of presbyopia. In some individuals, the steady accumulation of chromophores and complex, insoluble crystallin aggregates in the lens nucleus leads to the formation of a brown nuclear cataract. The process is homogeneous and the affected lens fibres retain their gross morphology. Cortical opacities are due to changes in membrane permeability and enzyme function and shear-stress damage to lens fibres with continued accommodative effort. Unlike nuclear cataract, progression is intermittent, stepwise and non-uniform.

**Keywords:** cortical cataract; nuclear cataract; lens morphology; light-scattering

## 1. INTRODUCTION

### (a) *Ageing, lens dysfunction and cataract*

The term ageing implies cellular changes that accumulate with time and ultimately lead to functional impairment. Ageing is not a homogeneous process in the individual, and in the same way the components of the crystalline lens respond asymmetrically to the effects of ageing.

The lens is a key refractive element of the eye which, with the cornea, focuses images of the visual world onto the retina. This is achieved by its biconvex shape, high refractive index, almost perfect transparency and, in youth, the ability to bring near objects into focus by the act of accommodation. Ciliary muscle contraction allows the lens to take up a more curved shape. From an early age, two crucial features of the lens decline. A progressive loss of transparency is accompanied by a precipitous fall in the rate and amplitude of accommodation. The latter is the basis of presbyopia, which reaches its height by the age of 50 years. The biochemical and cellular changes that give rise to these events are part of a continuous process of structural and functional change that is modified genetically and amplified by environmental

risk factors. These events are the forerunners of cataract, a regional increase in light-scattering within the substance of the lens.

## 2. LENS ANATOMY AND PHYSIOLOGY

### (a) *Organization, energy supply and ionic homeostasis*

The lens is composed of ectodermal cells at various stages of differentiation, surrounded by a basal lamina, the lens capsule. Anteriorly they form an epithelial monolayer while internally they are represented by shells of concentrically arranged fibre cells, which form the bulk of the lens. The most superficial fibres are metabolically active, nucleated cells while the deeper fibres, making up most of the adult lens, are organelle-free. The energy required for growth and transparency derives chiefly from glucose. Fifty per cent of epithelial ATP is derived aerobically, while for the lens as a whole about 70 per cent arises from anaerobic glycolysis [1].

The water and ionic environment of the lens is maintained by ion pumps, such as Na<sup>+</sup>/K<sup>+</sup>ATPase and Ca<sup>2+</sup>ATPase, clustered in the pre-equatorial epithelium [2]. Ion channels cooperate in this regulatory function. Ionic equilibrium is facilitated by gap junctions, which in the human lens occupy a small fraction of the membranes compared with other species. Major intrinsic polypeptide (MIP26 or

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aquaporin 0, AQP0), which makes up 60 per cent of the lens membrane protein, is concerned with water transport between cells and performs a volume regulatory function. Gap-junctional proteins, connexin (Cx)43 in the epithelium, and Cx46 and Cx50 in the fibres, are involved in the movement of nutrients and other small molecules between cells.

### (b) *Antioxidants and free-radical scavengers*

Living cells are constantly exposed to oxidative stress from reactive oxygen species such as  $\text{H}_2\text{O}_2$  and hypochlorous acid (HClO) and the free radicals superoxide ( $\text{O}_2^-$ ) and hydroxyl radical ( $\cdot\text{OH}$ ). Endogenous sources include mitochondria, peroxisomes, lipoxygenases, NADPH oxidase and cytochrome p450. Mitochondrial superoxide, formed by the incomplete reduction of oxygen in the electron transport chain, is rapidly converted to diffusible  $\text{H}_2\text{O}_2$  by superoxide dismutase and thence to water by catalase or glutathione peroxidase. Nonetheless, lens cells are constantly exposed to  $\text{H}_2\text{O}_2$  and other xenobiotics, and there is a constant need to protect susceptible proteins from oxidation.

Redox homeostasis is achieved in the lens by additional scavenger molecules and repair systems located in cell membranes (e.g. vitamin E) and the cytosol (reduced glutathione (GSH), ascorbic acid, cysteine, methionine, glutathione reductase (GR), glutathione peroxidase, thioredoxin (TRx) and thioltransferase (TTase)), and found also in the mitochondria. These systems achieve a stable redox environment [3–5]. The lens also possesses systems for the repair or removal of damaged proteins [6] and nucleic acids [7].

GSH is the most important antioxidant molecule of the lens [8], present at a concentration of 2–4 mM [4,9]. It is synthesized by the lens epithelium where it is present almost entirely in its reduced form. Any oxidized glutathione (GSSG) is rapidly reduced to GSH by GR in the presence of NADPH. GSH scavenges reactive molecules directly, protecting exposed protein thiols from oxidation. While ascorbate also performs an important antioxidant role, its first oxidation product, dehydroascorbic acid (DHA), can induce cataract experimentally in lenses cultured in the absence of glucose or in the presence of an inhibitor of GSH synthesis [8]. GSH will reduce DHA directly, but is more reduced by the GSH-dependent, TTase system (see below). GSH is able to protect lens epithelial targets from oxidation, including  $\text{Na}^+/\text{K}^+$  ATPase, proteins associated with membrane permeability and certain cytoskeletal proteins. Also, absence of GSH protection in the lenses of GSH-deficient transgenic mice permits the formation of DNA strand breaks on exposure to  $\text{H}_2\text{O}_2$  [10,11].

The synthesis and recycling of GSH falls with age [12], leading to a progressive loss and a rise in GSSG [3,7,9,13]. This is partly due to a marked fall in GR activity [14,15]. The relatively low ratio of GSH to protein-SH in the adult nucleus of the lens, combined with low activity of the GSH redox cycle, makes the nucleus especially vulnerable to oxidative stress, as has been demonstrated in experimental

animal models exposed to hyperbaric oxygen and UVA exposure and in the glutathione peroxidase knockout mouse [8]. A further loss of GSH occurs in cataractous lenses [7], and over 50 per cent of the methionine and nearly all of the cysteine are also oxidized [16]. The impairment of  $\alpha$ -crystallin chaperone function by methionine sulfoxide oxidation can be reversed *in vitro* by methionine sulfoxide reductase A [17].

With increasing levels of oxidative stress, proteins become thiolated by GSSG, cysteine and to a lesser extent  $\gamma$ -glutamyl cysteine, to form the mixed disulphides, PSSG, PSSC and PSS $\gamma$ GC [5]. These mixed disulphides may be further oxidized to form protein–protein disulphides (PSSPs), which are found increasingly in the high-molecular-weight, water-insoluble (WIS) fraction of the lens proteins, containing large, light-scattering, protein aggregates [18].

Mixed disulphides and protein disulphides of this kind can be partially restored to their native state by two key redox repair systems. The GSH-dependent enzyme system, TTase, also known as glutaredoxin, exists in cytosolic and mitochondrial forms and catalyses the dethiolation of PSSG. The GSSG formed is recycled to GSH. Lens epithelial glyceraldehyde-3-phosphate dehydrogenase (G3PD) activity can be restored by TTase after  $\text{H}_2\text{O}_2$  challenge, as may other SH-sensitive glycolytic enzymes such as hexokinase and pyruvate kinase [19].

The NADPH-dependent enzyme TRx, present in both cytosolic and mitochondrial forms, reduces intra- and inter-molecular protein disulphides (PSSP). TRx is restored to its reduced state by TRx reductase (TR), with NADPH acting as a hydrogen donor. TRx works cooperatively with TTase to restore protein structure, conformation and function. Like TTase, TRx activity is also upregulated in response to oxidative stress. Both TTase and TRx systems can reactivate G3PD oxidized during the exposure of human epithelial cells to  $\text{H}_2\text{O}_2$ . Their activity, together with that of GR, falls with age [15].

### (c) *Lens composition*

The proteins of the lens make up about 33 per cent of its wet weight and account for its high refractive index. The lens crystallins, alpha, beta and gamma, make up over 90 per cent of these proteins. Other proteins include cytoskeletal and membrane proteins such as actin, filensin and spectrin, transporters and channel proteins, junctional proteins concerned with cell communication and many enzymes involved in metabolism, protein synthesis and degradation.

A number of excellent reviews of crystallin structure and function are available [20–22]. The three crystallins of the human lens are made up of monomeric proteins of roughly 20 000 Da, which in a dilute solution are found as water-soluble (WS) hetero-oligomers of about 800 000 Da (the  $\alpha$ -crystallins), as hetero-oligomers in the range of 50 000–250 000 Da (the  $\beta$ -crystallins) and, in the case of the  $\gamma$ -crystallins, as monomers. The high concentration of these proteins in living lens fibres and the molecular crowding that this creates enhance  $\alpha$ - $\beta$ -,  $\alpha$ - $\beta$ / $\gamma$ -,  $\beta$ - $\gamma$ - and

$\gamma$ -/ $\gamma$ - associations and interactions between the crystallin and non-crystallin proteins, such as actin and the lipids of the fibre membrane.

Alpha-crystallin performs a key role in preserving lens transparency, not only as a structural protein, but as a lens chaperone, conserving proteins in their native state. This is particularly relevant to the preservation of the  $\beta$ - and  $\gamma$ -crystallins but also applies to a number of enzymes and functional proteins, such as  $\text{Na}^+/\text{K}^+$ ATPase. A key function is to minimize the unfolding or conformational changes that characterize protein denaturation. The oligomeric  $\alpha$ -crystallin molecule exists in a dynamic state in which its subunits are continuously exchanged by rapid association and dissociation. This is important for chaperone function. The  $\beta$ - and  $\gamma$ -crystallins are compact and stable proteins that are members of a superfamily, related in sequence and structure [21]. They contain more sulphhydryl residues than  $\alpha$ -crystallins, and their exposure produces the mixed disulphides (GS-protein) and covalently cross-linked proteins (Pr-Pr) which are a feature of denaturation.

The ratio of cholesterol to phospholipid in fibre membranes of the superficial cortex is about 0.8, rising to over 5 in the deep cortex and nucleus of the adult lens [23]. It has been suggested that in the lens core, an increase in membrane rigidity contributes to the stiffness of the lens nucleus with age.

#### (d) *Lens transparency*

The transparency of the crystalline lens depends on its avascularity, paucity of organelles, narrow inter-fibre spaces and the regular organization of its cells and proteins [24]. At the cellular level, there is limited light-scattering by cellular organelles, which are relatively sparse in the central epithelium and displaced to the equator in the fibres, away from the light path.

Within the fibre cells, the crystallins exist with a short-range order less than the wavelength of light, similar to that of glass. This is due to the small size of the protein molecules, less than 10 nm in diameter, and their close packing at high concentration. Benedek [25] predicted that transparency could be achieved in the absence of long-range periodicity, by a short-range spatial order of protein molecules, and this was later confirmed by Delaye & Tardieu [26]. Currently, it is envisaged that soluble crystallin aggregates are present as 'hard', interacting spheres whose dense packing reduces fluctuations of protein density and refractive index below the wavelength of light. Hence, they do not give rise to significant scattering.

In the lens cortex, transparency is enhanced by the high spatial order of the fibre architecture and the narrow intercellular spaces. This compensates for light-scattering caused by fluctuations of the refractive index between membranes and cytoplasm. In the lens nucleus, high spatial order of the crystallins is not a prerequisite since there are only minor differences in the refractive index between fibre membranes and cytoplasm so that scattering is minimal [27,28].

#### (e) *Lens growth*

Lens growth is achieved by the addition of new fibres to the surface of the fibre mass over the lifespan.

From the moment of their formation, the fibres undergo a process of *terminal differentiation* involving a programmed sequence of organelle loss, culminating in *denucleation*. At a certain depth, the superficial, active, nucleated fibres lose their organelles and become transcriptionally incompetent, relatively inactive metabolically and lacking in synthetic capability [24,29–31]. The homeostasis and structural integrity of this organelle-free zone (OFZ) is maintained by the metabolic activity of the lens epithelium. The sharp boundary between the superficial, nucleated fibres and the deeper cohorts of the OFZ marks a stage through which all fibres pass, as they mature. Once formed, the OFZ increases in size at the same rate as the lens and comes to represent the major component of the lens mass.

According to Augusteyn [32], growth in lens mass is rapid and asymptotic during gestation, continuing at a much slower rate from about 3 years postnatally.

To understand the impact of ageing on the lens and the evolution of cataract, it is important to distinguish between the lens nucleus and cortex since they are affected differently by the ageing process. Here, we use the term *lens nucleus* to refer only to that body of lens fibres laid down prior to birth. The *lens cortex* refers to all those lens fibres added after birth.

The nucleus corresponds to the entire prenatal lens fibre mass. Since the lens is just under 4 mm in sagittal width at birth and about 6 mm in equatorial diameter, these dimensions define the maximum dimensions of a nuclear cataract. Owing to the process of compaction, the actual size of the true nucleus reduces over the years, so that in the adult it is somewhat smaller.

It is possible to measure the sagittal width of the postnatal lens *in vivo*, by Scheimpflug photography or ultrasound and thereby obtain values for the growth rate of the lens in this plane. From the age of about 11 years, cortical growth is linear in the sagittal plane at about  $25 \mu\text{m yr}^{-1}$  [33].

Studies using ultrasound have shown a more complex picture. Richdale *et al.* [34] reported the average sagittal width of the lens to be  $3.91 \text{ mm} \pm 0.163$  at three months and to fall steadily to a minimum thickness of  $\pm 3.36 \text{ mm}$  at 11.2 years. This was followed by an almost linear increase in thickness, returning to that in infancy at the age of 37 years. The reversal in sagittal width in the first decade was attributed to a continuing change in lens shape during development, with elongation in the equatorial plane at the expense of the sagittal plane. This makes an important contribution to nuclear compaction.

Another form of 'compaction' of the lens fibres is suggested by the finding that lens opacities affecting the most superficial cortical fibres (e.g. subcapsular cataract owing to blunt ocular injury, or the subepithelial 'glaukomflecken' of acute glaucoma) recede from the lens surface, in the sagittal plane, at a rate almost twice that expected from the growth rate of the lens [35]. This compaction of the cortex is independent of age.

#### (f) *The optical zones of the lens*

In the sagittal section, the transparent, young, adult human lens shows a number of zones of optical



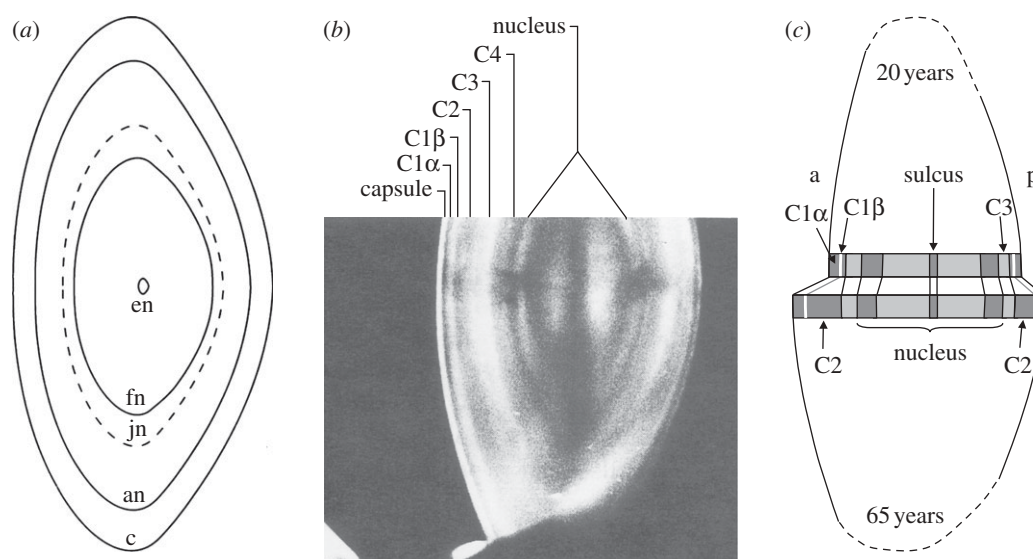


Figure 1. (a) Diagram of the lens zones drawn to scale based on a lens equatorial diameter of 9.6 mm in meridional section. The embryonic nucleus (en) represents the size of the fibre mass at the end of embryonic life; the foetal nucleus (fn) is the size of the fibre mass at the time of birth. This is referred to as the 'true nucleus' in this paper. The terms juvenile nucleus (jn) and adult nucleus (an) are also used in the literature to convey, respectively, those parts of the lens mass formed by the end of the second decade and later in adult life [38]. However, this terminology is not used here. (b) Scheimpflug image of an adult normal lens to show the zones according to the Oxford Classification (see text for details) [37]. (c) Schematic of the zones in the lens of a 20-year-old subject (upper part) and a 65-year-old subject to indicate lens growth with ageing. As the lens grows, only C2 is seen to increase in thickness. The 'sulcus' of the lens refers to the drop in light-scattering that occurs at the very centre of the lens (in the region of the embryonic nucleus). The 'true nucleus' includes the sulcus and the light grey zone on either side. The dark band immediately outside the true nucleus corresponds to C4 of the Oxford grading system. Note that Dubbelman includes C4 in his descriptions of the nucleus [39]. Figure 1a from Taylor *et al.* [38], © 1996 by Investigative Ophthalmology & Visual Science. Adapted from Investigative Ophthalmology & Visual Science in the format Journal via Copyright Clearance Center. Figure 1b reprinted from Sparrow *et al.* [37] with kind permission from Springer Science + Business Media. Figure 1c reprinted from Dubbelman *et al.* [39], © 2003, with permission from Elsevier.

discontinuity in which transparent regions are separated by bands of increased light-scattering and reflection [36]. These are due to changes in the optical properties of the lens fibres and are well shown by Scheimpflug photography.

The Oxford system of lens zoning divides the lens cortex into four major zones [37] (figure 1). Anteriorly, a bright, light-scattering line identifies the lens capsule and epithelium. Immediately deep to this is the highly transparent, first cortical zone, C1 $\alpha$ , which contains the youngest lens fibres and is of constant thickness over the lifespan—about 125  $\mu$ m. Directly behind C1 $\alpha$  is a narrow light-scattering zone, C1 $\beta$ , and behind this is the transparent C2, which increases in thickness with the growth of the lens. Since new fibres are added continuously to the surface of the lens fibre mass and C1 maintains its thickness, the steady increase in the thickness of C2 implies a change in the light-scattering properties of the fibres as they age, i.e. at a certain age, the highly transparent fibres of C1 $\alpha$  increase their light-scattering properties and they form C1 $\beta$ . Then, after a shorter period of time, these same fibres lose their light-scattering properties to regain their original transparency, as C2 fibres.

We have postulated that the anterior clear zone, C1 $\alpha$ , corresponds to the nucleated fibre region of the lens and that C1 $\beta$  represents the zone of denucleation [35]. This is supported by both the constancy of thickness of C1 $\alpha$  in the human lens and of the nucleated

zone of the primate lens [29,30] and their similar width. The increased light-scattering properties of C1 $\beta$  are probably explained by a transient increase in particulate content, as the fibres denucleate, and the irregular morphology and markedly convoluted membranes of the fibres in this zone, observed by confocal microscopy [40].

Cortical zone C3 forms as a result of an increase in the light-scattering properties in a band of fibres originally designated as part of C2. Possibly, this represents a region of fibres compacted during the period of post-natal shape change. Zone C4 is immediately perinuclear.

Zone C1 is of particular interest in relation to subcapsular cataract.

#### (g) The circulation of water and small molecules

The existence of the OFZ, lacking the machinery for protein synthesis and repair, places a homeostatic burden on the lens. Mathias has proposed that the outward pumping of Na<sup>+</sup> by the lens epithelium generates a circulation of water, ions, amino acids, nutrients and scavenger molecules that maintains the viability of the deep cortex and nucleus [2]. It is envisaged that the outward transport of Na<sup>+</sup> ions by Na<sup>+</sup>/K<sup>+</sup>ATPase generates a gradient that transports Na<sup>+</sup> ions to the lens core via a paracellular route. Here, it is proposed, Na<sup>+</sup> ions diffuse into the central fibres of the OFZ, flow back towards the lens surface across gap junctions and, on reaching the nucleated zone, are directed to

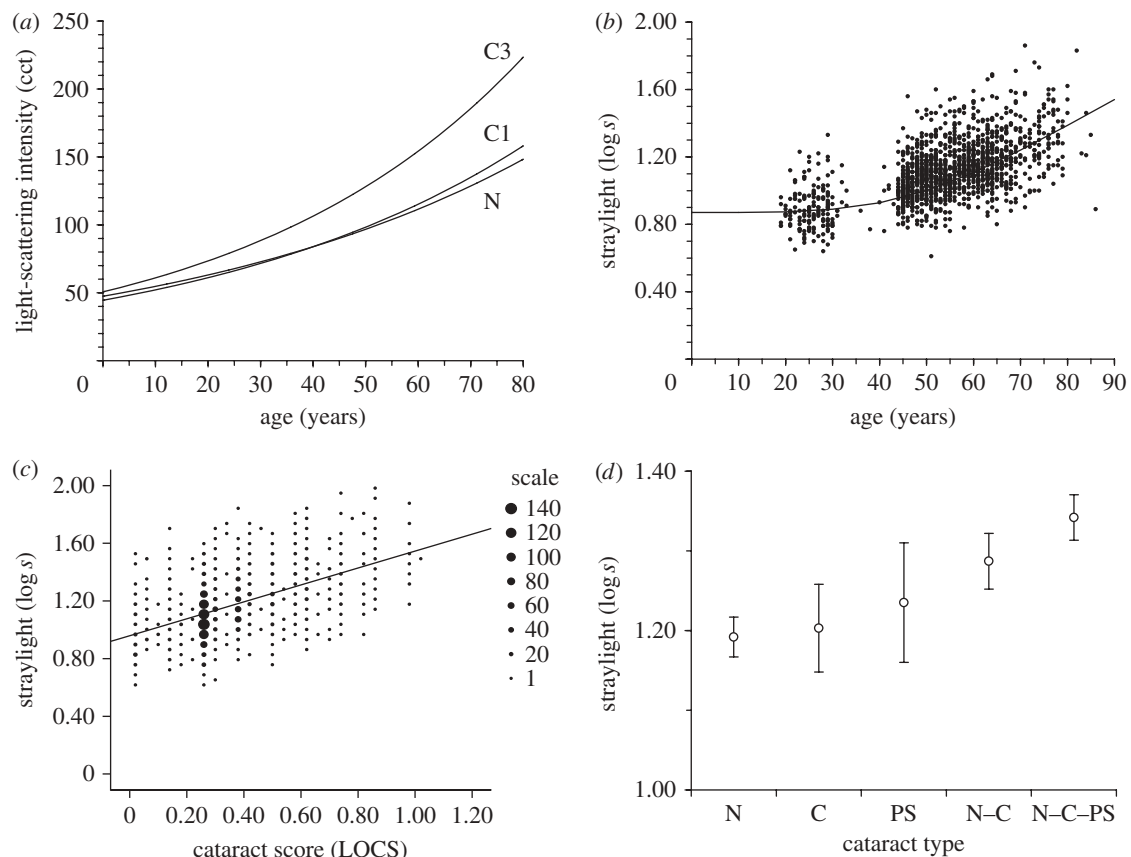


Figure 2. (a) Densitometric evaluation of Scheimpflug images to measure backward light-scattering from the lens and (b–d) psychophysical measurements of forward intraocular light-scattering. Light-scattering is shown as a function of (a,b) age, (c) the cataract score and (d) cataract type. (a) C1, C3 and N (nucleus) are lens zones according to figure 1b. (d) N, nuclear; C, cortical; PS, posterior subcapsular; N–C, mixed nuclear and cortical; N–C–PS, mixed nuclear, cortical and posterior subcapsular. Error bars show the confidence interval for the mean. Figure 2a reprinted from Sasaki [41], with permission from Deutsche Akademie der Naturforscher Leopoldina—Nationale Akademie der Wissenschaften. Figure 2b reprinted from van den Berg *et al.* [42], © 2007, with permission from Elsevier. Figure 2c reprinted from Michael *et al.* [43], with permission from John Wiley and Sons. Figure 2d reprinted from Nischler *et al.* [44], with permission from Wichtig Editore Srl.

the equator by the high gap-junctional coupling conductance of the equatorial fibres. On reaching the epithelium,  $\text{Na}^+$  ions are transported out of the lens by the  $\text{Na}^+$  pumps concentrated at this location. It is proposed that this lens circulation delivers GSH and nutrients to the central lens fibres.

As will be seen later, the development of a barrier to this circulation, by middle age, may play an important part in the evolution of nuclear cataract.

### 3. AGE-RELATED CHANGES LEADING TO CATARACT

#### (a) *Changes in physical behaviour with age*

A continuous series of biochemical and biophysical changes, starting prenatally, lead to increased light-scattering, coloration and stiffness of the lens. These affect the lens nucleus more than the cortex and are the basis for loss of accommodation over the first five decades of life. They may be seen as the forerunners of nuclear cataract and also contribute to the mechanism of cortical cataract.

##### (i) *Increasing light-scatter*

With age, in the absence of cataract, there is a steady increase in the overall light-scattering by the lens starting

after the age of 40 years. Large-scale Scheimpflug studies (1040 eyes of 1685 individuals) have revealed an exponential increase in light-scattering with age [41] (figure 2a), which is steeper in the deep cortex (C3) than in the most superficial cortex (C1) and the nucleus (N). Smith *et al.* [33] also found the greatest increase in the deep cortex (C3), then in the nucleus and then the superficial cortex.

There is also an exponential increase in intraocular light-scattering with age [42]. In a study including 2044 eyes without clinical cataract, light-scattering remained rather constant up to the age of 40, but then doubled by the age of 65 years and tripled by the age of 77 years (figure 2b).

##### (ii) *Decreasing elasticity*

The increase in the refractive power of the lens that occurs with accommodation is brought about by a change in the thickness and curvature of the lens, induced by ciliary muscle contraction. Scheimpflug photography and magnetic resonance imaging indicate that 90 per cent of the increase in axial lens thickness is due to thickening of the lens nucleus [45]. However, the steady increase in the stiffness of the lens with age, probably starting from birth [46], affects the

nucleus more than the cortex and is the chief factor determining the onset and progression of presbyopia. Up to the age of about 40 years, the lens nucleus is highly deformable and its stiffness is lower than that of the surrounding cortex; after this age the situation is reversed.

There is a continuous increase in lens stiffness with age, greater in the lens nucleus than in the cortex [47]. In young adults, the nucleus is readily deformable and its elastic modulus is lower than that of the cortex. At around 40 years it is about equal in both regions, and above 50 years the lens nucleus is stiffer than the lens cortex. By the age of 50 years, ciliary muscle contraction is no longer able to change the shape of the lens. This is the limiting factor for accommodation and the main basis of presbyopia [48].

These changes in the elastic properties of the lens are in large part due to age-related changes in the lens proteins, though the size of the lens and stiffness of the lens capsule also contribute.

### **(b) Changes in the lens proteins with age**

#### *(i) Post-translational changes to the lens crystallins*

The crystallins are intrinsically stable proteins, tightly folded in their native state but undergo major non-enzymatic modifications to their structure and function from early life. Changes include thiolation, deamidation, glycation, carbamylation, cys-methylation, phosphorylation and acetylation and also proteolysis, leading to truncation and the release of crystallin fragments [4,22].

Deamidation begins *in utero* and progresses with age and particularly with cataract, changing tertiary structure and encouraging unfolding and insolubility of  $\alpha$ - and  $\beta$ -crystallins. Deamidated crystallins are found more in the WIS than in the WS protein fractions of the lens.

Post-translational modification of crystallins by sugar derivatives occurs in the ageing lens and cataract and correlates well with loss in transparency. Glycation involves non-enzymatic, covalent modification, by reaction of a sugar aldehyde group with free amino groups of the protein. The chief glycaters are glucose, fructose and selected pentoses and glyoxal, and ascorbate degradation products such as threose [49]. These form Schiff-base compounds, followed by an Amadori rearrangement to form more stable compounds such as fructoselysine [50]. Later, the non-fluorescent carboxy-lysine and brown fluorescent Maillard products, including pentosidine, are formed and are included under the general heading of advanced glycation end products (AGEs) [51]. Extensive modification of  $\alpha$ A- and  $\alpha$ B-crystallin by glycation leads to aggregation and decreased chaperone function [9], probably, in part, by altering the dynamic state of the protein [52].

Denatured and unfolded proteins are susceptible to oxidation and the proteins of the lens are no exception. This is facilitated by the decline in the antioxidant capacity of the lens with age as indicated by a fall in GSH and GSH-regenerating enzymes, and leads to the accumulation of mixed disulphides, disulphide cross-linked crystallins and oxidized methionine residues [53]. While the thiol-rich  $\beta$ -/ $\gamma$ -crystallins are

most susceptible to oxidation, oxidation of  $\alpha$ A- and  $\alpha$ B-crystallins also occurs, leading to structural changes and loss of chaperone activity.

Both  $\alpha$ - and  $\beta$ -crystallins undergo cleavage to yield unstable, truncated products, with higher amounts of cleaved  $\alpha$ A and  $\alpha$ B in the WIS than in the WS protein fractions. C-terminal truncation of  $\alpha$ A- or  $\alpha$ B-crystallin affects both oligomerization and subunit exchange and leads to a loss of chaperone activity, probably by removing part of the sequence that maintains the chaperone-substrate complex in a soluble form.

There are increasing amounts of crystallin fragments in the lens fibres with age, with greater amounts in the nucleus than in the cortex and in the WIS than in the WS protein fraction [54]. It has been proposed that crystallin fragments generated from oxidized crystallins in aged lenses may interfere with  $\alpha$ -chaperone activity and enhance the aggregation of denaturing proteins, probably reflecting the presence of fragments with antichaperone properties [52].

There is an important ubiquitin-proteasome pathway in the lens, involved in the degradation and removal of oxidized proteins [55]. Ubiquitin conjugation activity falls in the ageing lens, leading to the accumulation of oxidized crystallins, particularly the nucleus that contributes to aggregation and light-scattering.

#### *(ii) Conformational changes*

The oxidative attack on unfolded or otherwise modified crystallins results in cross-linking, insolubility and the formation of high-molecular-weight aggregates. This, in turn, disturbs the short-range order of the crystallins, on the one hand leading to increased light-scatter and loss of lens transparency and on the other to progressive hardening, particularly of the lens nucleus. In the nucleus, these changes gradually take on the features of nuclear cataract, leading either to a grey-white nuclear opacity, or more often, with the accumulation of fluorescent chromophores, to a yellow, brown or dark brunescent nuclear opacity. The increased spectral absorption by these chromophores, particularly at the blue end of the spectrum, alters the apparent colour of the visual world.

One major contributor to the accumulation of chromophores is the formation of Maillard products and AGEs as the outcome of glycation or ascorbylation. Additionally, fluorescent chromophores are formed from tryptophan ('UV filter' compounds) such as GSH-3-OHKG, and 3-hydroxy kynurenine, which forms cross-linked derivatives with the crystallins. Modification of crystallins by *n*-formylkynurenine occurs in the lens and is thought to have structural and functional effects [46].

#### *(iii) Loss of chaperone function*

The decline of  $\alpha$ -crystallin chaperone activity with age, reaching a maximum in the fifth decade, accounts for an increased aggregation, protein insolubility, light-scattering and loss of lens transparency. These are features of the ageing human lens and are precursors of cataract. Changes are amplified by the reduced availability of free-radical scavengers able to protect vulnerable proteins against oxidation [8].

In the young lens,  $\alpha$ -crystallin interactions lead to the formation of soluble protein aggregates containing  $\alpha$ -,  $\beta$ - and  $\gamma$ -crystallins, which conserve their functions. However, by middle age, in the absence of new protein synthesis, nuclear  $\alpha$ -crystallin becomes depleted, and aggregates containing mainly  $\beta$ - and  $\gamma$ -crystallins appear. Above the age of 50 years, almost all  $\alpha$ -crystallins are found in the WIS fraction of the lens nucleus [56], and over time, the nucleus contains a larger proportion of both modified and cross-linked proteins than the cortex. In addition to the consumption of  $\alpha$ -crystallin, there is also a decline in subunit exchange and chaperone function.

(iv) *Loss of antioxidant and free-radical scavenging capacity*

The progressive loss of chaperone function with the approach of middle age is accompanied by a corresponding fall in the free-radical scavenging capacity of the lens, so that its proteins are increasingly exposed to the risk of oxidation. The level of reduced GSH decreases almost linearly with age [57], and the concentration of oxidized GSH (GSSG) shows a corresponding increase. There is also a progressive fall of cysteine in the nucleus but not in the cortex. Low or unmeasurable GSH levels are found in the lens nucleus in nuclear cataract.

An explanation for this relative lack of protection of the lens nucleus from oxidative attack has been provided by Sweeney & Truscott [58], who demonstrated the appearance of a barrier to the inward diffusion of GSH, forming around the nucleus after the age of 30 years. This would explain why the nucleus is peculiarly at risk of oxidative damage after this time. The increasing cross-linking between the crystallins themselves and with other cytoskeletal and membrane proteins would favour such an obstruction and would provide an explanation for the retention of fluorescent chromophores in the lens nucleus. A nucleus whose structural proteins are 'frozen' by cross-linking could also explain the relative preservation of fibre morphology despite the presence of open-ended fibres, in advanced nuclear cataract [28].

#### 4. AGE-RELATED CATARACT

##### (a) *Forms of cataract*

There are several distinct forms of age-related cataract, whose morphologies imply different aetiologies or susceptibilities of different lens regions [35]. Different forms may occur independently or in combination. In addition to nuclear cataract, the cortical cataracts that will be discussed here include lens retrodots, dot opacities, shades and spoke-like opacities. Posterior subcapsular cataract (PSC) is also a form of cortical cataract. The structural changes in various forms of cataract have been well reviewed by Vrensen [59,60] and by Costello and colleagues [28,61].

In this account, nuclear and spoke-shaped cortical cataracts and radial shades are regarded as fibre-based cataracts, which retain the onion-skin organization of the lens fibre system. Retrodot and dot opacities, circular shades and PSC are examples

of non-fibre-based cataracts, which break through the boundaries imposed by fibre architecture [62].

##### (b) *Nuclear cataract*

Strictly defined, a nuclear cataract is a lens opacity confined to the true nucleus of the lens whose shape is determined by the concentric arrangement of the fibres that compose it. Since the light-scattering properties of the lens nucleus increase progressively after the fourth decade, the point at which an increase in light-scatter may be designated a nuclear cataract becomes a matter of clinical judgement. While in some respects the molecular basis of nuclear cataract may be seen as an extension of those age-related events responsible for increased stiffness, light-scattering and coloration of the lens nucleus, it is the oxidative events discussed above, facilitated by the lack of nuclear GSH, that are the hallmark of nuclear cataract [63]. These are responsible for the formation of mixed disulphides and PSSPs, high molecular weight aggregates and increasing protein insolubility, which lead to lens opacity and the augmented accumulation of chromophores. These changes occur within the fibres of the lens nucleus with limited structural effect, which explains the gross morphology of the cataract.

The biomicroscopic features include an increase in light-scattering, to produce a grey-white opacity, and/or a colour change ranging from yellow-brown in its early stages to the deep, blackish-brown of advanced nuclear cataract (*cataracta nigra*) (figure 3a,b,d,e). These changes are distributed in a relatively homogeneous manner across the profile of the nucleus. The lens nucleus of a nuclear cataract is characteristically hard, the degree of hardness correlating with both age and the density of nuclear colour. Its elastic properties therefore differ markedly from those of the young lens nucleus or the nucleus of a transparent lens at the same age. Such nuclei are relatively resistant to fragmentation by phacoemulsification.

The changes that affect the true nucleus can, in time, spread to affect the deep cortex and produce a 'nuclear' cataract that exceeds the confines of the true nucleus. Such large nuclear cataracts may create surgical difficulties during extracapsular extraction.

The ultrastructural features of nuclear cataract have been studied in particular by Costello *et al.* [28,61,65,66]. They observed that in a typical nuclear cataract, although changes occur, there is no major fibre disruption or extracellular debris in the core of the nucleus to explain the opacity (figure 4). The strong implication is that local fluctuations in crystallin density, owing to the formation of insoluble aggregates, are the major cause of nuclear opacification. In more advanced nuclear cataracts, more severe, membrane-related structural changes occurred in the perimeter of the opacity [65]. In the nuclear core, there were membrane breaks, loss of membrane segments and exposure of fibre contents to the extracellular space, which was enlarged in many regions and contained dense deposits of protein-like material [28]. Additionally, low-density regions were seen. These fluctuations in density and refractive index were considered to produce significant light-scattering.



### (c) *Cortical cataract*

The superficial, nucleated cortical fibres of the lens (C1) are better able to resist oxidative damage than fibres of the OFZ. Their proteins are exposed for a shorter period to post-translational modification. Nonetheless, there is an increase in membrane permeability of the lens cells with age that leads to an increase in internal  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ion content. These changes are increased in cortical cataract and diabetes and are accompanied by a reduced activity of  $\text{Na}^+/\text{K}^+$  ATPase. This leads to overhydration, protein loss and an increased lenticular  $\text{Na}^+$  and  $\text{Ca}^{2+}$  and decreased  $\text{K}^+$  content [67]. Duncan *et al.* [68] proposed that the rise in cell  $\text{Ca}^{2+}$  ion content, favouring protein aggregation and proteolysis, contributed to the parallel increase in lens optical density from the fifth decade [69].

In this report, all forms of cataract involving opacity of the postnatal lens fibres are regarded as cortical cataracts.

#### (i) *Dot-like opacities and radial and circular shades*

The earliest changes to be noted in the lens cortex are small, dot-like opacities measuring several micrometres in diameter (figure 5a). At the ultrastructural level, they correspond to multilamellar bodies frequently found in the normal cortex within or between otherwise normal lens fibre cells (figure 5c). More advanced changes include *radial* and *circular* lens opacities, originally termed 'shades' by Obazawa *et al.* [72] (figure 5b), which are often in close proximity to one another. These occupy a region ranging from a tiny sector to the full extent of the lens circumference, where they form a band opacity (figure 5d). The extent affected increases with age. In the equatorial plane, they lie consistently at around 500  $\mu\text{m}$  deep to the lens surface and extend centrally to a depth of about 200  $\mu\text{m}$  [64]. The cortex superficial to these opacities is always clear.

Shades are very peripheral lens opacities but with full mydriasis, they can usually be observed if the lens is viewed obliquely. *Radial shades* run perpendicular to the equatorial circumference of the lens, following the course of the fibres anteriorly and posteriorly (figure 5d). They comprise parts of small groups of cortical fibres filled with globular elements [73]. *Circular shades* are well delineated and run parallel to the equatorial circumference. They originate in relation to equatorial fractures, perpendicular to the course of large groups of cortical fibres. Fractured ends are slightly swollen and membranes are folded, remotely from the break [74], but the membranes on either side of the fractures are normal, as is the architecture of fibres superficial and deep to the opacities [64]. Their formation involves a repair mechanism that anneals ruptured membranes and seals off the damaged from undamaged parts of the fibres [62]. Because these lens opacities break across the morphological boundaries of the cortical fibres, they are non-fibre based.

The prevalence of radial and circular shades is age related, radial shades occurring earlier than circular shades [60]. It is of interest that their onset roughly corresponds to the appearance of the lens circulation

barrier and the time when the shear modulus of the lens nucleus rises above that of the lens cortex [75].

#### (ii) *Spoke-shaped opacities*

The most prominent cortical opacities are spoke-shaped cataracts, also referred to as 'cuneiform' and 'wedge-shaped' cataracts (figures 3c,f and 6b,c,e,f). These fibre-based opacities owe their wedge-shaped morphology to the pattern of organization of the lens fibres. In the sagittal plane, they lie at a depth of 200–780  $\mu\text{m}$  from the anterior lens surface and hence lie in the relatively inert OFZ of the cortex [76]. Their development appears to start in the anterior and posterior para-equatorial zones, at first with small numbers of opaque fibre bundles (figure 6e). These progress to form larger, opaque areas that extend towards the lens poles and lens equator to produce thicker and denser opacities (figure 6f). There is ultrastructural evidence to suggest that opacification spreads both along individual fibres and also to adjacent fibres, so that they advance both centripetally and circumferentially at the equator [73]. In the region of the opacities, scanning electron microscopy reveals small and large groups of cortical fibres with broken ends, located in the pre-equatorial region (figure 6h,i). The sealed ends of these ruptured but transparent fibre segments explain their integrity and how they remain regularly arranged and mutually aligned, protected from exposure to the extracellular space. Their ultrastructural appearance contrasts with the regular architecture of lens fibres in a normal, aged lens (figure 6g). Those parts of the fibres beyond the opacities, anterior and/or posterior to the breaks, appear folded and undulating, suggesting that they have been released from tension in their long axes, while the deeper or more superficial neighbouring cortical fibres exhibit a normal structure and architecture [64,76].

In an earlier paper, based on clinical observation, an annealing process was proposed to exist within the lens, able to seal off damaged regions of a fibre from normal parts by a reconstitution of membranes [62]. In addition, it was suggested that, in a syncytial organ like the lens, there must be an uncoupling mechanism that would prevent the leak of ions from damaged fibres and the extracellular space into normal fibres, or conversely, a leak of ions such as potassium out of the normal fibres. Accordingly, it was proposed that with the onset of fibre breakdown, normal fibres adjacent to regions of fibre breakdown were protected from the spread of opacity by the uncoupling of intact fibres from damaged regions. This prediction was confirmed by Vrensen *et al.*, who found evidence of the annealing mechanism and demonstrated, using scanning electron microscopy and freeze fracture, that small opacities are bordered by membranes poor in intramembranous particles (concerned with cell communication) and rich in membrane *square arrays*, considered to be associated with non-leaky, uncoupled membranes [73,77]. This mechanism of annealing, sequestration and uncoupling may delay the progression of these forms of cortical cataract, and explain why, although opacities may present by the age of 40 years, more



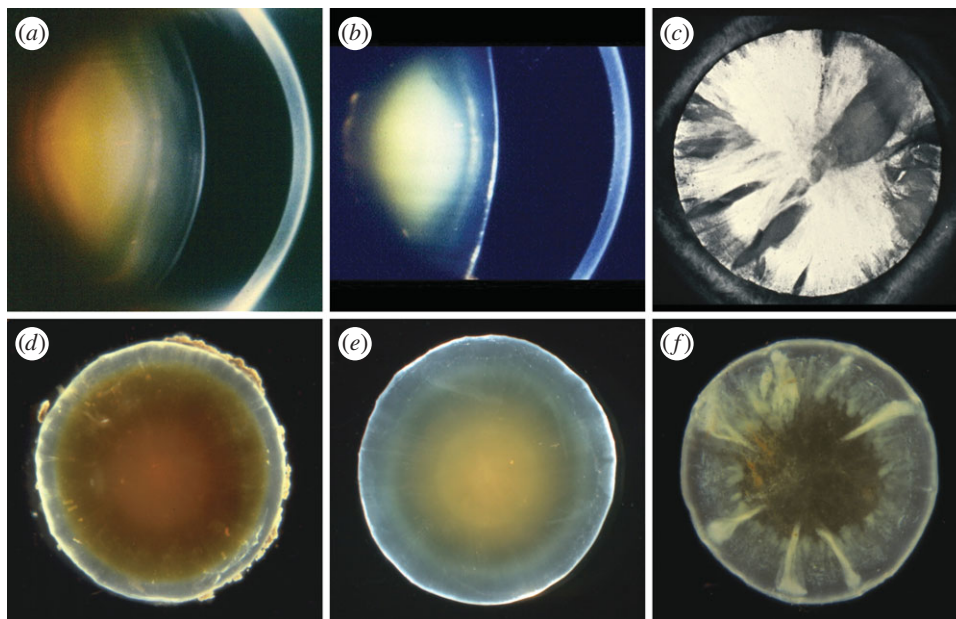


Figure 3. (a,d) Brunescence nuclear cataract of moderate-to-marked density. The deep cortex is also coloured a yellowish brown. In (a) the broad light-scattering zone in the deep cortex is C3. Note that the cortical zone, C1, is intact. (b,e) A dense, non-brunescence, white nuclear cataract. Anterior and posterior subcapsular cataracts are also present. (a,b) Scheimpflug photography (courtesy of J. M. Sparrow) with the cornea seen to the right. (d,e) Dark-field micrographs of human donor lenses. (c,f) Spoke cataract of varying density and extent, viewed by retroillumination in a living patient (c) and dark-field illumination of an extracted lens (f); in neither case is there an associated nuclear cataract. Scheimpflug and retroillumination images (a–c) and dark-field micrographs (d–f) are from different subjects. Figure 3d reprinted from Michael *et al.* [64], © 2008, with permission from Elsevier.

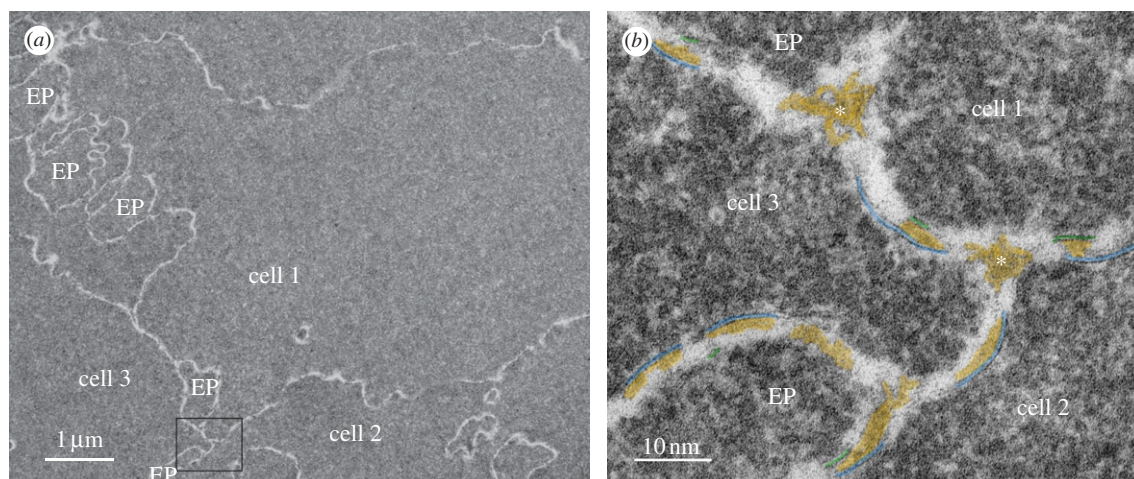


Figure 4. Ultrastructural images of fibre, cell–cell and cell–process interactions, in the nucleus of an advanced nuclear cataract from a 51-year-old patient from India. (a) The interfaces between three fibre cells and several edge processes (EP) are shown. (b) High-magnification view of the region boxed in (a), revealing damaged membranes from three cells and two edge processes. Extracellular space deposits (yellow) appear on curved membranes (blue and green lines) and similarly staining material occurs at trigonal intersections (asterisk). The trigonal points are extended extracellular channels that are partially filled with protein-like material. Figure 4 from Costello *et al.* [28], © 2008 by Elsevier Science and Technology Journals. Adapted from Elsevier Science & Technology Journals in the format Journal via Copyright Clearance Center.

advanced, spoke cataracts may take a further 25 years to develop [59]. The sealed ends of fibres associated with these cortical cataracts contrast with open-ended fibres found in nuclear cataract, and it may be that in nuclear cataract the high degree of crystallin and membrane cross-linking plays a role in preserving fibre architecture.

A contribution to these cortical cataracts is made by *fibre folds* that occur 1–2 mm central to equatorial breaks that cut directly across affected fibres. Bio-microscopically, these appear as so-called ‘lamellar

separations’, a non-cataractous, biomicroscopic appearance caused by the presence of undulating lens fibres. The folds appear to arise from a release of tension in the severed fibres and are strongly correlated with circular shades and spoke cataract [76]. Since both fibre folds and radial shades are associated with equatorial fibre breaks, it is difficult to escape the conclusion that they are initiated by circumferential breaks across cohorts of fibres as they arch over the lens equator. This would give rise, on the one hand, to fibre folds and secondarily, in time, to radial shades. It could also initiate the

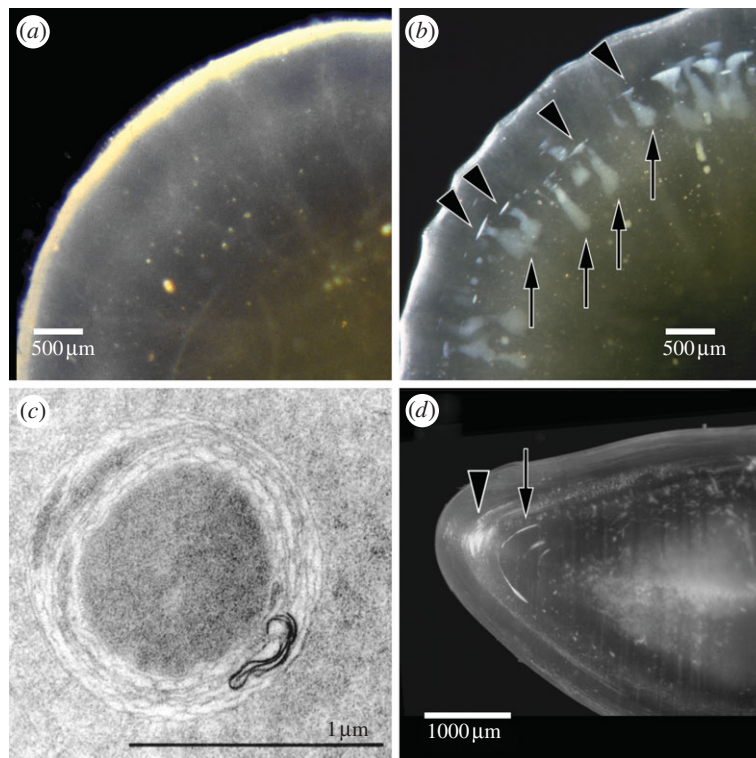


Figure 5. Dark-field micrographs of aged human donor lenses, illustrating (a) small, dot-like opacities and (b) radial and circular shades. (c) Multilamellar body, as frequently found in human lenses with early cortical opacities probably causing the star-like opacities seen in (a). A slice cut in the axial plane of the fixed donor lens (b) is shown in (d). Arrows, radial shades and arrow heads, circular shades. Figure 5a,b reprinted from Michael *et al.* [64], © 2008, with permission from Elsevier. Figure 5c reprinted from Vrensen *et al.* [70], with permission from Taylor & Francis. Figure 5d reprinted from Michael [71], © 2010, with permission from Elsevier. Scale bars, (a,b) 500 μm, (c) 1 μm, (d) 1000 μm.

formation of circumferential shades. The relationship between these events and cortical spokes is less clear. There is delay of many years between the detection of shades and the appearance and progression of spoke cataracts, which appear to lack the equatorial breaks characteristic of radial shades [73]. Thus, it would appear that radial shades and cortical spokes affect different fibre cohorts. It is possible that the existence of the fibre breaks affecting some cohorts of lens fibres places stresses on adjacent fibre cohorts, which in turn leads to the formation of spoke opacities. While, at the present time, not all elements of the story fit together, they offer a reasonable hypothesis for further study.

Cortical spoke cataracts are more common than nuclear cataract or PSC [41]. They can be restricted to a narrow sector or quadrant, or may affect the entire circumference of the lens; their extent is not directly related to age. Segmental cortical cataract is more prevalent in the lower nasal quadrant of the lens.

In comparing the progression of nuclear cataract with that of radial, circular and spoke cataracts, it should be stressed that the progression of nuclear cataract is a steady, continuous process, giving rise to a uniform, homogeneous opacity, while the cortical varieties involve a discontinuous process in which progression occurs in an asymmetrical, stepwise manner.

#### (iii) *Lens retrodots*

Retrodots are smooth-contoured, round or oval features, observed in the perinuclear cortex (C3 and

C4), often arranged in a circular or spiral pattern [62]. They are well seen by retroillumination but barely by focal illumination and are not opacities. They bear a resemblance to the 'spheruliths' of brunescant, Morgagnian nuclear cataract and like them are composed of calcium oxalate and therefore are birefringent in circular polarized light [78,79].

Oxalate is a final oxidation product of ascorbic acid, a scavenger molecule in high concentration in the aqueous humour and young human lens. Both ascorbate and GSH levels fall in cataract [78] and the common association of retrodots with nuclear cataract [80] probably reflects the oxidative environment in the lens core.

#### (iv) *Mechanism of cortical cataract*

Cortical spokes and shades evolve in a stepwise fashion to produce sectoral opacities, next door to transparent fibres in the same plane, and superficially and deep to them. Transparent fibres of the same cohort have experienced the same post-translational and oxidative stresses as the damaged fibres and therefore represent an internal control. Therefore, it is unlikely that these biochemical changes alone are the sole basis for structural breakdown. Perhaps this is not too surprising, since post-translational events decrease towards the surface of the lens and the superficial cortex is better supplied with scavenger molecules to combat their effects than the nucleus.

One explanation that has been proposed to explain the radial, circular and spoke-like opacities of the



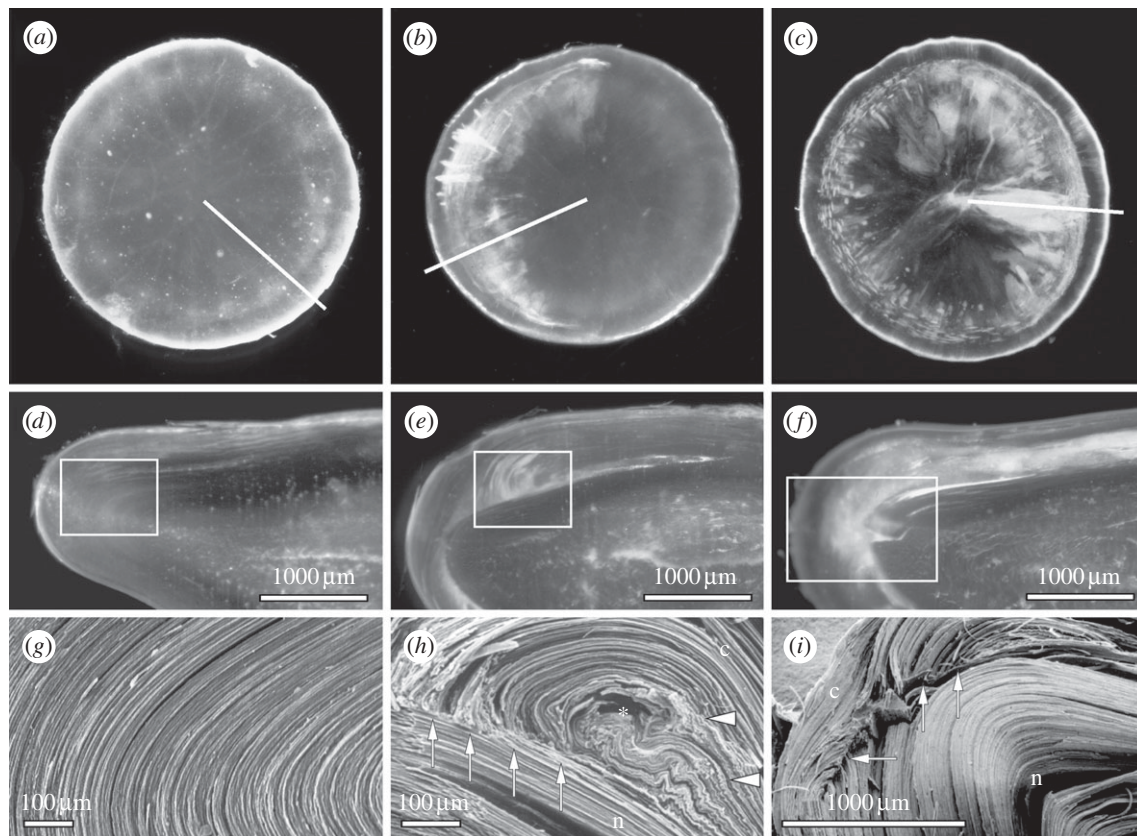


Figure 6. (a–c) Panel of dark-field micrographs of aged human donor lenses and (d–f) of slices cut in the axial plane of the fixed donor lenses. The cutting plane is indicated by a white line in (a–c). Apart from some irregular scattering owing to imperfect slicing, the nuclear parts of the slices are free of opacification. In (b) a band-like opacity is seen. Except for the spokes in (c), the opacities are outside the pupillary space and will not have seriously influenced vision. Below is the fibre organization in a lens without cortical cataract and in two cases of cortical opacities (boxed areas in d–f), as visualized by scanning electron microscopy (g–i). (h) Fibres at the border zone between the C3 and C2 regions are broken (arrows) and the broken ends are directed towards the nuclear fibres, which maintain regular, uninterrupted organization. Further, note the curled (asterisk) and folded (arrowheads) fibres in the region adjoining the broken fibres. (i) The scanning electron microscopy micrograph shows broken fibres at several places (arrows) in the border zone between the C3 and C2 regions. The central fibres are regularly organized, as are the more superficial cortical fibres bridging the break zone. ep, epithelium; n, nuclear side; c, cortical side. Scale bars, (d–f, i) 1000  $\mu\text{m}$  and (g, h) 100  $\mu\text{m}$ . Figure 6 reprinted from Michael *et al.* [64], © 2008, with permission from Elsevier.

cortex is a differential influence of mechanical stress on the lens cortex. During accommodation, the lens changes its shape by deforming its nucleus. With the onset of presbyopia, the elasticity of the lens centre decreases and the lens no longer changes shape, although the ciliary muscle continues to act, by way of its zonular insertion into the lens equator. It has been suggested by a number of authors, partly on the basis of experiments on the excised human lens, that mechanical stress at the C3–C2 border zone creates a shearing force that initiates fibre fractures [64,81,82].

Cataract is a multifactorial disease. If mechanical stress is the most important determinant of cortical cataract, it presumably interacts in some way with other risk factors such as diabetes, vascular disease, hormonal factors in women and corticosteroid intake.

Exposure to ultraviolet radiation (UVR) is also a risk factor for cortical cataract, and several epidemiological studies have demonstrated a relationship with personal exposure to UVR-B (wavelengths between 280 and 315 nm) [83]. The common finding that

cortical cataract appears more frequently in the lower nasal quadrant is in keeping with a role for sunlight since direct exposure of the eye to the sun usually takes place from above and the lateral side, because the nose has a shadowing effect [41].

Genetic factors are discussed in a specific contribution to this issue [84].

#### (d) *Posterior subcapsular cataract*

PSC is a discoid opacity subjacent to the lens capsule at the posterior pole. Because of its location at the nodal point of the lens, it has an effect on vision that is out of proportion to its density. Pathologically, it is associated with the posterior migration of metaplastic cells from the lens equator to the posterior pole; additionally, some agents may affect the posterior tips of the lens fibres directly. The most common form of PSC is age-related.

PSC is due to defective fibre production by the epithelium and is associated with a failure of lens growth. Since new fibres form the basis of C1 and the process of denucleation continues unabated, the

thickness of C1 decreases progressively and is an important clinical sign. In age-related PSC, the process is irreversible, whereas following exposure to cataractogenic agents, such as hypocalcaemia or corticosteroids, it is reversible, and on removing the cause new fibres are laid down superficial to the lens opacity [85].

#### (e) *The impact of age-related cataract on vision and its prevalence*

The visibility of lens opacities *in vitro* depends on their light-scattering properties. Membrane-bound bodies disturb the regular refractive index distribution of the protein-filled lens fibre cells. The resulting forward light-scatter renders them visible as small, spot- or star-like opacities (figure 5a,c). The same applies to the globular material within the radial and circular lens opacities together with the abnormal membranes found at these locations (figure 5b). In the normal lens cortex, the high spatial order of the lens fibre architecture (figure 6g) compensates for light-scattering caused by fluctuations in the refractive index between membranes and cytoplasm. This results in a relatively transparent lens cortex (figure 6a). When this spatial order is disturbed (figure 6h,i), light is scattered, and the peripheral band- and spoke-shaped opacities become visible (figure 6e,f).

The effect of such opacities on vision depends on their location and on pupil size. In daylight, when the pupil diameter is small (say 3 mm), only those wedge-shaped opacities that extend into the pupillary zone are likely to affect vision. Small, spot- or star-like opacities and radial and circular opacities are usually located outside this zone and do not affect vision (figure 5a,b). The same holds for peripheral band-like opacities (figure 6b). However, spoke-like opacities (figure 6c), extending into the pupillary area, affect vision. As the ambient illumination is reduced and the pupil dilates, vision is further affected as an increasing amount of straylight falls on the retina. Some cortical cataracts can induce astigmatism, probably resulting from localized refractive index changes along wedge-like opacities within the pupillary area. At night, when the pupil may dilate to 5–8 mm, the radial, circular and band opacities may be too peripheral to affect vision.

Measured intraocular straylight increases continuously with cataract severity as estimated by the mean Lens Opacities Classification System (LOCS) score, which averages nuclear colour, nuclear opacity, cortical opacity and posterior subcapsular scores (figure 2c) [43]. Mean intraocular straylight for the lowest LOCS score (0.1) is about  $1.0 \log[s]$ , with an LOCS score for mild cataract (greater than 0.75) about  $1.4 \log[s]$ , where  $s$  is the straylight parameter. This corresponds to a more than threefold increase in straylight. Intraocular straylight is much better correlated to cataract severity than both visual acuity and contrast sensitivity [43]. Stifter *et al.* [86] found a low correlation between individual LOCS scores and the Visual Functioning Questionnaire VF-14. Only the LOCS score on posterior subcapsular opacity gave a high correlation.

Lowest values of intraocular straylight are found in nuclear cataracts ( $1.19 \log[s]$ ), followed by cortical cataract ( $1.20 \log[s]$ ) and PSC ( $1.23 \log[s]$ ) (figure 2d). Mixed nuclear and cortical cataracts have a mean of  $1.30 \log[s]$  and mixed nuclear cataract, cortical cataract and PSC a mean of  $1.35 \log[s]$ . Nuclear cataracts have significantly better visual acuity and straylight values than mixed cataracts. In addition, pure cortical cataracts differed significantly from mixed cataracts in visual acuity and from mixed cataracts with a posterior subcapsular component in straylight and contrast sensitivity [44].

Nuclear cataract acts to lower contrast sensitivity of low frequency, acting as a filter over a narrower range than PSC. Retrodot opacities independently reduce both visual acuity and contrast sensitivity. Nuclear cataract and PSC are the types that are most associated with cataract surgery; a slight opaque area of PSC can necessitate lens removal.

Epidemiological studies using slit lamp and Scheimpflug camera observations have shown that, in temperate regions of the world, cortical cataract is by far the most prevalent age-related cataract, about four times more common than nuclear opacification [41,87,88].

Considering the age group 70–79 years, moderate-to-severe cortical cataract has a prevalence between 30 and 40 per cent in temperate regions and about 45 per cent in tropical or subtropical regions based on observations in Iceland, Japan and Singapore [89]. For a rural area in the USA, cortical cataracts involving at least 5 per cent of the lens area were found in 42 per cent of the population aged 75 years and older according to the Beaver Dam Study [90]. Similar data are reported from Australia with a prevalence of about 40 per cent [91].

For the same age group, moderate-to-severe nuclear cataracts are found in 10–15% of the population in temperate regions and in 20–60% in tropical or subtropical regions [89] and in 80 per cent in a rural population in the USA [90].

PSC is much less common, with 2–3% in temperate regions and 10–15% in tropical or subtropical regions [89].

Studies on post-mortem lenses in the Netherlands have shown similar prevalence data. Small dot-like and spoke-like cortical opacities were found in 20 per cent in the age group of 31–45 years and in 30 per cent in the age group 76–90 years. Larger segmental and annular cortical opacities were found in 10 per cent in the age group 31–45 years and in 45 per cent in the age group 76–90 years [92]. While these cortical opacities can be either restricted to a sector or quadrant or found around the entire circumference of the lens, their extent is not directly related to lens age [90]. The segmental cortical cataract is more prevalent in the inferior nasal sectors of the lens [90].

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