CHAPTER 1

INTRODUCTION
Sight is the man's richest sense and his link to unravel the mysteries of the universe. The eye can detect intensities ranging over six orders of magnitude and is able to perceive images over great distances. In fact, the accuracy with which the eye responds to intensity and wavelength has not been matched with even the most sophisticated photomultiplier. The most important property of lens is its transparency. Anything that interferes the transparency of the lens will produce visual disturbances. The disturbance in the optical homogeneity of lens causes cataract. Cataract is the leading cause of blindness among adults, which amounts to one out of every seven cases of blindness in people aged 45 and above. Cataract, in other words, is the loss of transparency of the lens, develops as a result of altered physical and chemical process in its colloids. An effective anticataract medication can be effected only by an expanded and intensified programme of cataract research directed towards the understanding of the chemistry and physiology of the normal and cataractous lens. The works on various types of cataract may uncover the mechanism of opacification and help in finding ways of delaying and preventing this disorder. Extensive research has revealed much about the underlying mechanism responsible for the development of opacities. Experimental cataract has helped a lot to elucidate the underlying mysterious biochemical mechanism of cataract formation. Galactose cataract in rats has been established as an important model system in cataract research.

The crystalline lens is an encapsulated, avascular organ with a layer of...
epithelium overlying concentric layers of fiber cells. Lens helps to focus light on the retina. In a normal eye, light passes through the lens and gets focused on the retina from where the visual signals originate and are transmitted to the brain. To produce a sharp image, the lens must remain clear. The lens is made mostly of water and protein. The arrangement of lens protein is in such a way that light passes through the lens and is focused on the retina. Sometimes some of the proteins clump together. This may result in the appearance of cloudiness in certain areas of the lens, preventing light from reaching the retina and thereby interfering with vision.

Cataract may be classified as developmental cataract and degenerative cataract. In developmental cataract the normal development of the lens fibers and epithelium are affected during growth by hereditary, nutritional or inflammatory changes, with consequent loss of transparency. This group includes the congenital forms of anterior and posterior polar cataract, central cataract, zonular (lamellar) cataract, coronary and punctate cataract and complete congenital and juvenile cataract. In degenerative cataract, the normally developed lens loses its transparency as a result of degenerative changes. This group includes senile nuclear and cortical cataract, radiation cataract, lightening, electric and heat ray cataract, complicated cataract, cataract associated with systemic disease or poisoning and traumatic cataract.

Experimental cataract is characterized by abnormalities of fiber permeability that results in vacuoles or clefts in the lens cortex. The lens is a dehydrated organ, the adult human or animal lens containing approximately 66% water and 33% protein. The lens cortex is more hydrated than the lens nucleus. Lens dehydration is achieved by an active sodium ion-water pump that resides within the membrane cells of the lens epithelium and each lens fiber.
These fibers constitute the bulk of the lens cortex and nucleus. The spaces between the lens fibers, the extracellular spaces of the lens, are very small and is only about 5% of the lens volume. These spaces are enlarged in human and experimental cataract. Fluid collection between the fibers and destruction of many lens fibers result in the formation of vacuoles or clefts which were seen by slit lamp observation. The spaces between the fibers cannot be greatly increased unless the membranes of the lens fibers are broken.

The lens is avascular and obtains nutrition from the surrounding aqueous and vitreous humor. Glucose present in these fluids provides the lens with chemical energy required for growth and maintenance of transparency. Glucose from the aqueous and vitreous humor diffuses into the lens and is rapidly metabolized through the glycolytic pathway, the hexose monophosphate shunt and the sorbitol pathway. End products of glucose metabolism are lactic acid, carbon dioxide and water. Lactic acid from the lens diffuses into the aqueous humor and is eliminated via the circulating fluid. The breakdown of ATP generated from the metabolism of glucose, is required for active transport of ions and amino acids, maintenance of lens dehydration and transparency and for continuous protein and glutathione synthesis. Lens metabolizes 1μmol of glucose/lens/hour. The pentose pathway is extremely active in the lens, a feature common in red blood cells.

The lens contains an unusually high concentration of glutathione. Glutathione is a tripeptide synthesized in the lens which is made up of glycine, cysteine and glutamic acid. Most of the lens glutathione is in the reduced form (GSH). Only 6.8% of total lens glutathione is in the oxidized form (GSSG). Lens proteins contain reduced sulphydryl groups (PSH) and oxidized disulfide groups (PSSP), maintaining high levels of GSH. Thus decreased GSH or increased GSSG
will result in PSH oxidation and alteration in protein linkage, solubility and transparency.

Glutathione plays an important role in the metabolism of the lens, particularly in the maintenance of transparency of lens tissue. Enzymes for the synthesis and degradation of glutathione are extremely active in animal lens. GSH is enzymatically synthesized in the lens and also plays the role of a scavenger for free radicals produced by oxidative stress via, oxidation-reduction system. In all types of cataract, the concentration of these peptides or GSH/GSSG ratio is found to be decreased. Depending on the magnitude and persistence of the cataractogenic insult, the leakage of glutathione may continue or stop. To maintain normal levels of glutathione, increased levels of NADPH is needed, which lead to the stimulation of glucose metabolism through the pentose shunt.

Galactosemic cataract results from an excess of galactose. Two clinical forms of galactosemia are recognised viz., classic galactosemia (in which the enzyme galactose-1-phosphate uridyl transferase is absent) and galactokinase deficiency. Excessive galactose in serum and lens results in a shift toward the formation of galactitol. The key event in the galactose induced cataract is believed to be the activation of the polyol pathway, with the conversion of galactose to galactitol by aldose reductase. Galactitol will not undergo oxidation by the polyol dehydrogenase. As the cellular membrane of the lens is impermeable to galactitol, it leads to hyperosmotic swelling of the cell, which produces scattering of light and thereby diminishing lens transparency. The cataract in young rats appears as vacuoles in the equatorial region of the lens and with the progress of cataractogenesis, the vacuoles become more numerous and eventually a dense nuclear opacity develops.

The lens has got high protein content which provide refractive index sufficient to focus light on the retina. Most of the lens proteins have no clear-cut
enzymic or other specific function and so the major protein groups, the lens crystallins, have been regarded as structural proteins. When the lens is homogenized in water or saline and the homogenate is spun down at low centrifugal forces, most proteins remain in suspension called the soluble protein. The water soluble proteins of the lens (85%) are divided into 3 major fractions, called α,β and γ crystallins. Lens proteins are organ specific but not species specific. In normal lens, the membrane of the lens fibres and the lens capsule do not allow the passage of protein molecules from the lens to the aqueous humor. However, with the onset of maturation of cataract, the membranes of the lens fibers may get lysed and the capsule becomes more permeable causing leakage of proteins.

The long term goal of cataract research is directed towards retarding or preventing cataract. The elucidation of the biochemical changes in lens in experimental animals can provide a more vigorous base for the assessment of cataract. With these views, the present study was designed to elucidate the biochemical mechanism involved in the formation of cataract as evidenced from the changes in erythrocytes and lens of galactose fed rats at three different stages of cataractogenesis.

The objectives include:-

a) the study of generation of reducing power (NADPH) through the pentose pathway and its utilization through glutathione cycle in relation to cataractogenesis.

b) the assessment of glutathione and its linked enzymes in relation to cataractogenesis

c) the assessment of possible utilization of pentoses in HMP shunt pathway through the action of transketolase and transaldolase.
d) the evaluation of lipid peroxidative changes in relation to various stages of cataractogenesis.

e) the study of antioxidant scavenger enzymes in relation to cataractogenesis.

f) the assessment of protein through the soluble and insoluble fraction in relation to the above said changes during the progress of cataract.