CHAPTER I

INTRODUCTION

1.1 EYE AND THE FIRST STEP OF HUMAN VISION

Eye sight, the most precious gift needs no explanation or is beyond any terms of scientific explanation. Aided by this unique sense of vision, man and animal define what the images of the world are.

From the beginning of time human have tried to explain the complex process of vision. It is interesting to examine a few of the ancient theories and to compare them to our modern knowledge. Recorded studies of human vision date back to the time of Aristotle. Aristotle's explanation of the process of human vision was that the object being looked at somehow altered the "medium" (now known to be air) between the object itself and the viewer's eye. This alteration of the medium was thought to propagate to the eye, allowing the object to be seen.

Vision is a complicated process that requires numerous components of the human eye and the brain to work together. The initial step of this fascinating and powerful sense is carried out by the retina of the eye. Specifically the photoreceptor neurons in the retina collect the light and send signals to a network of neurons that then generate electrical impulses that go to the brain. The brain then processes those impulses and gives information about what we are seeing.
Different part of the eye and the functioning is well visualized in figures 1 and 2.

FIGURE 1

FIGURE 2
The ability to see is dependant on the actions of several structures in and around the eye. Light rays are reflected from the object to the cornea, which is where the miracle begins. The light rays are bent, refracted and focused by the cornea, lens, and vitreous. The lens job is to make sure the rays come to a sharp focus on the retina. The resulting image on the retina is upside-down. Here at the retina, the light rays are converted to electrical impulses which are then transmitted through the optic nerve, to the brain, where the image is translated and perceived in an upright position!

**EXTERNAL STRUCTURE:** The eye is roughly a spherical structure which is covered externally by thin transparent covering of the skin known as conjunctiva. It is very sensitive and is kept moist by the secretion of three glands:

- **Meibomium glands** - these are found at the corner of both the eyelids and discharge an oily secretion which lubricates the conjunctiva.

- **Lacrymal glands** - it is also known as the tear glands and is situated on the outer side of the upper eyelid and produces a watery liquid which keeps the orbit and the eye ball moist.
Hardenian glands - these glands are situated on the inner side of the lower eyelid. The fluid of the gland keeps the cornea moist and clean from foreign elements.

**INTERNAL STRUCTURE:** internally eye is divided in three layers-

SCLEROTIC: it is the outer opaque layer of the eyeball formed of rough connective tissue. Its outer exposed part forms a protuberance in front of the lens, and is cornea, which is the thick and transparent.

CHOROID: it is the middle vascular and highly pigmented layer. It is differentiated into 3 parts:-

Choroid - it is highly vascular and pigmented thin layer in between the sclerotic and the retina and extends upto the junction of sclerotic and the cornea, after which it is continued with the iris. It serves to provide nourishment to the parts of the eye ball.

Ciliary body -it is the expansion of choroid coat at the front end of the eyeball in relation with the iris. It is formed of hair like secretory ciliary processes and meridional ciliary muscles. The lens and the suspensory ligaments rest upon the ciliary body. The latter operates the mechanism of accommodation.

Iris - behind the cornea, the choroid seperates from the sclerotic and forms a thin,circular,diaphragm,thiris,which hangs vertically in the
front of the lens. The iris is perforated in the centre by a small aperture, the pupil. Two types of special intrinsic muscles, the dilator and the sphincter muscles control the diameter of the pupil.

**RETINA**: it is the innermost thin delicate semi-transparent and sensory layer of the eyeball. The retina is differentiated into following four layers:

- Layer of pigment cells
- Layer of rods and cones
- Layer of bipolar cells
- Layer of neurosensory cells

**Rod cells** - the cytoplasm contains a photoreceptive pigment rhodopsin or the visual purple. They are responsible for weak light stimuli and therefore adapted for seeing in dim light.

**Cone cells** - the cytoplasm contains idopsin. The cone cells respond to bright light and hence adapted to see in day time.

The optic nerve which enters the eyeball after piercing the sclerotic and the choroid spreads in the form of minute fibers over the entire surface. The point of entrance of the optic nerve into the retina is not sensory due to complete absence of rods and cones cells and is known as the blind spot. Near the blind spot and in the straight line with the pupil is situated the yellow spot which is the
most sensitive part of the iris and is the seat of brightest vision. In the centre of the yellow spot is a small depression which is fovea centralis.

1.2 THE LENS

1.2.1 STRUCTURE AND FORMATION OF LENS

The fundamentals of the functional architecture of human organ of sight may be outlined as spherical eyeball, housing an optical apparatus that produces an inverted and reduced images of the outside world on a layer of nerve cells constituting the sensory apparatus. The optical apparatus of the eye, thus plays a significant role in the sense of interpreting the world. This optical apparatus consists of two refracting elements, the cornea and the crystalline lens.

The existence of the lens (Latin: Lentin or Lentil shaped) in the eye was recognized by the ancient Greeks, and by the 1st Century A.D, its anatomical location was established by the Alexandrian School (Duke, Elder and Wybar, 1961). With the pioneering microscopic studies of van Leeuwhock (1952), the structure and function of lens in normal healthy and diseased condition became a subject of general interest. In recent years, with the rapid advance in microscopic technology, molecular biology, immuno-cytochemistry and analytical biophysics and biochemistry, have contributed so immensely to our understanding of the lens system that we stand at the threshold of the medical cure of an age old malady, the cataract.
but still a more researches are needed to achieve the goal "cure or prevention of cataract".

1.2.2 MORPHOLOGIC SPECIALISATION OF THE LENS

The eye lens, one of the most important tissue in the body, is formed by a group of modified ectodermal cells that give rise to a highly organized, transparent, refractive, biconvex, elliptical, semisolid, cellular organ with smooth shining surfaces. The lens is usually described as a biconvex structure with the anterior surface facing the cornea having a less spherical form than the posterior surface facing the vitreous. The crystalline lens contains no blood vessels, lymphatics, nerves or connective tissue and it has remarkably little extra cellular space in its interior (Paterson, 1970). In post natal life the lens is nourished entirely by the freshly formed aqueous humor in which it is bathed. Since the lens is enveloped completely by a thickened basement membrane or capsules, and new lens cells are continuously formed, the older fibers cannot disquamate or discarded, instead they are preserved in the interior of the lens, accounting for its continuous increase in size throughout the life. The human lens does not have a static shape and the shape changes rapidly depending on the visual focus and with aging. It has been seen that the human lens increases in size with each decade of life and the growth is accounted for the increase in the cortex and not in the nucleus. The unique design of the lens with a total refractive power of about 17 diopters, has the sole purpose of
refracting incident light on the retina. The focusing or accommodative power decreases progressively and almost linearly with advancing age.

Dynamic changes in the curvature of the lens are brought about by the contraction of the ciliary musculature, the inherent elasticity of the lens capsule and by the plasticity of the lens substance. The lens plays a relatively passive role in the process of accommodation. Its major metabolic activities are directed toward maintaining transparency and growth. Weakness of the lens capsule and loss of the natural pliability of the lens substance are the major factors responsible for presbyopia.

On gross inspection, the virtually transparent lens has a slight yellow tinge which becomes deeper with advancing age. This yellow tinge permits the lens to serve as an ultraviolet filter that protects the retina from photopic damage, it also corrects chromatic aberration, thereby improving visual acuity (Lerman). The light transmissibility of the lens, however decreases linearly with age.

DEVELOPMENTAL ANATOMY

At about the 4.5mm Stage (2 weeks) of the embryo, as the neuro ectodermally derived, primitive optic vesicle reaches the surface ectoderm, the latter undergoes columnarization or palisading to form the lens placode. Physical contact between two cell layers does not seem necessary to induce differentiation of the lens placode. At about the 7 mm stage (4 weeks) lens vesicle begins to
separate from the parent surface ectoderm and with the formation of the primitive cornea by about the 9 mm stage, the approximately 0.2 mm diameter spherical lens vesicle comes to lie inside the eye. The apices of the cuboidal cells forming the lens vesicle project toward its central cavity whereas their bases are directed outward and are applied to the original enveloping basal lamina. With continued secretory activities of the cell the basal lamina thickens and forms the conspicuous lens capsule. (Lerche W and Wulle KG).

The cells of anterior wall of the vesicle remain relatively unchanged and constitute the embryonic and subsequently the postnatal, lens epithelium. Whereas the cells of the posterior wall of the vesicle elongate (beginning at about the 12mm stage or 5 weeks) during embryonic life to form the so-called primary lens fibers and by the 17mm embryonic stage (about 6 weeks) gradually occlude the lumen of the vesicle, the cell nuclei, which migrate anteriorly, eventually disappear. Thus during the first seven to eight weeks of embryogenesis, the cells of the posterior layer of the vesicle are responsible for the major growth of the lens. These are preserved as the core of the lens, known as the embryonic nucleus, the posterior part of the lens therefore becomes devoid of the epithelium.

The epithelial cells in the pre-equatorial region retain their mitotic and proliferative activity throughout life, the secondary lens cells that are formed elongate axially toward the two poles, extending directly beneath the epithelium anteriorly and the capsule posteriorly, thereby encircling and covering the primary lens fibers.
Initially, during the transient stage, the contra-lateral fibers originating from the different quadrants of the equatorial region are long enough to reach both the anterior and posterior poles, but with the successive internalization of fibers and consequent increase in lens volume, new fibers cannot reach from one pole to the other pole, instead they meet at radiating lines or sutures resembling an erect Y-anteriorly and an inverted Y-posteriorly. The y-sutures, which appear at about the 35mm stage (8.5 weeks) run through the whole thickness of the fetal nucleus.

In the infantile nucleus, the sutures assume a quadripartite or star shape, in the adult nucleus, they become more complex, with bifurcating lines above and below a central vertical line. In the adult cortex, the vertical suture line radiates with 9 to 12 branches in a dendritic pattern to form the lens star. The joining of the apices of the lens fibers gives rise to the anterior suture, whereas union of their bases from the posterior suture. Ends of opposing fibers from different quadrants of the lens meet at the suture line inter-digitate and overlap in a simple fashion or with ball and socket and tongue and groove arrangements.

In the embryonic and fetal life, the lens is nourished by the tunica vasculosa lentis. The vessels around the posterior capsule originate from the hyaloid artery at about the 12mm stage (5 weeks). The tunica vasculosa lentis begins to regress with the onset of aqueous humor circulation and usually disappears completely before birth. Remnants of the hyaloid vascular system
attached to the posterior capsule may project into the vitreous in the form of twisted or corkscrew-like strands.

1.2.3 ANATOMIC LOCATION OF THE LENS

The lens is located between the vitreous and the iris, the pupillary portion of the iris glides over its anterior surface. The anterior central region of the lens exposed by the pupil, forms part of the posterior boundary of the anterior chamber. Posteriorly, the lens is supported by the vitreous and lies in its anterior hollow, the patellar fossa. About 1mm from the periphery, the anterior vitreous face adheres to the posterior lens capsule in a circular zone, the so called “hyaloideo-capsular ligament of Weiger”. This attachment weakens progressively with age, hence in older eyes, the lens may be extracted with the vitreous loss. The posterior pole of the lens is separated from the anterior vitreous face by the capillary space of Berger, through which the aqueous humor reaches the posterior part of the lens. The lens is suspended in a fairly stable position in the visual axis by the zonule, or the suspensory ligaments which extends across the posterior chamber from the ciliary epithelium to a 2.5 mm broad circular zone on either side of the equatorial lens capsule. The equatorial region of the lens projects into the posterior chamber and is separated from the ciliary processes by a 0.5 mm wide space.
DIMENSIONS OF THE LENS

The dimensions of the lens vary with age and with the refractive state of the eye. The marked increase in the size and weight of the lens with age is in clear contrast to that of other ocular structures and indeed, of the eye as a whole. The human lens does not have a static shape and the shape changes rapidly depending on the visual focus and with aging. It has been seen that the human lens increases in size with each decade of life and the growth is accounted for the increase in the cortex and not in the nucleus.

The shape of the lens is determined by the tension of the zonular system which in turn, is influenced by the tone of the ciliary muscle and the inherent resilience of the lens tissue. The anterior surface of the lens is a flattened ellipsoid with a central anterior pole. The posterior surface is a paraboloid with a central posterior pole. The line joining the two poles is called the axis, and the rounded lateral border of the lens is called the equator.

The weight of the lens also increases with age, accounting for a two-third (65 mg) to the second year and nearly a four fold increase by the ninth decade of life. A myopic lens is heavier (234 mg) than the hypermetropic lens (218 mg). Male lenses are heavier than the female lenses at the same age (Harding JJ, Rixon KC).

The radii of curvature vary widely, depending upon the age. At birth, the lens is almost spherical with a diameter of 3.5-4mm. By the second year, it flattens significantly, with an anterior curvature of 5mm and a posterior curvature of 4mm, in adults, the lens reaches to
an average anterior surface diameter of 10mm (range 8.4-13.8 mm) and a posterior surface diameter of 6mm (range 4.6 -7.5 mm).

1.3 STRUCTURE OF THE LENS

Structurally, the lens consists of three components; the capsule, the epithelium, and the lens cells or fibers.

LENS CAPSULE

The lens capsule is a transparent, homogenous, resistant and highly elastic envelope that encloses the lens substance and anchors the jocular insertion. It is one of the thickest basement membranes in the body. Despite its thickening with age, the lens capsule gradually decreases in mechanical strength (Fisher RF and Wakely J). The capsule is non-selectively permeable to electrolytes, some dyes and smaller molecules of plasma proteins, but does not allow the passage of large molecules of albumin and globulin and generally forms a barrier to the passage of bacteria and inflammatory cells.

The lens capsule contains about 10 % carbohydrate ; the major component is collagen (hydroxyproline, proline and other amino acids) and the interstices are filled with glycoproteins. The superficial or zonular layer (0.5 to 1μm thick) is added to the capsule by about the 65-70mm stage(3 months) by condensation of the tertiary vitreous that forms the zonular system . In the central region, as seen by scanning electron microscopy, the surface of the capsule
has a pebble like, granular appearance. The lens capsule consists of extremely fine, filamentous, striated collagenous material (0.9 nm in diameter) arranged in a laminar fashion. The capsule is highly elastic, although it contains no elastic fibers, when it is cut or ruptured, the edges curl up so that the inner surface is outermost. The elasticity of the lens capsule is attributed to the super helical constitution of the collagen filaments, the helix angle being about 50 degrees to the long axis of the filaments (Fisher RF and Wakely J).

The thickness of the lens capsule varies in different regions of the lens. The capsule is thicker anteriorly (where it is elaborated by the basal surface of the epithelial cells) than posteriorly (where it is augmented only slowly by the basal surface of the lens fiber), and it is thickest peripherally on either side of the equator in the region corresponding to the attachment zone of the suspensory ligaments. The capsule thickness increases with the age, but decreases at an advanced age and with the formation of cataract. The differences in the regional thickness of the lens capsule may have a decisive influence on the hyperbolic shape of the lens during accommodation. It has been suggested that the major role of the capsule is that of maintaining the proper cyto architecture of the lens during fiber genesis, rather than in lens molding (Worgul BV, Rothstein H and Salzmann M).
THE LENS EPITHELIUM

The lens epithelium is organized as a single layer of cells beneath the anterior capsule and extends as far as the equator (Fig 9). It is derived from the original cells of the lens vesicle that did not differentiate into primary fibers. According to its proliferative morphology, the lens epithelium may be divided into three regions; the central, the intermediate or germinative, and the equatorial region. The cells of the central region, i.e; the region of the anterior pole are pale and polygonal (in flat section) to cuboidal (in meridional section) in shape. The basal surface is smooth and firmly bound to the capsule at various points so that during accommodation, the epithelium and the capsule move together.

The epithelial cells contain a moderate number of organelles typical of metabolically active cells. Unless severely injured or influenced by hormones and inflammatory and toxic effects, the cells of the central regions normally do not undergo mitosis thus they represent a true collection of aged ectodermal cells (Muggleton – Harris AL). Compared with the central region the cells of the germinative zones are smaller and more cylindrical, they enter in a digitate in a more complex pattern, and the cytoplasm contains a large number of organelles. The spherical nuclei are positioned centrally or nearer to the cell apex and frequently show karyo-kinetic activity. Around the equator, the epithelial cells gradually becomes columnar in shape. As the cells elongate, they tend to be arranged in meridional rows and assumes a pyramidal shape.
The cytoskeletal system of the epithelial cells includes actin filaments, intermediate filaments and microtubules. Besides being scattered throughout the cytoplasm, the actin and intermediate filaments are aggregated along the apical surface of the cells, especially at the epithelial/fiber junctional interface. Microtubules are more abundant in the germinative epithelium where they take part in cell division.

With advancing age there is an overall reduction in the heights of the cells and nuclei. In the germinative zone, the mitotic activity slows down. The intercellular spaces widen, the cytoplasmic density becomes variably, the mitochondria swells, the endoplasmic reticulum becomes elaborate, and electron dense inclusions may accumulate. In some cases, the epithelium may show proliferative and even metaplastic changes, especially in response to injury and to hormonal, toxic and inflammatory effects.

THE LENS FIBRES OR CELLS

Lens fiber or lens cells, is a popular term because of the morphologic appearance of the cells. The young lens fibers originate from the cells of the transitional zone at the equator. As the equatorial epithelial cells elongate, they orient themselves obliquely and come to lie beneath the epithelium of the anterior capsule. An elongated cell or fiber rotates through 90 degrees so that its basal
surface moves medially along the posterior capsule, while its apical surface extends anteriorly to reach the anterior epithelium.

An adult lens contains some 2,200 fiber lamellae, and that of a three month old child about 1,500. Mature lens fibers are 8 to 10mm long and have a six sided ribbon shape (8 to 12μm wide and 2 to 5 μm thick). They are fitted together to form smooth lamellae which lie parallel to the lens surface, as well as regular columns or rows in the radial direction. In antero-posterior section, therefore, the lens fibers are cut transversely, giving the appearance of superimposed concentric layers.

As the fibers mature, their ribosomal content increases, the round-oval nuclei elongate, the nucleoli increase in size, and gradually the nuclear membrane becomes indiscernible. The fragmentation and disintegration of the nucleus and nucleolus eventually result in dispersion of their contents in the cell cytoplasm (Kuwabara T and Imaizumi M). The fiber detaches from the epithelium anteriorly and from the capsule posteriorly, the detached ends of contra lateral fibers now called the mature fiber.

In the deeper cortical fibers, the intracellular organelles and ribosomes progressively disappear. The cells become dense and show irregular surfaces which give the appearance of fusion or indistinctness of adjacent cell membranes.

With advancing age, the lens fibers in the nuclear regions become more compactly arranged. With the gradual loss of the intercellular spaces, the cell membranes become ill-defined and with
progressive physiologic compression, a state of cell fusion may develop. There is an overall shrinkage of the cells with some loss of water and the cytoplasmic density and granularity increase with a deposition of yellow/brown pigments the refractive index increases. Consequently, the light transmissibility of the nuclear region gradually decreases and a state of nuclear sclerosis sets in.

The lens plays a relatively passive role in the process of accommodation. Dynamic changes in the curvature of the lens are brought about by the contraction of the ciliary musculature, the inherent elasticity of the lens capsule and by the plasticity of the lens substance. The refractive power and the transparency of the normal lens depends on a smooth refractive index gradient for visible lights. This occurs due to regular arrangement of fibre cells and the presence of stable intra cellular lens specific proteins, i.e the various types of crystallins.

High concentration of these crystallins provide the medium of high refractive index necessary for the function of the lens and the gradient of the increasing refractive index from the cortex to the nuclear region is associated with increasing concentration of crystallins relative to water. Irregularities in the refractive index which induce light scattering are often found in certain types of cataract and in senile cataract these are associated with increased degradation of lens protein, cross linking (including disulphide bonds and aggregation of crystallins).

The human lens is comprised primarily of water and closely-packed proteins, called crystallins and the crystallins account for 90 % of the
soluble proteins of the lens and consists of three antigenically distinct families of polypeptides called alpha, beta, and gamma. The α, β, and γ crystallins make up the bulk of the lens mass and are responsible for the larger refractive index of the lens. The α-crystallins, comprises of two highly related chains (αA and αB), and accounts for approximately 40 percent of lens dry weight, while the families of β and γ crystallins, comprises of a least nine related proteins, accounts for almost all of the remaining dry weight of the lens. The relative contributions of each of the α, β, and γ proteins to the total refractile properties of the lens are unknown. In addition, nothing is known concerning the importance of each of the β and γ species in maintaining normal lens transparency, especially under conditions of metabolic stress. The roles of the α, β, and γ crystallins in the possible control of molecular processes that occur during differentiation of the lens epithelial cells also remain undefined.

Recent findings indicate that α crystallins possess molecular chaperone properties that enable them to inhibit non-specific protein aggregation. This discovery has demonstrated a physiological role as well as a structural role for α crystallin. In addition, significant amounts of αβ crystallin have been found in other tissues besides the lens, including the retina, the heart, and the brain. Abnormally large amounts of αβ crystallin are also found in some human neurological disorders. Both these observations suggest the intriguing possibility that the αβ crystallin may also play physiological roles in other tissues.
The discovery that α crystallins, a major component of lens fiber and epithelial cells, prevent denaturation and aggregation of proteins in vitro was unexpected. This novel finding suggested a particularly significant role for this important class of proteins, that of a molecular chaperone. Chaperones are proteins that affect protein-protein interactions by stabilizing protein conformations and preventing nonspecific protein aggregation in the face of heat denaturation or other environmental stresses. In vitro studies have shown that the molecular chaperone properties of the α crystallins decrease during aging of the lens perhaps, as studies suggest, as a consequence of environmental insults (e.g., oxidizing agents, ultraviolet [UV] light, glycation) to the human lens. Further support for α crystallin as a chaperone comes from studies of the central nervous system; αB crystallin expression is greatly enhanced in neurons of patients with neurodegenerative diseases such as Alexander's disease and Alzheimer's disease, where αB crystallin colocalizes with aggregates of aberrant proteins. These findings are consistent with an increase in α-crystallin expression to prevent aggregation in cells that are stressed.

This discovery of chaperone activity has provided the impetus for conducting further studies to characterize the structural and biochemical properties of this physiologically important process. The ability to undertake structural and functional studies has been aided by the techniques of molecular biology. The production of large amounts of unmodified crystallins is now possible. Genetic manipulations in mice have permitted the development of animal lines that either lack or
overexpress specific α, β, or γ crystallin polypeptides. Recent refinements in the use of cryoelectron microscopy and NMR spectroscopy now make the structural elucidation of large proteins that comprise macromolecular aggregates like α crystallin feasible.

The gamma crystallins are found mainly at the central core region of the mammalian eye lens, where the refractive index is maximum and the water content is minimum. The core of the adult mammalian lens is formed from the original fetal structure and since there is little or no protein turnover within it, the lifetimes of the crystallins molecules are same as that of the animal. It is important for these proteins to have great stability in the individual tertiary structures and the interaction with other cell components. The gamma crystallins are rich in the sulphur containing residues, cysteine and methionine and other aromatic residues, all of which are susceptible to oxidative process.

Possible roles for gamma crystallins in the transparent lens and in the cataractous condition: the gamma crystallins are predominant in the nuclear regions of those vertebrate lenses that have a steep refractive index gradient and a relatively low water content. With respect to cataract, it is established that the increased light scattering of senile nuclear cataracts is associated with protein aggregation, together with chemical cross-linking, including disulphide bridges and methionine oxidation and un-indentified covalent cross-links. Alteration of the surface properties of these gamma crystallins might well be expected to lead to super...
aggregation to other crystallins giving rise to light scattering. Such alterations could be caused by chemical modification and the resulting non-covalent aggregation could then be followed by covalent cross-linking.

Although most cells of the body undergo sequential processes of differentiation and aging, the lens cell is perhaps the simplest and most elegant system to study the molecular mechanisms involved in these two fundamental processes. In contrast to the cellular and molecular complexities present in most other tissues, the lens is a much simpler system, comprised of a single layer of epithelial cells that differentiate into fiber cells. Because of the very low turnover of proteins in the differentiated fiber cells, our lenses contain proteins that have been made during all ages of our life. The ease of obtaining lens epithelial and fiber cells, plus the relative molecular simplicity of the fully differentiated fiber cells, make the lens one of the best tissues to study the mechanisms that control the fundamental events of cell differentiation and aging.

Differentiation of epithelial cells to lens fiber cells involves the cessation of proliferation, remodeling of cellular architecture, and significant changes in the collection of genes that are expressed, resulting in a restriction of protein synthesis to the high-level expression of a few classes of proteins.

Progress in characterizing changes to lens proteins during human lens aging and cataract- A great deal of progress has been made in characterizing structural changes that occur to lens proteins
during the normal aging process. Identifying sites where post-translational modifications occur has been aided by mass spectroscopy. Spectroscopic analysis and two-dimensional gel electrophoresis have permitted testing of the hypothesis that specific post-translational modifications to lens proteins lead to cataract formation. Surprisingly, although many modifications have been identified, none of these have been specifically associated with age-related cataract. Post-translational modifications of lens proteins seem to be a function of normal aging rather than cataractogenesis. However, post-translational protein modifications of α crystallin may be significant because the physical and chemical properties of the α crystallins are known to change during aging.

1.4 LENS TRANSPARENCY

The transparency and the refractive power of the normal lens depend on a smooth refractive index gradient for visible light. These properties are achieved not only by the regular arrangement of the fiber cells but also the presence of stable intra-cellular lens specific proteins called the crystallins. Ever since Kepler proved, the lens to have a capacity for light refraction and not perceptive properties, many attempts have been made to determine the refractive index of the whole eye lens and its various parts.

High concentration of these proteins provide the medium of high refractive index necessary for the functions of the lens. Irregularities in the refractive index which induce light scattering are often found in certain
types of cataract and in the senile nuclear cataract these are associated with increased degradation of the lens proteins, cross linking (including disulphide bonds and aggregation of the crystallins). The refractive properties are related to the quantitative chemical composition of the lens. The major composition of the lens is protein which constitutes about 35% of the wet weight or about 95% of the dry weight, including peptides and lipoprotein (Philipson 1969). The remaining portion is mainly lipids and the electrolytes (van Heyningen, 1962).

It has been shown that the distribution of the proteins in the normal lens is very even, within each layer and shows a smooth increase within the cortex. Because of this unique protein concentration, the tissue is not translucent but dramatically transparent in the wavelength region beyond the range of protein absorption. Such observation suggests, a uniformity of the refractive index throughout the lens, indicative of short spatial order, as reported by Delaye and Tardieu (1982)

The uniform distribution of the protein in the lens fiber, described by Philipson (1973) is consistent with an absence of the optical anisotropy revealed by a negligible birefringence. The absence of birefringence is due to the cancellation of negative form birefringence, governed by the orderly spacing of the lens membrane at the right angles to the optic axis and a positive intrinsic birefringence, due to an ordered arrangement of macromolecules in the cytoplasm, and it may be that the special feature of the lens crystallins, that permit this orientation of the aggregates is an adaptation that allows cancellation of the form birefringence to give increased transparency. Most researchers consider the biophysical basis
for the increased light scattering, along with the loss of transparency, to be fluctuations or sudden changes in the refractive index due to uneven distribution of the protein (Bettelheim, 1979).

1.5 CATARACT

Cataract is clouding of the lens in the eye that affects vision or more precisely cataract can be defined in terms of abnormal morphology or biochemistry, decreased light transmission, decreased visual acuity, optical aberrations or all of these parameters. Morphologically, a cataract is any disturbance of the optical homogeneity of the crystalline lens. This definition includes vacuoles, water clefts, dense areas reflecting or refracting light. Cataract can occur in either or both the eyes. It can not spread from one eye to other.

It is natural that a condition so common and obvious, associated with effects, so dramatic upon vision should have been known as early as historical records survive. Indeed the history of cataract goes back some 4000 years and probably further. In 1705, a French physician, Micheal Pierre Brisseau examined a cataractous patient, and he communicated to the Academic Royale des Sciences in Paris the fact that cataract was indeed due to the opacity of the lens.

THE INCIDENCE AND PREVENTION OF CATARACT

Cataract is one of the main cause that leads to blindness and constitutes the main surgical work load in the ophthalmic world. Cataract formation represents a serious problem in the elderly with approximately...
25% of the population over 65 years and about 50% over 80 years suffering serious loss of vision as a result of this condition. Not only do cataracts diminish quality of life, but they also impose a severe strain on global health care budgets. Cataract develop slowly, producing a gradually diminishing visual acuity, that finally requires the surgical removal of the lens. It is not possible to estimate accurately, the economic loss associated with the disease but in terms of individual productivity and pre and post operative costs far exceeds to billions of dollars.

It was estimated that cataract blinded or disabled 1.25 million people annually (Sorsby 1962). A WHO reports on blindness in different countries showed widely varying percentages of blindness due to cataract, i.e. Kenya (46%), India (39%), Sri Lanka (28%) Israel (28%) 22% England and Wales and about 28 % in the USA. Elsewhere in Asia ,it was reported that in Korea, cataract was responsible for 36% of all blindness (Koo and Chai 1974). In Thailand, 40%of blindness was due to cataract (Lim, Pahayom and Wangape 1972). On the African continent, a study of rural Kenya revealed senile cataract to be the cause of 43.6% of all blindness (Whitfield,1973), while in Nigeria it was about 35%. There are some indications that the prevalence of senile cataract is higher in Southern parts of Rumania, where the amount of sunshine is greater than the rest of the country (Pacurariu and Marin,1973).

In India an attempt was made to study the incidence of cataract in different geographical areas with varying temperature, rainfall and altitude (Chatterjee 1973).The data revealed less cataract patient in colder climate and higher altitude,although other variables(diet,light etc) cannot be
excluded. The magnitude of this burden of cataract indicated by a recent survey in Punjab, India has shown, age related cataract prevalence of 44% in persons aged between 53 or older which is almost about 3 times higher than that found in the USA (Chatterjee et al. 1982). The age related cataract is the major cause of blindness, worldwide especially in the tropical belt, where most of the densely populated developing countries are located (Liu et al. 1977). The incidence of cataract in the world may be now, be as high as 7 to 12 millions per year (Sommer 1977), and in India alone, it accounts for about 75% of the total population.

Age-related cataracts develop in two ways:

1. Clumps of protein reduce the sharpness of the image reaching the retina.

   The lens consists mostly of water and protein. When the protein clumps up, it clouds the lens and reduces the light that reaches the retina. The clouding may become severe enough to cause blurred vision. Most age-related cataracts develop from protein clumpings. When a cataract is small, the cloudiness affects only a small part of the lens. No change may be noticed in the vision. Cataracts tend to "grow" slowly, so vision gets worse gradually. Over time, the cloudy area in the lens may get larger, and the cataract may increase in size. Seeing may become more difficult. The vision may get duller or blurrier.
2. The clear lens slowly changes to a yellowish/brownish color, adding a brownish tint to vision.

As the clear lens slowly colors with age, the vision gradually may acquire a brownish shade. At first, the amount of tinting may be small and may not cause a vision problem. Over time, increased tinting may make it more difficult to read and perform other routine activities. This gradual change in the amount of tinting does not affect the sharpness of the image transmitted to the retina.

CAUSES OF CATARACT

- Injury to the eye
- Inflammations of the eye
- Eye infections
- General systemic diseases - such as diabetes
- Certain medications - such as cortisone
- Metabolic imbalances - such as kidney disease
- Long term solar (UV) damage
- Family history
- Association with glaucoma
- Personal behavior (smoking, alcohol use).

Most cataracts, however, will occur for no known reason. It is believed that the natural lens fibers of the eye simply wear out in time. At present, there is no medication or diet that will cure a cataract. There is no way to polish clean the cloudy lens. The only treatment involves surgery.
Cataract is detected through a comprehensive eye examinations that includes:

1. **Visual acuity test**: This eye charts measures how well you see at various distances.

2. **Dilated eye test**: Drops are placed in the eye to widen, or dilate the pupils. The eye professional uses a special magnifying lens to examine the retina and the optic nerve for signs of damage and other eye problems. After the test the close up vision remains blurred for several hours.

3. **Tonometry**: An instrument measures the pressure inside the eye. Numbing drops may be applied to the eye for the test.

Cataract develop slowly, producing a gradually diminishing visual acuity, that finally requires the surgical removal of the lens. It is not possible to estimate accurately, the economic loss associated with the disease but in terms of individual productivity and pre and post operative costs far exceeds to billions of dollars every year.
The symptoms of early cataract may be improved with new eyeglasses, brighter lighting, anti-glare sunglasses, or magnifying lenses. If these measures do not help, surgery is the only effective treatment. Surgery involves removing the cloudy lens and replacing it with an artificial lens.

Cataract removal is one of the most common operations performed in the United States and India. It also is one of the safest and most effective types of surgery. In about 90 percent of cases, people who have cataract surgery have better vision afterward.

There are two types of cataract surgery:

1. **Phacoemulsification, or phaco**: A small incision is made on the side of the cornea, the clear, dome-shaped surface that covers the front of the eye. The doctor inserts a tiny probe into the eye. This device emits ultrasound waves that soften and break up the lens so that it can be removed by suction. Most cataract surgery today is done by phacoemulsification, also called "small incision cataract surgery."

2. **Extracapsular surgery**: The doctor makes a longer incision on the side of the cornea and removes the cloudy core of the lens in one piece. The rest of the lens is removed by suction.

After the natural lens has been removed, it often is replaced by an artificial lens, called an intraocular lens (IOL). An IOL is a clear, plastic lens that requires no care and becomes a permanent part of your eye. Light is focused clearly by the IOL onto the retina, improving the vision.
Some people cannot have an IOL. They may have another eye disease or have problems during surgery. For these patients, a soft contact lens, or glasses that provide high magnification, may be suggested.

As with any surgery, cataract surgery poses risks, such as infection and bleeding. Before the cataract surgery, taking certain medications that increases the risk of bleeding is temporarily stopped by the doctor. After surgery, the eyes must be kept clean, and the prescribed medications should be used to help minimize the risk of infection. Serious infection can result in loss of vision.

Cataract surgery slightly increases the risk of retinal detachment. Other eye disorders, such as high myopia (nearsightedness), can further increase your risk of retinal detachment after cataract surgery. One sign of a retinal detachment is a sudden increase in flashes or floaters. Floaters are little "cobwebs" or specks that seem to float about in the field of vision. If a sudden increase in floaters or flashes is noticed, an eye care professional must be seen immediately. A retinal detachment is a medical emergency. If necessary, one has to go to emergency service or hospital. The eye must be examined by an eye surgeon as soon as possible. A retinal detachment causes no pain. Early treatment for retinal detachment often can prevent permanent loss of vision. The longer the retina stays detached, the less likely you will regain good vision once you are treated. Even if you are treated promptly, some vision may be lost.
1.5.1 DIFFERENT TYPES OF CATARACT

SENILE CATARACTS

An opacity or clouding of the crystalline lens producing a whitish appearance of the pupil and impairing or obstructing the passage of light, occurs with advanced age, usually above 60 years. If there are no direct causes assigned to this progress, it is generally known as senile cataract. The changes in the lens capsule, epithelium and lens fibers generally progress with advancing age and contribute to senile opacification of the lens (Worgul and Kinsey, 1982, Bettelheim and Siew, 1982, Tripathi and Tripathi, 1983). Age related changes in the protein structure and concentrations can be linked to the alternation in the optical property of the lens (Gamer and Spector, 1979). There is also the appearance of a high molecular weight protein fraction which appears to be an intermediate in the formation of the water insoluble protein (Jedziniak et al., 1979. Roy and Spector, 1976). In senile cataract, both the nucleus and the cortex are frequently involved and the nuclear and cortical cataracts may progress at different rates.

Anterior and posterior sub-capsular cataracts result from abnormal proliferative and migratory activity of the epithelium. Such changes are however, more common after injury, inflammatory and toxic insults and hormonal imbalance, than as a purely senile change (Tripathi et al., 1982). The anterior sub-capsular cataract results from necrotic changes in the epithelium of the anterior pole to form a sub capsular fibrous plaque (Tripathi and Tripathi, 1983). The mechanism of cataract formation and the morphological features of the anterior sub-capsular cataracts, have
certain features in common with other clinical conditions (Tripathi et al. 1980, Yanoff and Fine 1981).

The post clinical type of senile cataract is the cortical cataract (Bellows and Bellows, 1975). Histopathologically, cataractous changes in the lens cortex take a variety of forms such as irregular, entangling of fibers, various swelling and hydropic degeneration, stain irregularities, formation of cytoplasmic granules, cystic space with or without inclusions and water vacuoles, concentric arrangement of membranous lamellar bodies, crystalloid arrays of membranes, and elaboration of complex lipids from degenerating fibers (Creighton et al., 1978, Tripathi and Tripathi et al., 1983). During cataract formation, there is progressive loss of glutathione, inositol and soluble protein, most likely due to abnormal transport and increased permeability (Augusteyn, 1977). A build up of free amino acids in another feature of cataract formation (Takemoto and Azari, 1976).

**NUCLEAR CATARACTS**

People with nuclear cataract have a great difficulty in distant vision than near vision. The formation of nuclear cataract is accompanied by a large progressive increase in the amount of insoluble protein in the nucleus, a concomitant increase in the soluble proteins (Augusteyn, 1977) and number of oxidative changes involving the sulphur containing amino acids (Truscott and Augusteyn, 1977). The non-sulfide links in the nuclear proteins have shown an increase in the nuclear cataract formation (Kramps et al., 1978). In nuclear cataract, it appears that light-scattering
of high molecular weight aggregates of protein could be occurring (Garcia-Castineiras et al., 1978). There is also the appearance of a high molecular weight protein fraction which appear to be an intermediate in the formation of water insoluble protein (Garner and Spector, 1978).

CATARACTS DUE TO PHYSICAL CAUSES

Reversible lens opacities can be induced in experimental animals, subjected to severe anoxic conditions (Takugi et al. 1959). Asphyxia that is, a decrease in the available oxygen and increase of carbon dioxide in tissues, also induced reversible cataracts in animals (Bonavolants, 1953). Cataracts due to anoxic and asphyxia are unknown in men.

Profound dehydration due to cholera and diarrhoea as well as the prolonged deprivation of drinking water may cause cataract development (Harding, 1980). Changes in blood osmolarity, certainly appears to be major cause of lens opacities, that develop after haemodialysis (Orth et al., 1978). It is widely recognized, that in vitro, the lens volume responds to the change in the osmolarity of the bathing medium (Kern and Ingalls, 1983, Marcantonio, 1983).

DRUG INDUCED CATARACTS

Chlorpromazine is used extensively for the management of psychotic disorders and is, more recently, being employed in the treatment of cholera. Grenier and Berry (1964) described lens opacities, in psychotic patients receiving chronic doses of chlorpromazine and this finding, has since been confirmed by other investigators (Howard et al.
Chlorpromazine induced cataracts have been produced experimentally in guinea pigs. Chlorpromazine is found to disrupt electrolyte and water balance in the lens, in vitro.

Cortiosteroids (e.g. Wysolone) Drugs which are used to treat conditions such as bronchial asthma, Rheumatid arthritis etc

Phenothiazines: used in the treatment of psychiatric disorders

Amiodorone: Drug used in the treatment of certain heart ailments (arrhythmias). These are rarely visually significant.

A form of long standing skin disease associated with itching in people with allergies, bronchial asthma and skin disorder known as Atopic dermatitis is associated with cataract.

**COMPLICATED CATARACT**

These occur secondary to other eye problems such as retinal detachment, which is the detachment of the retina over which the light rays fall.

**CONGENITAL CATARACT**

Cataract seen at birth which may be due to hereditary causes, unknown causes and maternal infections. Cigarette smoking and alcohol intake are also being considered as risk factors but those have to be further confirmed.